Pharmacy Compounding: Defining the New Landscape for Safe Practice Advances and Professional Responsibility

by Nicole Van Hoey

Upon successful completion of this article, the pharmacist should be able to:
1. Compare the following definitions related to pharmaceutical preparations: sterile compounding, nonsterile compounding, manufacturing, traditional compounding, and nontraditional compounding.
2. Explain the 2012 NECC meningitis outbreaks in the context of contrasting manufacturing activities and compounding pharmacy practice.
3. Identify the specific steps that community nonsterile compounding pharmacies should enact to comply with regulatory-preferred USP 795 standards.
4. Discuss changes in state and federal oversight of compounding pharmacies and outsourcing facilities.
5. List certification or training programs that pharmacists and pharmacy technicians can complete to enhance professionalism and maintain skills.

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 DEFINING COMPOUNDING IN HISTORY AND TODAY

The Who, What, How, and Why

Compounding plays an important role in the profession of pharmacy in the United States throughout history and even today. In the earliest days of the profession, pharmacists were skilled at developing specialized products according to standard recipes and raw ingredients—a practice that made up the bulk of an early pharmacist’s work in tandem with physician diagnoses. Today, compounding is a professional niche, comprising only 1-5 percent of all prescriptions annually in 2006, not including pre-formulated admixtures and oral suspensions for reconstitution. The amount of compounding activity in a pharmacy ranges from infrequent, simple formulations to almost-exclusive compounding practices. Approximately 7,000 compounding pharmacies, out of 56,000 community pharmacies overall, exist across the country. In 2012, 63 percent of independent pharmacy owners reported in a NCPA Digest sponsored by Cardinal Health survey that they offer compounding services and on the whole, independent pharmacies compound at least once weekly, according to an AJPE 2009 survey, primarily for topical dermatologic products (91 percent in some pharmacies).

Outpatient compounds range from custom vehicles for topical application to unique oral formulations to suppositories. Compounding for inpatient or home infusion patients extends into sterile parenteral products such as radiopharmaceuticals, analgesics, antibiotics, and chemotherapy. Professional education for such compounding varies. Historically, self-directed book and experiential knowledge was the norm. After 1975, though, most schools provided more formal education on compounding, introducing hands-on skills development. For example, pharmacists who are certified in nuclear pharmacy must log 4,000 hours of education and training before they are eligible for the certification exam. Although not required, 98 percent of compounding pharmacists in 2009 reported postgraduate education beyond classroom laboratory experiences in compounding techniques. Pharmacy technician qualifications vary by state but may include completing a pharmacy technician training program, passing a pharmacy technician certification exam, possessing an associate’s degree or earning a certificate from a course on aseptic technique.

Reasons to compound are as varied as the types of products themselves and include therapeutic problems with the patient, drug, or dosage form of existing available products. In fact, 76 percent of compounds are not commercially available formulations for those ingredients; 63 percent are new dosage forms, and 44 percent are new strengths. More specific driving forces of compounding needs include patient allergies to excipients and patient needs for adapted administration methods (such as liquid formulations made from commercial capsule contents for hospice or oncology patients).

Three Defining Aspects

The Food and Drug Administration differentiates between compounded drugs and manufactured drugs. Compounded drugs are excluded from FDA regulation in a 200-plus word definition that assigns regulatory responsibility to state pharmacy licensing bodies. The National Association of Boards of Pharmacy (NABP) Model State Pharmacy Act defines compounding as “the preparation of Components into a Drug product as the result of a Practitioner’s Prescription Drug Order based on the Practitioner/patient/Pharmacist relationship in the course of professional practice,” adding that “[c]ompounding includes the preparation of limited amounts of Drugs or Devices in anticipation of receiving Prescription Drug Orders based on routine, regularly observed prescribing patterns.” Today, customized formulations often are necessary beyond an individual patient’s needs in light of drug shortages from manufacturers. Compounded drugs do not replicate the commercial products, but use the same or similar active pharmaceutical ingredient in a different form to provide treatment options when appropriate manufactured drugs are not available. Commercial manufacturing is regulated by FDA and typically involves mass production for intermediaries (not end users) and resale according to FDA approval. The legal definition of manufacturing also includes bulk repackaging of an FDA-approved entity.

A more specific definition of compounding from the US Pharmacopeia (USP) further distinguishes compounding from manufacturing and outlines the three defining aspects of compounding practice for pharmacy: the quantity specifications of limited, individual use of a prepared product; the necessary established relationship among a physician, pharmacist, and patient; and the identifiable end user (patient) of a medication order. Compounded drugs meet a unique need while adhering to the restrictions of required physician orders and single-use quantities (reasonable for the patient’s individual use and only in limited amounts ahead of expectation, if at all). Compounds prepared within this structure are the ultimate responsibility of the supervising pharmacist, and their safety relies on an established relationship, especially between the pharmacist and the patient. Although these specifications seem clear cut, the triad of distinctions that clarify how compounding is defined by the profession still form the basis of today’s debate over regulation of compounded products across the United States.
Rules and Regulations: Distinctions from Approved Drug Products
Compounded drugs do not require FDA approval, but pharmacists are limited to compounding API and inactive ingredients that comply with the standards of a USP-NF monograph and the USP chapters on compounding. States report pharmacies or products of concern to the FDA, who may issue warning letters to, and perform general inspections of, the sites in question. The result is rules that vary by state, sporadic evaluations, and slow or inadequate consequences for product quality problems. Accreditation of compounding pharmacies and training of pharmacists are not required though both are available and prudent to achieve the overarching goal of high-quality patient care.

In contrast, manufactured commercial products require FDA approval and are highly regulated. The drug product is approved based on clinical trials demonstrating safety and efficacy. FDA also inspects manufacturing facilities worldwide to ensure drugs are made in facilities following current good manufacturing practices (cGMPs). Certain facilities which register with the state board of pharmacy but whose operations fail to meet all three of USP’s criteria for the practice of compounding remain a current grey area, though the pharmacy community is waiting for rules to come from recently passed legislation. The companies call themselves compounding pharmacies under state board authority, but their practices of interstate shipping of bulk quantities to intermediary entities are closer to those of pharmaceutical manufacturing—but without mandatory FDA oversight.

BEYOND NECC: BURGEONING CONTENT AND REGULATORY PROBLEMS
Monitoring Loopholes, on Display
Compounding is inherently an art as well as a science, so consistent technique and quality control (QC) actions are as important to monitor as the recipe instructions. However, sporadic or uneven implementation of QC efforts by pharmacies complicates the poorly defined compounding landscape and opens the door for product errors or contaminations that risk patient safety. These concerns are exponential when poor regulation allows manufacturers to register with the board of pharmacy and flourish without mandatory FDA oversight.

The risk of insufficient scheduled facility inspections are exactly embodied by recent finding of contamination, and the subsequent infection outbreaks, attributed to products shipped from New England Compounding Center (NECC). As a result of poor standards for sterility at NECC, more than 700 cases of fungal meningitis or related disease, identified in 23 states, were directly connected to contamination of products shipped across the country by NECC; at least 64 deaths occurred after patients received injectable corticosteroids for back pain. Though not the first time contamination in a sterile compounding center has impacted patient safety, the widespread and deadly impact of the NECC event initiated public and professional outrage. Eventually the finding that six items ultimately recalled by NECC for contamination were on FDA drug shortage lists because of commercial manufacturer delays stirred up demand for practice reform by regulators and the profession. In the 12 months following the NECC recall, state and federal inspectors have found sterility and quality problems at a number of other manufacturers and pharmacies and one analytic lab.

Compounding pharmacy owners must reassure the public that companies like NECC are not local compounding pharmacies but instead are large-volume production facilities that ship to intermediaries, not patients, across state lines. This is no longer an uncommon process, because of demand for drugs in shortage and for drugs with alternate routes of administration. Companies like NECC are not in the truest sense compounding pharmacies but instead are manufacturers outside the scope of compounding pharmacy as defined by the profession and state boards. Doctors and hospitals that are outsourcing to a small manufacturer rather than compounding in-house must exercise due diligence to ensure product safety and quality. The ability of these facilities to operate without quality and safety standard enforcement is directly connected with overextended professional and regulatory responsibilities and inadequate communication between regulators and facilities.

Generally Poor History of Proactive Quality Assurance
Outsourcing facilities that bypass the patient relationship have a high risk of adverse events and drug errors especially because of their poor history of batch testing. For example, 3,000 sterile facilities such as NECC exist across the United States to provide high-volume compounding; in 2001, a voluntary-enrollment, third-party evaluation by EmLab of these centers reported FDA-deficient product standards in 34 percent of evaluated products.

Even the NECC outbreak was not entirely unexpected. MedWatch received its first report of meningitis from an NECC product in 2002; the FDA was tracking potential manufacturing activity of NECC as early as 2003, and marketing concerns in 2006. NECC itself complicated any efforts at oversight even more by exceeding its Massachusetts pharmacy license and failing to properly register practices across state lines with multiple state pharmacy boards, such as Colorado and Indiana.
Poor adherence to procedures for quality assurance by NECC and missed opportunities for intervention by authorities capture the lack of proactive, streamlined actions that can prevent errors from reaching the patients. Federal authority to regulate companies that act beyond usual compounding practices is ambiguous and inefficient, resulting in harm to patients and to the reputation of the pharmacy profession.

Two primary issues blocking quality regulation efforts that are embodied by the NECC crisis are the lack of federal registration of these facilities, and the still-unanswered question of who should regularly evaluate them. Though outsourcing facilities supply more of the country’s sterile products than in-house hospital pharmacies now, they still operate under the FDA radar and have no required certifications; only an optional registration. The sites are nominally under state board control, but their practices do not fall under usual compounding activities governed by those boards.

**Failed Federal Regulatory Efforts**

State board regulation of community pharmacies, including those that compound, is the standard for legal and professional practice compliance. However, the FDA has a lengthy history of involvement with the fluctuating compounding regulations, too.

Though changes are in store after passage of legislation in 2013, under current practices, the FDA oversees good manufacturing practices of commercial manufacturers but has only facility warning or inspection capabilities for manufacturers that register as pharmacies. State boards maintain all responsibility for inspection and regulation and enforcement of standards, which vary by state, of individual compounding actions.

The FDA’s past efforts to increase regulatory control over compounding have been uneven but have opened a path for partnership regulations today. In 1992, the FDA took its first steps to describe its compounding regulation goals with a Compliance Policy Guide on Compounding. This document was simply a statement of enforcement, without backing legislation for clarity. Pharmacists requested legislation, and the 1997 FDA Modernization Act (FDAMA) was the response. FDAMA section 503a described and clarified compounding legally as a product (not simply a reconstitution) made in response to or in anticipation of receipt of a prescription order. The act required medically necessary prescriptions to be written by a licensed practitioner for one individual, innately limiting the product to a small quantity (in line with professional definitions of compounding). Section 503a separated compounding from manufacturing even more by addressing FDA authority on compounding; it exempted compounds from three “critical provisions” of manufactured drugs: 1) premarket new drug approval in the forms of NDA, ANDAs, or INDs; 2) current Good Manufacturing Practice (cGMP) standards required for FDA-approved manufacturing; and 3) adequate directions and labels standardized as for approved drugs. Section 503a of FDAMA also legally limited the scope of compounding by preventing advertising of the compounding products or process by pharmacies. This portion of the legislation, and thus the entire section, was ruled unconstitutional for limiting free speech in 2001.

Throughout the differing legislation, the grey area of mass compounding grew but remained unaddressed. The Safe Drug Compound Act of 2007 tried to reinstate the compounding exemptions of FDAMA but did not distinctly separate manufacturing from compounding activity to prevent the development of mass compounding centers like the NECC. Despite this, the act has become one preliminary example of how to address the current regulation needs by giving the FDA widespread but clear regulatory control of compounding pharmacies for inspection and product approval.

By 2008, with compounding regulation efforts still unclear, the FDA attempted its biggest effort to control a specific form of compounding: bioidentical hormone compounding as an alternative to synthetic hormones, following safety concerns that arose out of the Women’s Health Initiative postmenopausal hormone therapy trials. Of particular concern to the FDA was the terminology used to advertise these products, specifically the health claims made about a non-FDA-approved active ingredient (estriol). The profession responded to FDA warning letters on two fronts: first, compounders argued that the products were not legally considered new drugs that required FDA approval and that estriol, as an ingredient in natural drug compendia, had grandfathered approval.

Second, APhA argued not about hormones but about the compounding attack itself—because a compounded drug is not regulated as a new drug, ingredients used should not be limited by the FDA, because that is outside its jurisdiction. The bottom line issues, which are still being resolved, are “Should compounds be considered new drugs under FDA authority?” and “Who should regulate their formulations for safety?”

The FDA has emphasized the need for more regulatory control and suggests now that compounds must qualify for exemption of approved-drug requirements, primarily by being deemed not too difficult to compound with maintained safety or effectiveness. Examples of compounded products that the FDA believes are demonstrably difficult to compound with consistency for
safety and effectiveness include metered-dose inhalers, some sterile compound liquid formulations, and transdermal products. Additional contributing factors that the FDA considers relevant to decisions on a difficulty designation include sophistication of pharmacy equipment for their procedures, results of uniform bioavailability testing of products, and the complexity of compounding steps that could introduce high error rates. However, none of these evaluations or designations are currently part of active regulations on compounding.

While regulatory efforts are still in flux, practicing compounders must rely on professional judgment and already-established standards to maintain safety and professional ability. Total FDA regulation is not the only answer, and pharmacy has much to contribute to the discussion. Practitioners must act to maintain safety for patients and integrity of compounding practices. Pharmacists can do that effectively by complying with USP standards and requirements for safe compounding. Many pharmacists are aware of USP, but need more information about USP chapters relating to compounding.

EXISTING STANDARDS—LONGSTANDING USP GUIDANCE
United States Pharmacopeia, despite not being a government regulatory agency, has provided the profession with precision compounding guidance for more than 140 years. Its recommendations have been standardized since 1820 and officially recognized as a key resource since 1906. The recommended standard operating procedures (SOPs) guide opinions of professional organizations as well as state boards, and they are distinct for sterile and nonsterile procedures and settings. Since 1992, sterile compound SOPs in particular have been set apart by USP and were further honed by an expert panel into its current format in 2004. These standards were updated most recently for best practices in 2008. Goals of USP compounding guidance in general are products of desired and consistent strength, quality, and purity. Standards for sterile compounds extend these to prevention from harm by contamination, toxins, and product errors, too.

USP is a logical standard setter for enforceable practices because it is thorough, available, accessible, and evergreen in scope and appropriateness. However, poor awareness and insufficient implementation by practitioners at the more than 7,000 compounding pharmacies across the country impede the standards’ usefulness.

Product preparation is only one small part of compounding practice in community or sterile settings. USP SOP recommendations are available for all pharmacists and every setting about equipment, scenarios, ingredients, QA procedures, training, and more to ensure the lowest possible error rate in compounded medications. It is the responsibility of a compounding pharmacy and its staff to observe standards in their entirety, not just in the drug product preparation step.

USP chapters 795 and 797 guide nonsterile and sterile standards of practice, respectively. USP 795 holds greater relevance for community pharmacists, but the separation of guidance is significant: it enhances the distinction between pharmacists compounding simple, non-sterile drugs observing 795 standards and compounders, outsourcing facilities and manufacturers producing sterile drugs guided by 797 sterility principles.

USP 797 directs facilities that regularly make injectable drugs (such as intra-articular, intrathecal, intravenous, transdermal, aerosolized inhalations, ophthalmic drops, and more. In hospitals, USP 797 is endorsed and used by the Joint Commission (formerly, JCAHO) and the Accreditation Commission for Health Care (ACHC) to reduce infections from sterile compounds and guide compliance checks consistent with USP safety standards for state-based compliance. USP 797 and JC or ACHC standards categorize drug products into risk groups; create separated physical work; regulate air and surface cleanliness; and require stringent procedures for shift sanitization and microorganism monitoring. Community pharmacies should observe 797 standards if they compound drugs more complex than topical or simple oral products (such as sterile ophthalmic solutions).

USP 795, which defines nonsterile actions, is most relevant at community pharmacy settings. Nonsterile compounding in retail settings ranges in complexity from simple admixtures to entirely unique products with custom doses. Importantly, even complex recipes do not approach the level of manufacturing if they are made for a specific need or individual relationship.

USP 795 FOR NONSTERILE PRACTICE: SOPS FOR THE COMMUNITY PHARMACY
Nonsterile Systems: Levels of Difficulty
Nonsterile compounding as a professional responsibility aims for consistent strength, quality, and purity aspects. The process is ranked into three difficulty levels that are based, in part, on the complexity and difficulty of techniques, the ingredients and the potential risks of harm.

Simple nonsterile compounding is any process guided by published USP monographs or journal articles that detail the steps and known stability data and that require only basic manipulation. Indomethacin topical gel is a good example of a simple nonsterile compound.

Moderate nonsterile compounding builds upon basic compounds by requiring more extensive steps or pre-mixing calculations for correct concentrations or consistency. Alternatively, moderate compound recipes
may not be more difficult to complete, but the end results may have uncertain stability features. Diphenhydramine HCl troches with precision formulation steps or unique topical creams that mix two unrelated drug products without available stability data fall into this category.

Complex nonsterile compounds demand pharmacists to obtain specialized training beyond basic professional skills to complete the preparation, even if directions are already established. For example, some extended-release or transdermal formulations require high-level skill and attention for qualitative and quantitative accuracy.

**Quality Assurance**

Generally speaking, quality assurance refers to activities that ensure quality standards are being met. Standard operating procedures (SOPs) that are continually monitored and evaluated are one element of a quality assurance program. That is, a written SOP that outlines the steps for dispensing to ensure that the final prescription the patient receives is accurate and safe. SOPs are written instructions for a specific task or routine and limit variability between pharmacy staff. Though they may give it a different name, pharmacies have an SOP for dispensing. Quality assurance in compounding is similar. A compounding pharmacy should have SOPs that start with the compounded drug formula, address sourcing ingredients, cleaning, production and testing of the finished product. Continuous quality improvement is another element of a quality assurance program and often consists of training, error reporting, error analysis and modifying procedures.

**USP Standards: Processing Essentials**

Purity of ingredients and the precision of calculations to achieve accurate end results are subjected to quality assurance guidance by USP. Master formulas and compounding records should be maintained in the same manner as other dispensing records for the timeframe required by state and federal laws. The following factors for best practice must be fulfilled for every compound:

1. A master formulation record, designed at the first use of a compounding monograph, should be retained to guide subsequent preparations.
   - Official or assigned name, strength, and dosage form
   - Calculations, verified, for quantities of ingredients to achieve goal dose of the APIs
   - Descriptions and amounts of each ingredient
   - Stability and compatibility details and references (when available)
   - Equipment used in preparation

2. A compounding record of each preparation, which adheres to the master formulation record, documents every step of each preparation in detail. Compounding Records should include notes specific to the individual product preparation:
   - Reference to Master Formulation Record
   - Name, source, lot and expiration details from each ingredient used for that product
   - Quantity compounded
   - An assigned prescription or control number along with a duplicate of the label used
   - The specific BUD assigned to the final product
   - Documentation of the procedure, including compounder and/or reviewer initials and date
   - A description of the final compounded drug
   - Quality control procedures and findings, including issues or adverse reactions or problems reported by the patient

**Assigning Beyond Use Dates (BUD)**

Setting the BUD depends on considerations of individual ingredient expirations, published data about stability of combined ingredients, and the date of compounding. The end-product stability—especially to avoid microbial growth and ingredient degradation—is key to patient safety and adequate treatment, because the BUD implies adequate potency, purity, and quality from the compound development through that date. Key points to consider before assigning a BUD include the following:

- Any assigned BUD must not exceed the earliest expiration date of any ingredient used in preparing the compound.
- Active ingredient expiration dates cannot be directly repurposed for the compound; stability of the ingredient in its new formulation must be researched in the literature (such as USP Chapter 1191) or estimated with professional experience.
- Storage requirements for stability of ingredients must be observed for the final product as well.
BUDs are determined from each product’s preparation date and should be conservative estimates of stability. Amounts of compounded products should be within range for reasonable use before the assigned expiration. Maximum BUDs recommended by USP should be used for nonsterile compounds kept at room temperature and in light-resistant containers when stability data are unavailable (See table below).

### Packaging for Compounded Drugs
Package safety and label accuracy involve using clean, closed, non-leaching containers and rotating container stock to use the oldest items first. Labels do not have a standardized format requirement but must contain the statement “This is a compounded preparation.” In addition to state and federal prescription label requirements, compounded products without preservatives might require controlled cold-temperature storage or a short BUD.

### QUALITY CONTROL
A final review assesses product accuracy through qualitative and quantitative measures like appearance, weight, color, odor, and consistency. In this review, calculations, ingredients, and processes on the record are checked against the master and against the end product before it is approved for dispensing. This final quality control check, or a second final check, should be performed by a trained pharmacist who was not the compounder for optimal verification.

### Extended Sterile Considerations
USP 797 guides more complex, sterile compounded drugs and seeks to prevent harm from toxins and contaminations. Therefore, compounded sterile products (CSPs) have unique sterility requirements on top of the quality assurance requirements of non-sterile compounding. USP 797 provides minimum standards, describes three categories of contamination risk, and addresses air quality. CSPs must be prepared with aseptic technique in an ISO Class 5 or better air quality environment. ISO class 5 has no more than 100 particles, 0.5 microns or larger, per cubic foot. Personnel sterility extends beyond hand and surface washing. Pharmacy staff preparing CSPs must perform garbing and gloving, maintain buffer zones, and monitor laminar air flows.

Even with explicit directives, compliance with 797 SOPs remains low (33 percent in surveyed pharmacies). Common gaps in 797 and 795 adherence alike include hand washing, garb cleanliness, surface samplings (at least twice yearly for sterile compounding sites), and other basic sterility issues.

### Implementing a USP-Based SOP in Your Pharmacy
The 795 or 797 SOPs are so detailed that they can become overwhelming, especially to a busy independent entity with a small compounding practice. To improve safety and quality and to prepare for the coming oversight, every pharmacy should become better acquainted with the USP chapters pertaining to compounding to reduce errors and improve safety. Prioritizing improvements helps use USP to its fullest for each unique setting. The U.S. Pharmacopeia publishes several references, some of which must be purchased, and some which are open access on its website. USP on Compounding is USP’s publication of all compounding-related chapters. Pharmacies that wish to have access to USP compounded drug monographs should consider USP-NF which contains all the chapters in USP on Compounding plus the compounded drug monographs. The current version of USP–NF standards deemed official by USP are enforceable by the FDA for medicines manufactured and marketed in the United States.

USP 795 concludes with pharmacy-level standards for program maintenance that can establish a routine and address the highest-impact practice gaps: those improvements that are low cost or quick turnaround. Making an action plan for compounding practices can start by identifying resources, distributing tasks like recordkeeping or equipment maintenance to specific pharmacists and supervisors.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>BUD</th>
</tr>
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<tbody>
<tr>
<td>Nonaqueous</td>
<td>Earliest active ingredient expiration or 6 months (choose soonest of the two)</td>
</tr>
<tr>
<td>Water-containing oral</td>
<td>No later than 14 days at controlled cold temperatures</td>
</tr>
<tr>
<td>Water-containing topical/dermal; mucosal liquid; semisolid</td>
<td>No later than 30 days</td>
</tr>
</tbody>
</table>

Note. USP offers extensive guidance for unique stability scenarios in Chapter 1136 on single-use container preservation, expiration/BUD, and packaging. Source: USP 37-NF 32
staff, and planning updates for the entire pharmacy team to stay current on high-quality compounding techniques. A workable action plan then becomes the basis of a pharmacy SOP for practical use, accreditation, and inspections. An SOP that extends to cover a site’s equipment, personnel, preparation, packaging, and storage needs is an essential reference for staff at any time, as it outlines consistent compounding practices.

**Using USP Training Considerations**
Just as USP 795 guides the process of preparation and formulation, it offers standards for quality control of training, too. Basic, documented training that occurs annually is the USP standard. At a minimum, training should incorporate an evaluation of staff techniques without instruction or prompting, followed as needed by education and assistance by trained staff. Techniques explored during annual training must cover preparation of the compounding area; cleanliness of the site, person, and equipment; documentation of a compounding record against a master; preparation of the compound ed drug; storage of the ingredients and final formulation; labeling of the product and its stability limits; and final review and clean-up. Annual training provides a refresher for experienced staff and is an orientation tool for new compounding personnel; it also encourages everyone to remain knowledgeable about updated reference materials, like safety data sheets (SDS, formerly MSDS), Remington’s, or the USP SOP chapters.

**Supplementary Support**
To assist the profession and regulatory authorities in achieving and evaluating compounding pharmacies, eight professional pharmacy organizations in 2004 voluntarily developed an approach to accredit compounding practices. These organizations—APhA, USP, NABP, NCRA, International Academy of Compounding Pharmacists (IACP), American College of Apothecaries (ACA), National Alliance of State Pharmacy Associations (NASPA), and the National Home Infusion Association (NHIA)—recognized the lack of predictability and consistency in compounding education and regulation in the 21st century and worked together to form the Pharmacy Compounding Accreditation Board (PCAB) for compounding standards. PCAB is an external standards organization with voluntary enrollment to increase quality, credibility, and product safety whether for sterile or nonsterile preparation. By virtue of meeting the standards for PCAB accreditation, compounding pharmacists meet or exceed USP standards for compounding drugs. The board provides tools such as its *Principles of Compounding and PCAB Standards*, and it suggests a list of publications and information resources compounding pharmacists should have on hand (such as SDS for chemicals on hand, SOPs, and *Remington: The Science and Practice of Pharmacy*).

APhA also offers support by publishing a textbook for practitioners. *The Art, Science, and Technology of Pharmacy Compounding* (edition four, 2012) is a foundation for compounding practice with instruction and technique to emphasize consistency as the backbone for safety and quality. It offers good manufacturing procedures (GMPs) for common compounds, describes adequate QC procedures, and describes 200-plus formulations with specific bases, vehicles, ingredients, and instructions.

**ADVANCES IN REGULATION TODAY**

**Growing Standardization of State Regulations**
Since 1990, 55 quality concerns have been documented by the FDA specifically in compounded products. This speaks to the need for compounding consistency and adherence to relevant standards to protect patient safety and for professional reputation.

Today, compounding pharmacies remain under state board enforcement that is increasingly based on USP standards. Before NECC, USP guided regulations for pharmacy compounding in as few as 17 states. However, in the wake of the NECC outbreaks, USP 797 has become the basis of enforceable laws in 30 states to minimize harm from sterile compounds. As of 2012, many states (including Massachusetts, Florida, Louisiana, Mississippi, and New Jersey) enacted emergency procedures, often specific for sterile sites. Examples of new requirements include reporting to state boards with affidavits (Massachusetts); limiting compounding to those with a prescription or provider relationship (Louisiana); and requiring PCAB accreditation (New Jersey).

The main concern the FDA has about compounded products stems from the three requirements for safety oversight of approved drugs that are not applicable to compounds: federal product approval, GMP standards, and labeling requirements. Because the compounding umbrella covers basic creams through injectable biologics, FDA considers one option to be full authority to sample all compounds and regulate all pharmacies to identify those that extend beyond traditional practice. However, total federal regulation, a shift from complete state oversight, is not the only answer. Separating individual community compounding practices from manufacturing-like activity is a natural and logical method of ensuring appropriate oversight with existing resources and funds.

**Separation of Local and Interstate Activity**
An important question from the pharmacy perspective
in this new regulatory landscape is “Can states meet oversight needs?” Also, what is the federal role for high-volume, interstate compounding centers? How can federal and state authorities balance and efficiently communicate about safety? How will “outsourcing facilities” be defined and regulated?

To answer the question of who should oversee compounding, which are not new approved drugs, state and federal practices must cooperate. Since the NECC outbreak, state boards, FDA, and legislators have been active in attempts to regulate compounding on every level. The NABP recommends adoption of USP 795 and 797 for uniform standards in all states. Penalties are still undefined if standards are breached, though, and enforcement bodies and capabilities are unclear. At least 25 regulations were in progress in 2013 that describe compounding drugs or centers; this has the potential to muddy an already complex situation instead of streamlining answers for clarity.

FDA and some in the pharmacy profession support greater oversight of compounding pharmacies, but they differ in their distinctions of that practice and their interest in the protection of compounding in the community. Professional organizations endorse separation of state-controlled community pharmacies from manufacturing facilities which they advocate are best regulated federally. The boards of pharmacy requested clear definitions of compounding versus manufacturing to appropriately designate authority. In the end, the recently enacted Drug Quality and Security Act allows compounding pharmacies producing sterile products to register with FDA, voluntarily, as outsourcing facilities. Using a voluntary registration does not impose unnecessary restrictions on professional pharmacists in community compounding settings but may provide hospitals and physician offices a level of confidence they have selected a reputable and compliant vendor.

FDA acknowledges the distinction between community pharmacies and outsourcing facilities, but has yet to get through the rule-making process. Ultimately, the FDA wants greater oversight responsibility and enforceability with outsourcing facility registration fees as a source of funds for proactive, scheduled inspections. For now, boards in each state will handle traditional compounding as usual, but require FDA assistance for manufacturing inspections and enforcement. Additionally, better FDA communication to individual state boards of pharmacy when it inspects compounding pharmacies and vice versa is essential for safety. The Drug Quality and Security Act creates a voluntary registration process with FDA. This act preserves the Food, Drug and Cosmetic Act Section 503(a) and a pharmacy’s ability to compound drugs. One change to this section is striking of language prohibiting marketing which was found to be unconstitutional. The majority of community pharmacies that offer compounding services will continue to be licensed and regulated by their state board of pharmacy. Pharmacies that are performing compounding activities that meet the criteria for registering as an outsourcing facility may voluntarily register with the FDA and state to purchasers that they have done so. The fee for this is expected to be $15,000 (adjusted annually for inflation) or one-third of that fee for small businesses with sales less than $1 million in a 12-month reporting period that ends April 1 of the preceding year.

Certification and Credibility
Transparency about qualifications will be key to any legislation passed into law. Organizations within pharmacy have developed tools, training options, and recommendations as well as individual-topic classes to grow knowledge bases and expertise. The American College of Apothecaries and compounding supply and chemical companies such as Fagron, Letco Medical, Medisca, and PCCA all offer technical and clinical education programs and webinars.

PCAB uses written SOP reviews and onsite pharmacy surveys to assess compliance and accreditation. Facilities that meet their standards, which may be downloaded at no cost from www.pcab.info. PCAB offers pharmacy owners external quality validation. Pharmacies and other interested individuals can learn about the standards, facility preparation, fee requirements, and processes for accreditation on its website and through a downloadable manual. Pharmacies who are not working toward accreditation can also turn to the PCAB website for downloadable answer sheet about equipment, beyond-use dates, and other practical aspects of compounding. Likewise, supply and chemical companies provide certificates and training classes for professionals that allow pharmacies to display their competency, specialized training and high standards in compounding across the entire process.

Prescribers, pharmacists, patients, and regulators who want to know a pharmacy’s record for compounding inspections and quality can begin looking to electronic databases. PCCA offers a “find a compounder” service; PCAB lets consumers browse accredited pharmacies by state; and the NABP is forming an e-database that will register any pharmacy considered a compounding practice. Similarly, IACP offers “Compounder Connect” to locate pharmacies, and the Compounding Pharmacy Assessment Questionnaire (CPAQ) for download that consumers and health professionals, including pharmacies that do not offer compounding.
Compounding is a useful expertise for pharmacists, but it is at risk of becoming highly regulated or limited in scope. Compounded products are essential for patients when commercial, FDA-approved products are not available, especially in specialties like pediatrics, oncology, and hospice care. Advocating for state control and consistent, enforceable standards of practice will demonstrate reliability and safety as well as professional commitment. Compounding is recognized by the FDA, also, as a professional privilege and obligation. At its best, compounding is a triad: care-based relationship, not a massive distributive project with individualized expert answer to a patient problem. However, large-volume interstate facilities have grown in number since 2000 and will continue; their higher risks suggest the need for distinction in terminology and federal regulations, not state ones. States face the challenge of standardizing compounding practices and oversight, but existing USP and NABP/PCAB guidances are poised to improve transparency, communication, training, and quality all in one.

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Continuing Education Quiz
Select the correct answer.

1. What percentage of community pharmacies dispense compounded drugs?
   a. 53 percent  
   b. 63 percent  
   c. 73 percent  
   d. 91 percent

2. Which of the following are acceptable reasons to dispense a compounded drug?
   a. Patient requires alternate route of administration
   b. Patient requires dye-free capsule
   c. Commercial product is out of stock at the pharmacy
   d. Commercial product is on the FDA Current Drug Shortages Index
   e. A, B and D are acceptable reasons to dispense a compounded drug

3. The three elements of NABP’s definition of compounding are:
   a. Customized formulations, small-quantity, individual-use products made for a physician’s office
   b. Customized formulation, practitioner/patient/pharmacist relationship, identifiable end user
   c. Individual use of a prepared product, practitioner/patient/pharmacist relationship, professional practice
   d. Prescription drug order, practitioner/patient/pharmacist relationship, professional practice

4. Manufacturers and outsourcing facilities now regulated by the board of pharmacy are subject to
   a. FDA recordkeeping evaluations
   b. NABP registration evaluations
   c. FDA general inspections
   d. NABP general inspections

5. Aseptic compounding requires sterility to avoid contamination from
   a. Laminar-vented air sources
   b. Poorly sealed product containers with condensation
   c. Surface disinfectants
   d. Aseptic techniques

6. Processes to promote sterility include
   a. Laminar air flow to reduce airborne contamination
   b. Sterile garbing to reduce contact contamination
   c. Maintaining ISO Class 100 air quality
   d. A and B above
   e. A, B and C above

7. Compounding pharmacies can reduce error risk by
   a. Performing batch testing
   b. Following a master formulation record
   c. Limiting the number of people involved in the preparation of a compound
   d. A pharmacy can reduce errors by doing all of the above.

8. FDAMA exempted compounds from
   a. Reconstitution rules
   b. Labeling products at all
   c. Obtaining a prescription before compounding a product
   d. Obtaining FDA approval as a new drug (by NDA/ANDA process)

9. FDAMA was ruled unconstitutional because it
   a. Exempted compounded drugs from FDA approval
   b. Exempted the need for a prescription
   c. Limited free speech in marketing for compounding
   d. Enacted required GMPs for compounding

10. The FDA prefers regulatory control of compounding that
    a. Encourages transdermal formulations
    b. Prohibits or limits the complex, high-risk compounding practices associated with variable safety/efficacy
    c. Requires bioavailability testing of every product
    d. Allows batch evaluations by state boards of pharmacy

11. USP established compounding recommendations as early as
    a. 1820
    b. 1906
    c. 1928
    d. 1976

12. Compounding according to USP practices involves
    a. Only admixture
    b. Only product preparation
    c. Preparation and documentation of every compound
    d. Preparation, documentation, and clean techniques even for nonsterile settings

13. Raymond is a pharmacist at a pharmacy that performs a modest amount of nonsterile compounding. Upon receipt of a prescription for 0.2 percent nitroglycerin ointment he retrieves the Master Formulation Record. Which of the following will be found in the Master Formulation Record?
    a. Instructions for assigning a BUD
    b. The name of the pharmacist(s) qualified to prepare the compound
    c. An ingredient list with lot numbers and expiration dates
    d. Photo copies of the FDA-approved package insert for 0.2 percent nitroglycerin ointment
14. A pharmacy technician under Raymond’s supervision has compounded 0.2 percent nitroglycerin ointment. The Compounding Record, dated March 5, 2014, that Raymond will now review contains which of the following?
   a. A duplicate of the label on the container to be dispensed to the patient
   b. The quantity of each ingredient used and the final weight, noting any variance from expected weight
   c. The name of the technician who compounded the ointment
   d. The actual, specific BUD assigned to the ointment
   e. All of the above are contained in the Compounding Record.

15. Which of the following factors determined the BUD that the technician assigned to the ointment?
   a. The December 2015 expiration date of the 2 percent nitroglycerin ointment used in the compound
   b. The July 2015 expiration date of the white petrolatum used in the compound
   c. The directions on the prescription for the patient to discontinue use after four weeks
   d. General compounding guidance to assign a six-month expiration date for nonaqueous compounds

16. Accreditation of pharmacies for compounding is available from
   a. PCAB
   b. NABP
   c. NCPA
   d. NHIA

17. Recent legislation to address outsourcing facilities enacted or proposed by states aims to
   a. Reduce compounding activities in the community
   b. Separate compounding activity from outsourcing activity law enforcement procedures
   c. Limit outsourcing facility activity by increasing registrations and tightening prescription order requirements
   d. Remove outsourcing facilities

18. Outsourcing facilities drew attention from regulators because they generally
   a. Do not compound for an identifiable end-user patient
   b. Ship across state lines
   c. May replicate FDA-approved drugs that are on manufacturer shortage
   d. All of the above

19. The pharmacy profession believes that nontraditional compounding
   a. Should be regulated by the state boards of pharmacy as compounding
   b. Should be regulated by the FDA along with all compounding facilities
   c. Should be renamed “outsourcing facilities” and be voluntarily regulated by the FDA in addition to the applicable state board of pharmacy
   d. Should be renamed “outsourcing facilities” and be registered with the state board of pharmacy; no FDA oversight is needed

20. Which of the following is a quality control practice a compounding pharmacy might perform?
   a. For tablets: weigh a sample of 10 tablets and compare to an expected weight in the Master Formulation Record
   b. For tablets: zero the balance with an unused weighing boat or paper away from drafts
   c. For suppositories: inspect melted polyethylene mixture for visible particles
   d. All of the above