

Ensuring Patient Safety in Compounding of Medicines



ISSUE: Injuries and deaths caused by poor quality compounded preparations have focused attention on patient safety and prompted changes in oversight; at the same time, compounding remains an important practice to meet unique or specific patient needs—providing specialized formulations for individual patients in circumstances where commercially available medicines may not be appropriate (e.g., dosing for pediatric, geriatric, or other vulnerable populations).

POSITION

USP¹ supports a comprehensive public policy framework² to advance compounding quality, promote patient safety, and respond to the evolving public health quality environment.

Key elements include building awareness, measuring and improving compounding quality, updating laws and regulations, establishing appropriate reimbursement reforms, and making enhanced investment in regulatory agencies responsible for surveillance and enforcement.

- 1. Build practitioner awareness** of appropriate circumstances and settings for medication compounding, including how to foster adherence to consistent procedures that promote patient safety.³
- 2. Advance compounding quality** through improved measurement, monitoring, tracking, and identification of areas for enhancement.⁴
- 3. Update state laws and regulations related to compounding.** Incorporate complete, up-to-date, standards for compounding quality⁵ into state laws and regulations to protect patients, support the work of the states, and bridge the gap between state and Federal responsibilities and oversight.

4. Create appropriate reimbursement and payment reforms.

Reimbursement and payment structure should align to support quality and account for investments in equipment upgrades and human resources necessary to drive the implementation of safer compounding practices.

5. Make adequate investment in Federal and state agencies responsible for surveillance and enforcement of the quality and safety of compounded preparations.

BACKGROUND

I. What is Compounding?

Compounding combines or alters ingredients to create a medication tailored to the unique medical needs of an individual patient. Compounding is essential for underserved and vulnerable populations, including seniors and children.⁶ In addition, it plays a critical role in treatment of rare diseases; in clinical trials; in situations where the strength or dosage of a medicine needs to be customized; reformulating a drug to exclude an unwanted, nonessential ingredient, such as lactose, gluten, or a dye to which a patient is allergic; and changing the form of the medication for patients who have difficulty swallowing or experience stomach upset when taking oral medication.⁷

The practice typically involves combining, mixing, or altering ingredients—such as finished drugs, active pharmaceutical ingredients, or excipients (inert ingredients). The FDA defines compounding as a practice in which a licensed pharmacist or licensed physician, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.⁸ Similarly, USP defines compounding as “the preparation, mixing, assembling, altering, packaging and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner’s prescription,



medication order or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice.”⁹

Type of Compounding	Examples
Sterile	Medicines administered through injection, intravenous infusion (IV), or into the eye.
Nonsterile	Medicines administered orally (by mouth) or topically (e.g., surface of the skin).
Locations Where Compounding Occurs	
Pharmacies, doctors’ offices, hospitals, outpatient clinics, veterinary practices, and other facilities.	
Outsourcing Facilities regulated by FDA.	

Compounding has a longstanding history—before the advent of manufactured medicines, all medicines were made through compounding—and today it continues to play an important role for many patients to provide them with access to medications they may not otherwise receive.

II. Why Should We Be Concerned?

A number of recent safety-related incidents involving compounded preparations have focused attention on the urgent need to protect patients. At the same time, increasing population demands have underscored the critical importance of patient access to compounded preparations, including for specialized purposes such as pediatric, geriatric, and other use.

In 2012, contaminated injectable compounded sterile preparations caused a fungal meningitis outbreak, resulting in significant injury and death: more than 70 people died, and 750 cases of infection were reported in 20 states¹⁰—prompting Congress and Federal and state officials to clarify and reaffirm Federal and state requirements.¹¹

The outbreak highlighted a number of potential areas of vulnerability in the practice of compounding. According to a report by the Congressional Research Service,¹² such potential risks include problems with potency (e.g., the dosage is inaccurate, either too strong or too weak), purity (e.g., the drug contains other chemicals that could be harmful), and contamination (e.g., with a bacteria, fungus, or virus). These risks may be associated with patient safety

issues such as inadequate therapy, adverse events, antimicrobial resistance, and healthcare associated infections (HAIs).

Facts
In 2011, 19 patients in 6 Alabama hospitals were harmed as a result of an outbreak of <i>Serratia marcescens</i> bacteremia (bacteria in the bloodstream). An investigation by the Centers for Disease Control and Prevention (CDC) identified as a common potential source total parenteral nutrition (TPN)—liquid nutrition that is fed through an IV using a catheter—that had been compounded and sent to these hospitals from a single pharmacy. ¹⁴
In 2012, over 70 deaths and 750 cases of fungal meningitis occurred nationally due to contaminated injectable compounded sterile preparations from a pharmacy in a single state.
In 2012, 43 patients were affected by fungal eye infections from contaminated compounded sterile ophthalmic drug products. At least 29 of those patients suffered vision loss. ¹⁵
A 2014 Pew report identified patient harm arising from compounding errors including 89 deaths and 1,049 adverse events from 2001-2014. Contamination of sterile products was the most common compounding error. ¹⁶
In 2016 serious adverse events occurred in 3 infants, leading FDA to call for a voluntary recall of compounded morphine sulfate injectable drug product that was superpotent by 2,460 percent. ¹⁷
A 2016 report (Pew) indicated that approximately half of states fully adopt quality standards for sterile compounding; ¹⁸ at the same time, states continue to update and revise their regulations to respond to a risk of health threats.
FDA is continuing to go into pharmacies, often partnering with the states—identifying public health risks associated with inadequate compounding practices—and continues to issue guidances, for example, on insanitary conditions. ¹⁹ Additionally, in 2016, as a result of various national incidents and a heightened sense of patient safety related to compounding, the Centers for Medicare and Medicaid Services (CMS) officially recognized the value of compounding standards by including requirements for safe compounding practices for hospitals seeking Medicare reimbursement.

It is also important that compounded preparations be consistently and accurately prepared to ensure continuity of patient care.¹³



Ultimately, failures in quality and a better understanding of the practice environment of compounding have prompted Congress, FDA, and the states to clarify the statutory and regulatory landscape and reaffirm the critical role of quality standards and other requirements in helping to ensure safe, quality compounded preparations. Although progress continues to be made there are still gaps in quality and regulation. A continued commitment to quality is therefore essential.

III. Federal-State Framework for Quality Continues to Evolve

A. Federal and State Responsibilities Intersect, Driving a Need for Clarity

States have taken a longstanding approach towards protecting public health and confronting issues surrounding compounding quality in the course of regulating the state practice of pharmacy and medicine. At the same time, the Federal government, through FDA, oversees the approval, manufacturing, and distribution of medicines and has a responsibility to ensure the safety and integrity of medicines nationally.

The lines between state and Federal responsibilities have not always been clear cut, for example, where a compounded preparation is made by a facility in one state for patient use in a number of states, or where a facility claims to be compounding but actually seems to be engaged in something more akin to manufacturing. As policymakers have identified these gray areas they have attempted to address them through changes in law.

B. Section 503A and Traditional Compounding- Congress Attempts to Delineate Responsibility

In order to help clarify this distinction between state and Federal governance, Congress enacted (in 1997) and later reaffirmed (in 2013) Section 503A of the Federal, Food, Drug, and Cosmetic Act (FDCA), on pharmacy compounding.²⁰

Section 503A and related FDA guidance²¹ generally allow a **traditionally compounded preparation** to be regulated under state pharmacy practice, where a compounder making individualized preparations by prescription adheres to specified requirements—including compounding in compliance with the USP chapters on pharmacy compounding, using bulk drug substances and ingredients that comply with the standards of an applicable USP

monograph (standard), if one exists. Additionally, the preparation and its ingredients must be compounded by a licensed pharmacist in a state-licensed facility or by a licensed physician; be compounded for an identified individual patient based on the unsolicited receipt of a valid prescription; and the facility may not compound inordinate amounts or copies of commercially available drugs. **(A background on USP and compounding is available at the following source: USP Quality Standards for Compounding.²²)**

If such requirements are met, these medicines are exempted from certain FDA new drug requirements, including the submission of a new drug application and compliance with federal current good manufacturing practices (CGMPs) (requirements for the design, monitoring, and control of manufacturing processes and facilities, designed to ensure the identity, strength, quality, and purity of drug products).

The 2013 amendment also created a new, intermediate, category of **“outsourcing facility”** (503B)²⁴ for compounding sterile products with or without individual prescriptions, typically at a higher volume. Products made in a facility that chooses to register as an outsourcing facility are exempt from the requirement to submit a new drug application to FDA, but are subject to CGMPs.

Working through complex issues—including those around the most recent amendment to 503A—has highlighted a need for continued awareness-building, collaboration, refinement of laws and regulations, and the necessity for additional resources. For example, while the regulation of traditional compounding in pharmacy settings is now more settled following recent Federal enactment and FDA guidance, oversight in some other settings is not as well understood.²⁵

IV. Where Do We Need to Go?

USP supports engagement and discussion with Federal policymakers, the states, and the stakeholder community around the public health impact of standards to advance quality compounding and the health and safety of patients.

Quality is Important

A number of states have been working to align laws and regulations on compounding with the overall Federal framework for appropriate and safe compounding, including quality standards.²⁶ This is a positive development in promoting public health through consistency. There can



correspondingly be risks where requirements diverge (i.e., not as strong, comprehensive, or up to date as current standards).

Many states have specifically incorporated references to USP compounding quality standards, although some gaps remain.²⁷ According to Pew, about half the states require sterile compounding to fully conform to USP standards while 30 percent mandate at least some part, but not all, of USP requirements.²⁸

Promoting Collaboration

USP supports collaborative efforts in advancing appropriate and safe compounding. States are working closely with the Federal government to clarify responsibilities, share information, and identify and address quality issues. Examples of state-Federal collaboration include seeking clearer delineation between compounding and manufacturing and between FDA and state responsibility;²⁹ working with FDA to explore ways to share information (e.g., from inspections, reports of contamination, adverse events, and knowledge about out of state compounders that may be shipping into a state^{30,31}); and jointly conducting inspections.³²

Additional State and Federal Resources

USP supports efforts to augment resources for surveillance and enforcement (for example, enabling states to hire more inspectors and provide them with training;³³ requiring a facility inspection before the registration/licensure of a new sterile compounding pharmacy and before renewal; increasing oversight of out-of-state sterile compounders;³⁴ and continuing to work toward improved reporting).

Reimbursement Policies Can Facilitate Adoption of Quality Products

Payment systems can be complex: reimbursement and payment structure can drive quality practice and facilitate patient safety and access;³⁵ such policies can also help assist practitioners and ensure the right physical environment and technique for the practice of compounding, especially in underserved areas, or, conversely, may have the unintended effect of discouraging practitioner implementation.³⁶ USP supports engaging with policymakers, private payers, and health systems to incentivize good practice and patient safety/access.

USP's Role

USP is an independent, nonprofit, science-based organization that safeguards the public's health globally by developing quality standards for medicines, compounded preparations, dietary supplements, food ingredients and healthcare quality. USP standards are developed through independent experts³⁷ in a transparent scientific process with input from stakeholders and Federal agencies such as FDA and the CDC.

USP's first pharmacopeia was published in 1820, and began as a "recipe" book to promote uniformity in the drugs prepared and dispensed by practitioners to their patients. Today USP standards are recognized in law and play a prominent role in federal and state compliance and enforcement activities. USP's standards are enforceable by the U.S. FDA for medicines and their ingredients imported into or marketed in the United States, and have been used in more than 140 countries globally.

USP public standards contribute to positive public health impacts and advance the quality and benefit of medicines; maintain public health protections and patient safety and access; assist healthcare practitioners in the delivery of optimal patient care; and help ensure uniformity across settings of care.

To learn more about USP, please go to usp.org/compounding and usp.org.

1 USP is an independent public health organization established in 1820. USP develops transparent standards of quality for medicines, compounded preparations, dietary supplements, and foods, working with a network of independent experts. USP collaborates with the U.S. Food and Drug Administration (FDA), and other Federal, State, and local agencies. USP standards for drug quality have been recognized in Federal law since 1906 and are enforceable by FDA. Additionally, USP standards are recognized in state laws and are enforceable by state regulatory bodies such as Boards of Pharmacy.

2 These recommendations cover traditional compounding (covered by 503A), not outsourcing compounding (covered by 503B), or manufacturing (covered by requirements for new drugs). Additionally, while the recent change in Federal law was limited to compounding for human patients, USP has also been active in setting standards for animal drugs for many years including supporting the public's access to customized drug therapy in veterinary settings. USP's public standards on compounding protect both human and animal patients and we seek to work closely with the Federal Government, states, practitioners, pharmacists and other interested stakeholders in advancing quality.

3 See Pew, Best Practices, for State Oversight of Drug Compounding (2016), http://www.pewtrusts.org/-/media/assets/2016/02/best_practices_for_state_oversight_of_drug_compounding.pdf (recommending training in sterile compounding for pharmacists who perform or supervise it).

4 See, e.g., Pharmacy Impact on Quality and Outcomes: New Era for Measuring Value, Patricia Kienle, M.P.A., B.S. Pharm., FASHP and Frank Federico, B.S. Pharm., Fifteenth Annual ASHP Conference for Leaders in Health-System Pharmacy (2010), http://www.ashpadvantage.com/leaders2010/Workshop_3_Pharmacy_Impact.pdf.



- 5 According to a Government Accountability Office (GAO) Report (November 2016), 33 states (66%) have provisions requiring compliance with USP Chapter ⁷⁹⁷ (on sterile compounding) in part or whole. United States Government Accountability Office, Drug Compounding, FDA Has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges, <http://www.gao.gov/assets/690/681096.pdf>; also see Pew Charitable Trusts, National Assessment of State Oversight of Sterile Drug Compounding, February 23, 2016, <http://www.pewtrusts.org/en/research-and-analysis/reports/2016/02/national-assessment-of-state-oversight-of-sterile-drug-compounding>.
- 6 Pharmacy Times, Compounding for Pediatric Patients, September 1, 2006, <http://www.pharmacytimes.com/publications/issue/2006/2006-09/2006-09-5890>
- 7 American Pharmacists Association, Frequently Asked Questions About Pharmaceutical Compounding, <http://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding>.
- 8 FDA, Human Drug Compounding, <https://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/>.
- 9 USP Chapter 795 *Pharmaceutical Compounding – Nonsterile Preparations*.
- 10 CDC, Multistate Outbreak of Fungal Meningitis and Other Infections-Resources for Clinicians, <https://www.cdc.gov/hai/outbreaks/clinicians/index.html> (last updated October 30, 2015); Boston Globe, CDC investigator says fungal meningitis outbreak rivaled Ebola epidemic, January 10, 2017, <https://www.bostonglobe.com/metro/2017/01/10/cdc-investigator-says-fungal-meningitis-outbreak-rivaled-ebola-epidemic/INVBXIZ9QMFV1Z1BOR6M/story.html>.
- 11 Drug Quality and Security Act, as enacted by Congress, Public Law No: 113-54 (2013), as further described below.
- 12 Congressional Research Service, Compounded Drugs, June 2013, <https://fas.org/sgp/crs/misc/R43082.pdf>.
- 13 USP standards for compounded preparations help ensure that a patient transferred from one facility to another or released home continues to take the same compounded preparation and avoid medical complications.
- 14 FDA archived content, CDC and ADPH Investigate Outbreak at Alabama Hospitals, Products Recalled (2011), <https://www.fda.gov/Safety/Recalls/ucm249068.htm>
- 15 FDA, Testimony of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, May 23, 2013, <https://www.fda.gov/NewsEvents/Testimony/ucm353654.htm>.
- 16 Pew, U.S. Illnesses and Deaths Associated with Compounded Medications (2014), <http://www.pewtrusts.org/en/research-and-analysis/analysis/2013/09/06/us-illnesses-and-deaths-associated-with-compounded-medications>; See Pew infographic: http://www.pewtrusts.org/-/media/assets/2014/09/compoundingoutbreaks_chartsept2014_v3.pdf?la=en.
- 17 FDA, Human Drug Compounding Progress Report, above.
- 18 Pew, Best Practices, above.
- 19 See, e.g., FDA draft guidance, Insanitary Conditions at Compounding Facilities, August 2016, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf>.
- 20 21 USC 353a, Sec. 503A. PHARMACY COMPOUNDING, as enacted by the 1997 Food and Drug Administration Modernization Act and as amended by the Drug Quality and Security Act (2013)—Title I, Drug Compounding (the Compounding Quality Act).
- 21 FDA, Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469119.pdf>.
- 22 USP Quality Standards for Compounding, <http://www.usp.org/sites/default/files/usp/document/about/usp-quality-standards-for-compounding.pdf>.
- 23 FDA, Facts About the Current Good Manufacturing Practices (CGMPs), <https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm>.
- 24 FDA, Outsourcing Facilities, <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm>.
- 25 For example, compounding in physicians' offices—which is addressed in the Federal law (503A, traditional compounding) but falls under the jurisdiction of state medical boards, not state boards of pharmacy. GAO recently found a lack of physician oversight for compounding: nearly all states reported having drug compounding laws, regulations, or policies, though few applied to non-pharmacists. (FDA has indicated it is studying the idea of future guidance around physician compounding). GAO report, above. (Note that this practice in a physician's office is different from compounding for "office use"—the non-patient-specific preparation by an outside compounder for use in physicians' offices or other clinical settings – e.g., doctor office stock). Both issues have been of interest to policymakers and stakeholders of late. For example, see H.R. 2871 (Griffith, Compounding Pharmacies), introduced in the 115th Congress, which would expand "traditional compounding" to include non-patient-specific compounding for use in a clinical setting (that is, expressly allow "office use").
- 26 Presentation of Scotti Russell of NABP, "State Update on Compounding," NCSL Fall Forum, December 5, 2013, <http://www.ncsl.org/documents/health/SRussellFF13.pdf>; See GAO table, "Reported Laws, Regulations, or Policies Related to Drug Compounding, by Reporting State, as of January, 2016," http://www.gao.gov/special.pubs/gao-17-363sp/e-supp_q12.html, part of GAO, "Drug Compounding: Survey of State Pharmacy Regulatory Bodies" (GAO-17-363SP, March 2017), an E-supplement to GAO-17-64, <http://www.gao.gov/special.pubs/gao-17-363sp/index.htm>. For current status of state legislation in the compounding arena, see: NCSL, http://www.ncsl.org/documents/health/compounding_pharmacies.pdf.
- 27 The Joint Commission, Pharmacy Rules and Regulations by State for Compliance with USP 797 Medication Compounding, 2/28/2017, https://www.jointcommission.org/assets/1/6/Feb_2017_State_Compounding_Regulations.pdf.
- 28 Pew, Best Practices, above. (Pew observes that quality standards can help address challenges in regulating out-of-state pharmacies and ensure that all traditional pharmacy compounding meet strong baseline criteria for preparing safe drugs and protecting patients. Pew recommends that states ensure that any updates to USP standards are reflected in state law or regulations.)
- 29 Russell, State Update, above.
- 30 FDA, Proceedings (2014), above.
- 31 FDA, Summary of Proceedings, September 20-21, 2016, Inter-governmental Working Meeting on Compounding, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM544595.pdf>.
- 32 According to GAO (2017), 78% of states report conducting joint pharmacy inspections with FDA inspectors. (The reasons states reported for not conducting joint inspections with the FDA included not being asked by FDA to conduct a joint inspection, not having pharmacy inspector positions in the state, and conducting inspections separately and then sharing certain information with the FDA from the inspection). GAO, Table II.6: the Number of States That Reported Conducting Joint Pharmacy Inspections with FDA Inspectors, in GAO E-supplement, above.
- 33 See, e.g., NABP, Multistate Pharmacy Inspection Blueprint, <https://nabp.pharmacy/member-services/multistate-pharmacy-inspection-blueprint/>.
- 34 See Table IV.1: States Reporting Inspecting Resident (In-State) and Nonresident (Out-of-State) Pharmacies, Sterile Compounding Pharmacies, Wholesale Distributors, and Outsourcing Facilities, in GAO E-supplement, above.
- 35 For example, certain facilities must comply with CMS requirements in order to participate and receive payment through Medicare and Medicaid—including adhering to appropriate practice for compounding preparations. CMS, State Operations Manual, Appendix W-Survey Protocols, Regulations, and Interpretive Guidelines for Critical Access Hospitals (CAHs) and Swing-Beds in CAHs, Rev. 163, 10/14/16, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/som107ap_w_cah.pdf. Additionally, hospitals must receive accreditation in order to receive CMS reimbursement; adherence to appropriate compounding practice is required by accrediting organizations such as the Joint Commission, <https://www.jointcommission.org>.
- 36 As an example, under Medicare Part B, reimbursement for allergen immunotherapy has separate categories for preparation and administration. 42 U.S.C. § 1395x(s)(2)(G); 42 C.F.R. 410.68 (b); CPT Code 95165.
- 37 <http://www.usp.org/expert-committees/compounding-expert-committee-work-plan>