



What's Next for Compounded Medicines

Advancing Quality and Supporting Patient Access

Compounding of medicines has a longstanding history and remains an important aspect of pharmacy practice. Before the advent of manufactured medicines, all medicines were made through compounding. Today, compounding still plays a critical role by meeting unique, specific patient needs when commercially manufactured medicines are not appropriate.

An individual patient may need a specialized formulation or customized dosage that is not available without compounding. This situation arises most frequently in pediatric, geriatric, and other patient populations with particular medical needs. However, by their very nature, compounded medicines present certain risks pertaining to quality and patient safety. In some circumstances, poor-quality compounded medicines have led to serious illness, injury, and other critical, adverse events including deaths.

The regulatory and enforcement framework established to ensure quality compounded medicines and promote patient safety is complex, with both state and federal entities, such as state Boards of Pharmacy and the U.S. Food and Drug Administration (FDA), having authority. Overall, compounded medicines are not subject to the same level of oversight as FDA-approved medicines. Policies to promote compounding quality should address the many factors at play, including the need for rigorous quality standards; the importance of patient access to quality, cost-effective compounded medicines; and the feasibility of implementing the standards in the variety of settings where compounders practice.

USP compounding standards serve as an integral part of the legal and regulatory frameworks addressing compounding quality. USP's pharmacy compounding standards, General Chapters <795> and <797>, were revised and released after extensive stakeholder engagement and deliberation by independent experts. These standards will significantly advance the quality of compounded medicines through scientific, pragmatic, and risk-based approaches that account for the realities and complexities of pharmacy practice and meet the needs of patients.



What is compounding?

Compounding is performed by a licensed pharmacist or physician who combines, mixes, and/or alters ingredients to create a drug that meets the unique needs of an individual patient when no conventionally manufactured drug can do so.¹ Compounding pharmacists can incorporate drugs into liquid forms, topical creams, transdermal gels, suppositories, or other dosage forms suitable for patients' specific needs.² Compounded medicines can be vital for a range of patients, including pediatric and geriatric patients, individuals with specific allergies, and patients who may experience side effects from the commercially manufactured medicine that is usually prescribed for their medical need. Compounding can include customizing the strength or dosage of a medicine; 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 other side effects when taking oral medication.

What are some of the quality challenges with compounded medicines?

It is essential to safeguard against potential risks associated with compounded medicines, including problems that can occur with

- **sterility** (e.g., microorganisms such as bacteria, fungi, or viruses)
- **purity** (e.g., the drug contains unintended contaminants that could be harmful)
- **potency** (e.g., the dosage is inaccurate, either too strong or too weak)

Problems with sterility, purity, and potency may lead to patient safety issues such as inadequate or ineffective therapy, adverse events, antimicrobial resistance, and healthcare-associated infections. Notably, there have been tragic incidents associated with poor-quality compounded drugs, resulting in serious injury or illness, illustrating why compounded product quality is critical.^{3,4} For example, in 2016, serious adverse events occurred in three infants, leading FDA to call for a voluntary recall of compounded morphine sulfate injectable drug product that was superpotent by 2,460 percent.⁵ In 2012, more than 75 deaths among nearly 800 cases of fungal meningitis occurred nationally due to contaminated injectable compounded sterile preparations.⁶

How is compounding regulated and how do USP standards fit in?

In the U.S., states have primary responsibility for oversight of the majority of compounding pharmacies, most of which are not required to register with FDA.⁷ USP's standards on compounding serve as the foundation for state laws and regulations that address compounding quality.⁸ State Boards of Pharmacy are generally responsible for oversight and inspection of compounding pharmacies for compliance with applicable laws and regulations, including compliance with USP's compounding standards where required.⁹ FDA's compounding program collaborates closely with state officials to oversee compounding.¹⁰

Under Section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), many federal requirements otherwise applicable to medicines¹¹ do not apply if a compounder making individualized preparations by prescription follows certain requirements. These requirements include compounding in compliance with the USP chapters on pharmacy compounding (General Chapters <795> and <797>)¹² and using bulk drug substances and ingredients that comply with an applicable USP monograph (standard), if one exists.¹³ Additionally, the compounding must be done by a licensed pharmacist in a state-licensed facility or by a licensed physician for an identified individual patient based on the unsolicited receipt of a valid prescription, and

the facility cannot be compounding inordinate amounts or copies of commercially available drugs.¹⁴ Compounded drugs that do not meet the conditions of Section 503A are subject to all the requirements of the FD&C Act applicable to conventional drug manufacturers, including but not limited to drug approval and compliance with federal current good manufacturing practices.

USP compounding standards: Evolving to advance medicines quality and support patient safety and access

As the science and clinical practice of compounding continue to evolve, so do USP's standards for quality. USP has just published its revised compounding standards: USP General Chapters <795> and <797>.¹⁵ USP's standards are based on current scientific evidence and undergo regular revision to ensure that they are up to date. Importantly, these standards reflect the intricate balance between prioritizing patient access to compounded medicines and the need for rigorous quality standards. The standards also consider the variety of settings in which compounders practice as well as issues related to regulatory oversight and enforcement.

- USP General Chapter <795> describes the minimum quality standards to be followed for the compounding of nonsterile medicines. For purposes of General Chapter <795>, nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance to create a nonsterile preparation.
- USP General Chapter <797> describes specific procedures, conditions, and other requirements that, when followed, are designed to prevent patient harm resulting from microbial contamination, excessive bacterial endotoxins, variability in intended strength, unintended chemical and physical contaminants, and ingredients of inappropriate quality in compounded sterile preparations.¹⁶

The USP standard-setting process is well established and transparent, including extensive stakeholder engagement and deliberation by the Compounding Expert Committee.¹⁷ Stakeholders representing pharmacists, physicians, healthcare organizations, academicians, industry, patient advocacy groups, and federal and state regulators have been highly engaged with USP throughout the lengthy revision process for both <795> and <797>. In addition to submitting thousands of comments as a part of USP's formal standards revision process, these stakeholders have participated actively in many USP-hosted discussions and forums. USP also conducted additional, targeted stakeholder outreach activities. This engagement and input have enabled the Expert Committee to consider a wide range of perspectives to inform the revisions, maintain scientific rigor, and account for current pharmacy practice needs.

The 2022 revisions to <795> and <797> will significantly advance compounding quality while accounting for the realities of pharmacy practice and the needs of patients. The following table presents examples of the improvements in the revised standards:

Previous chapters	Revised chapters	Impact
<p>Provided general principles for personal hygiene and garbing of compounding personnel.</p>	<p>Include more stringent requirements for personal hygiene and garb for compounders, including how often they should change their garb.</p>	<p>Helps to prevent contamination of the compounded product, as well as protect compounders from chemical exposure.</p>
<p>Decisions about cleaning frequency were left to the compounder's judgment. Testing for contamination had to be done "on a periodic basis," allowing variation in how often these quality steps were conducted.</p>	<p>Revised <795> establishes required minimum frequencies for cleaning and sanitizing work surfaces, floors, walls, ceilings, and storage shelving.</p> <p>Revised <797> establishes specific intervals for testing of surfaces in the compounding area for contamination.</p>	<p>Specific and standardized requirements play a significant role in controlling contamination.</p>
<p><795> provided overarching requirements for compounding facilities and equipment, including equipment components for selection, handling, and storage.</p>	<p>Revised <795> expands requirements and recommendations for the different buildings and facilities, including the compounding space, storage area, and water sources.</p> <p>Revised <797> provides clearer guidance on designing and controlling the spaces where compounded medicines are being prepared, including air quality control, cleanliness of surfaces, and certification of equipment.</p>	<p>Expanded and clarified requirements for the compounding environment help reduce risk of contamination of compounded preparations.</p>
<p><795> characterized preparations as "nonaqueous" or "water-containing."</p>	<p>New concept of "water activity" was introduced to assess the susceptibility of a nonsterile preparation to microbial contamination and the potential for degradation due to hydrolysis.</p>	<p>While water is needed in many products, it creates an environment that is conducive to microbial growth, which could cause patient harm and make the medicine chemically unstable. Assigning appropriate beyond-use dates (BUDs) based on water activity can help decrease risks to patients.</p>
<p><797> allowed compounders to assign BUDs based on general stability information and professional experience. BUDs could be extended without limits.</p>	<p>The revised standards in <797> establish BUDs by distinguishing three categories of compounded medicines based on factors that can significantly influence quality, such as:</p> <ul style="list-style-type: none"> • the compounding environment (segregated compounding area or cleanroom); • contamination controls (such as garbing and frequency of environmental monitoring, personnel qualification, and cleaning); • performance of sterility testing; and • availability of data on the product's ability to remain stable. 	<p>Expands requirements and recommendations for assigning BUDs to prevent contamination of the compounded medicine or its ingredients.</p>

Spotlight: Beyond-use dates and their impact on patient safety and access

The beyond-use date, or BUD, is the date after which a compounded medicine must not be used. There are many different settings in which compounders practice, such as community pharmacies, physicians' offices, and hospital pharmacies, as well as many different patient populations that need access to quality compounded medicines. In some cases, assigning longer BUDs helps patients have consistent access to quality compounded medicines throughout their treatment and can help make these medicines more affordable for patients.

While longer BUDs, and therefore longer storage times, have advantages, they can increase the likelihood of chemical degradation and microbial growth while potentially compromising the container-closure system. The revised chapters set forth a scientifically robust and risk-based approach to assigning BUDs that helps to ensure sterility, maintain product quality, and protect patient safety, while supporting patient access to compounded medicines.¹⁸



Looking ahead

USP is committed to ongoing, effective dialogue with all stakeholders and will update its standards based on advances in science and healthcare practice. Patient safety and quality of care will always remain at the center of any discussion. USP will work to ensure that its standards are clear and understandable so that users can apply them effectively. To achieve this goal, USP will continue to offer educational opportunities such as workshops and Open Forums where stakeholders can ask their questions, connecting directly with USP staff. Extensive training offerings will include on-demand e-learning modules and live in-person trainings that will prepare users to implement the standards, which become official November 1, 2023.

USP will also continue its ongoing collaborations with FDA, the Centers for Disease Control and Prevention, state Boards of Pharmacy, and relevant healthcare practitioner groups, among others, to make sure that USP standards continue to respond to public health needs while reflecting advances in science.

Recognizing that collaborative efforts are necessary to advance quality compounding, USP also supports:

- Increased resources to state and federal agencies responsible for surveillance and enforcement of the quality and safety of compounded preparations, including FDA.
- Enhanced federal-state cooperation and coordination of efforts to advance compounded medicine quality.
- Improved adverse event reporting for compounded medicines, with the goal of ensuring that patients, healthcare providers, compounding facilities, and regulators all have access to a common, centralized mechanism to report and record adverse events.

USP is an independent, nonprofit, science-based organization that helps to safeguard 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 experts¹⁹ in a transparent scientific process with input from stakeholders and federal agencies such as the FDA and the CDC.

USP published the first edition of a national, uniform set of guidelines in 1820 for the best understood medicinal substances and preparations of the day. 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.

References

1. FDA, Compounding and the FDA: Questions and Answers, <https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers>
2. Id.
3. FDA, FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality and Security Act (2017), <https://www.fda.gov/drugs/human-drug-compounding/fdas-human-drug-compounding-progress-report-three-years-after-enactment-drug-quality-and-security>.
4. FDA, Compounding: Inspections, Recalls, and other Actions, <https://www.fda.gov/drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions>.
5. FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality and Security Act (2017).
6. Pew Charitable Trusts, U.S. Illnesses and Deaths Associated with Compounded or Repackaged Medications, 2001-19 (2020), <https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2020/us-illnesses-and-deaths-associated-with-compounded-or-repackaged-medications-2001-19>.
7. FDA, Compounding Information for States, <https://www.fda.gov/drugs/human-drug-compounding/compounding-information-states>. In 2013, Federal law created a category of compounders of sterile (and sometimes non-sterile) medicines called "outsourcing facilities" or "503B compounders." Unlike "traditional" or "503A" compounders, outsourcing facilities can compound and distribute drugs without receiving prescriptions for individually identified patients and without a limit on the quantity of drugs that they ship interstate. Also, in contrast to traditional compounders, outsourcing facilities must comply with FDA's CGMP requirements, are inspected by FDA on a risk-based schedule and are subject to other FDA requirements such as those pertaining to labeling and reporting. Like traditional compounders, outsourcing facilities are not required to have FDA approval for the drugs they provide. See FDA, Center for Drug Evaluation and Research, Outsourcing Facility Information (2017), <https://www.fda.gov/media/107569/download>; Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, Draft Guidance (2020), <https://www.fda.gov/media/88905/download>.
8. As of 2018, 32 state boards of pharmacy required pharmacies to fully comply with USP standards for sterile compounding. Pew, State Oversight of Drug Compounding (2018), https://www.pewtrusts.org/-/media/assets/2018/02/drug_safety_assesment_web.pdf, at 2.
9. United States Government Accountability Office, Drug Compounding, FDA Has Taken Steps to Implement Compounding law, but Some States and Stakeholders Reported Challenges, <https://www.gao.gov/assets/gao-17-64.pdf>.
10. FDA, Compounding Information for States, <https://www.fda.gov/drugs/human-drug-compounding/compounding-information-states>.
11. If the requirements of section 503A are met, compounded medicines are exempted from several key FDA requirements, including drug approval and compliance with federal current good manufacturing practices (CGMP) (requirements for the design, monitoring, and control of manufacturing processes and facilities). 21 USC 353a.
12. FDA, Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance, <https://www.fda.gov/media/94393/download>.
13. 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); FDA, Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance (2016), <https://www.fda.gov/media/94393/download>.
14. 21 USC 353a. Compounded drugs that meet the conditions of section 503A are not exempt from all provisions of the FD&C Act; for example, they are still subject to the prohibition on insanitary conditions. FDA, Insanitary Conditions at Compounding Facilities, Guidance, <https://www.fda.gov/media/124948/download>.
15. Development and revision of USP standards is led by Expert Committees. The Compounding Expert Committee currently consists of 15 members representing a variety of disciplines including healthcare practitioners who have expertise in sterile and nonsterile compounding, veterinary compounding, aseptic technique, microbiology, environmental engineering, and analytical testing. Additionally, six government liaisons participate in the Compounding Expert Committee, including four representatives from the U.S. FDA and two from the Centers for Disease Control and Prevention (CDC).
16. <795> and <797> both describe compounded preparations that are required to be sterile or can be prepared as nonsterile. In general, preparations designed to be delivered to any body space that does not normally freely "communicate" with or have contact with the environment outside of the body, such as the bladder cavity or peritoneal cavity, are typically required to be sterile. Additionally, ophthalmic products and compounded aqueous inhalation solutions and suspensions are required to be sterile. Otic preparations are not required to be sterile unless being administered to a patient with a perforated eardrum. Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile, nor are nasal sprays.
17. FAQs: Standards-Setting Process, <https://www.usp.org/frequently-asked-questions/standards-setting-process>.
18. USP, BUD Scientific Rationale for the 2021 Proposed Revisions to <795> (2021) and USP, BUD Scientific Rationale for the 2021 Proposed Revisions to <797> (2021), https://go.usp.org/Proposed_2021_Revisions_795_797.
19. 2020-2025 Compounding Expert Committee Work Plan, <https://www.usp.org/expert-committees/compounding-expert-committee-work-plan>