



Best Practices for State Oversight of Drug Compounding

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The Pew Charitable Trusts is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public, and invigorate civic life.

Overview

In 2012 and 2013, contaminated injections compounded at a single pharmacy in Massachusetts were associated with 64 deaths and 753 illnesses in a nationwide outbreak of fungal meningitis. This unprecedented tragedy has driven state and federal officials to re-examine laws and regulations governing drug compounding—the traditional pharmacy practice of creating custom medicines to meet a patient’s unique medical needs.

Although the Food and Drug Administration (FDA) enforces federal laws that apply to pharmaceutical products, states are in most cases the primary regulators of pharmacy compounding. In response to the meningitis outbreak and similar events—The Pew Charitable Trusts has identified over 25 reported compounding incidents associated with patient harm or deaths since 2001—numerous states are revisiting compounding oversight systems to ensure they are sufficiently robust. But state regulatory approaches and enforcement systems vary. For example, states apply different quality standards for compounding or inspect pharmacies on different schedules.

States must also consider how to address federal legislation on compounding, the Drug Quality and Security Act of 2013¹ (DQSA), which established a new type of company, an “outsourcing facility,” that is allowed to compound supplies of medicine without receiving patient-specific prescriptions, permitting operation on a larger scale. To do this, outsourcing facilities must meet FDA’s applicable current Good Manufacturing Practices (cGMP) regulations—the quality requirements for drug manufacturers—and register with FDA, among other obligations. Although FDA will have oversight responsibility for outsourcing facilities, states must still make decisions about how to recognize these companies in their jurisdictions and what oversight, if any, they wish to exert as the new sector is established.

The DQSA also clarifies the enforceability of federal law that traditional pharmacies may compound only pursuant to prescriptions, or in limited quantities in anticipation of receiving a prescription, to be exempt from FDA’s drug approval, manufacturing, and labeling standards. Federal law does not permit traditional pharmacies to supply compounded drugs without prescriptions.

In 2014, Pew convened an advisory committee of state regulators and experts to examine state oversight of compounding and develop best practices. The committee reviewed several regulatory topics, including inspections of compounding pharmacies, requirements for quality, expectations for pharmacist training, and compounding without a prescription. The committee also discussed how states should harmonize these requirements with federal law and regulations, particularly on issues such as definition and recognition of the new outsourcing facility category.

Based on the advisory committee process, this document identifies the best practices that are most meaningful to patient safety and the most achievable—recognizing, however, that state funding may place limitations on oversight systems. The best practices provide a resource to state regulators, policymakers, and interested stakeholders who are reviewing oversight practices, and also support greater harmonization across states—a valuable pursuit, given the interstate movement of compounded drugs, to ensure evenly-applied oversight and help counter an incentive for businesses to locate in states with less rigorous regulations.

Best practice recommendations are described in each section of this report and include:

- Application of U.S. Pharmacopeial Convention (USP) quality standards on compounding.
- Training in sterile compounding for pharmacists who perform or supervise it.
- Annual inspections of facilities that perform sterile compounding.

- State mechanisms, such as separate licensure, to identify and apply specific standards to facilities performing sterile compounding.
- Recognition and definition of outsourcing facilities in a manner aligned with federal law.
- Harmonization of policies on compounding without prescriptions with federal law.
- Meaningful oversight of sterile compounding that occurs in physicians' offices.
- Mechanisms to track the compounding activities conducted by pharmacies within the state.

The Advisory Panel's Work

To develop best practices for state oversight of drug compounding, The Pew Charitable Trusts convened an advisory committee whose members included leaders from five state boards of pharmacy and the National Association of Boards of Pharmacy, plus an expert in compounding quality systems. (See a full list in the acknowledgments section.) The committee's goal was to develop practices that are meaningful, achievable, and important for patient safety and that take into account lessons learned from the 2012-13 meningitis outbreak linked to compounded injections and the regulatory oversight established by the Drug Quality and Security Act in 2013.

The committee identified and refined best practices through iterative review and discussion. First, Pew circulated a draft document to the committee that identified regulatory categories and potential standards for initial consideration; members then provided written feedback on this document. Committee members then met in person Oct. 9, 2014, at Pew's offices to review each regulatory area and potential standard in-depth. During that meeting, the group found a substantial degree of consensus on many of the regulatory categories. After the meeting, Pew again updated the best practices document and circulated it for two additional rounds of written review.

The best practices identified in this report were significantly informed by the advisory committee process and reflect a high level of consensus among the experts. However, the recommendations in this report are Pew's and may not represent the views of every participant. Where important differences of opinion were identified within the committee, they are described in the text that precedes the best practices for each category.

Best practices for state oversight of drug compounding

Quality standards

The U.S. Pharmacopeial Convention has established widely recognized quality standards for pharmacy compounding of sterile and nonsterile preparations—USP chapters <797> and <795>, respectively, as well as Chapter <800> on the compounding, handling, and administration of drugs that present physical or health hazards. Although many states reference or incorporate USP standards in their pharmacy laws and regulations,

many others do not, creating an uneven landscape of quality requirements. Furthermore, states may be even less likely to have regulatory safeguards that apply to compounding that occurs outside of a pharmacy, such as in a doctor's office. The advisory committee agreed that all traditional compounding facilities, whether an independent pharmacy, hospital pharmacy, or doctor's office, should comply, at minimum, with all applicable USP standards. Compounders that register with FDA as outsourcing facilities are in a separate category, because they are required by federal law to comply with cGMPs. However, states that elect to license and/or inspect outsourcing facilities may also wish to establish cGMPs as the required quality standard.

The committee also emphasized that drug compounding is an interstate operation; pharmacies may prepare medicines in one state and ship them to another. States can encounter oversight challenges if an out-of-state pharmacy shipping into their jurisdiction is held to a different quality or regulatory standard than in-state compounders.

Repackaged Drugs and Preparations Using Biologics

Federal law on compounding, which covers traditional pharmacies and outsourcing facilities, does not address repackaging or preparations made from biological products. The FDA is developing guidance to address these activities; depending on final language some quality elements, such as beyond-use dating (i.e., the date beyond which a compounded drug should not be used), may differ from USP standards. As delineated within the original statute, FDA guidance on repackaging also supersedes federal law (Section 506F of the Food, Drug, and Cosmetic Act*) that addresses hospital repackaging of drugs into smaller amounts to extend the supply during a shortage. States should examine FDA guidance closely to ensure their standards are aligned with federal expectations.

* <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434174.pdf>

Harmonized minimum quality standards across states would help address challenges in regulating out-of-state pharmacies and ensure that all traditional pharmacy compounding met strong baseline criteria for preparing safe drugs and protecting patients. Committee members emphasized the importance of minimum standards for sterile compounding, in particular, and identified core elements of USP Chapter <797>, the key standard for sterile compounding. They include:

- Personnel-related controls: hand hygiene, garbing (wearing protective garments), aseptic technique, and training.
- Environment-related controls: facility design and construction, cleaning, environmental monitoring, and equipment certification and calibration.
- Process-related controls: sterilization procedures and verification, control of components and materials, standard operating procedures, and documentation.

Advisory committee members noted that although minimum standards for traditional pharmacy compounding should be the same nationwide, states should be able to implement additional requirements. But regardless of

whether states choose to go beyond USP, they must ensure that any updates to USP standards are reflected in state law or regulations. USP regularly updates standards; for example, in September 2015 USP published a proposed revision to Chapter <797>.²

Best practice standards for states

- States should require traditional compounding pharmacies to comply, at minimum, with all applicable USP standards, including general chapters <795> and <797>, new chapter <800> when complete, and other referenced chapters.
- States should hold out-of-state traditional compounding pharmacies that ship into the state to USP standards at a minimum.
- States should ensure that revisions of USP standards are reflected in state requirements.

Equipment certification and laboratory accreditation

Compounders preparing sterile products must control the air quality in their facilities and keep contaminants at acceptable, low levels. USP <797> currently includes an expectation that sterile compounding facilities and critical air control devices be certified at least every six months by a qualified individual using standard testing protocols, such as those endorsed by the Controlled Environment Testing Association (CETA).³ The advisory committee supported requiring the use of CETA testing standards for certification in all cases.

Compounders may use external labs to test products for sterility, endotoxins, and potency. Labs that are not appropriately rigorous in testing practices may produce compromised test results. Investigations following the 2012-13 meningitis outbreak revealed quality problems at several external testing labs used by compounding facilities. FDA issued inspectional findings to five contract labs in 2012 and 2013, in several cases noting that labs were not following USP standards for sterility testing. The advisory committee also recommended appropriate accreditation, which can help ensure that labs are meeting sufficient standards to produce reliable test results.

Best practice standards for states

- States should require that all sterile compounding facilities and critical air control devices be certified by a qualified individual at least every six months (as required by USP <797>) using standard testing protocols, such as those endorsed by CETA.
- States should require that sterile compounders use only external testing labs that are clinical or environmental labs with appropriate accreditation.⁴ Labs should also meet the International Organization for Standardization and the International Electrotechnical Commission 17025:2005⁵ quality standard, General Requirements for the Competence of Testing and Calibration Laboratories.

Pharmacist training on sterile compounding

Although USP <797> requires compounders to train personnel and regularly evaluate them through compounding simulations known as media fills, the committee recommended that states set more specific expectations for specialized training in sterile compounding for pharmacists engaging in that activity. This could be done by requiring a certain number of hours of continuing education in sterile compounding or through a certification program, if one were to be developed. Of note, proposed revisions to USP <797> include new detailed training expectations for personnel involved in sterile compounding activity.⁶

Some states have made changes in this regard. As of 2014, Massachusetts requires that five out of 20 continuing education hours be devoted to sterile compounding.⁷ To renew a license in Texas, pharmacists engaging in high-risk sterile compounding, such as preparing sterile drugs from nonsterile ingredients, must receive four out of 30 required hours of continuing education in the practice, and pharmacists engaged in low- or medium-risk sterile compounding must have two hours of specific training.⁸

A pharmacist's compliance with training requirements can be checked during state audits of compounding facilities, though it may not always be easy for a state to match pharmacists it licensed to the facilities where the pharmacists work. Therefore, compounding facilities should be required to keep records demonstrating that all pharmacists engaged in sterile compounding on-site are qualified and have had appropriate training.

Requirements for training may help increase course offerings; the advisory committee noted that few courses in sterile compounding are available today. The committee supported encouraging the Accreditation Council for Pharmacy Education (ACPE)⁹ to adopt a core curriculum standard on compounding that is taught in conformance with applicable USP standards. The advisory panel also saw value in developing specialty certification programs for sterile compounding.

Best practice standards for states

- In addition to USP <797> training expectations, states should require pharmacists who perform or supervise sterile compounding to receive regular specialized training in the practice, whether through continuing education or certification programs.
- Training must include classroom and practical components and must cover core elements of USP <797>. (See section on quality standards.)
- States should require compounders to document that all personnel engaging in or supervising sterile compounding are qualified and have had appropriate training. Compounders should provide such documentation upon request.

Recommendations for other stakeholders: ACPE should adopt core curriculum standards for schools of pharmacy that include training on nonsterile and sterile compounding, in conformance with USP requirements.

Inspections

Site inspections are the most important tool used by states to assess pharmacy compliance with laws and regulations on compounding, whether in a community, specialty, or hospital setting. The advisory committee discussed several important aspects of inspections, including frequency, process, inspector qualifications, documentation, and follow-up.

The committee supported annual inspection of sterile compounding pharmacies as a best practice but acknowledged that some states may find this difficult because of resource constraints. States should work to allocate sufficient resources to achieve this level of oversight and could consider various funding sources, such as budget allocations from state funds, pharmacy registration fees, or pharmacy inspection fees, among others. Where resources are limited, the committee supported a risk-based approach, in which oversight of higher-risk activities, such as preparing sterile drugs using nonsterile starting ingredients, is prioritized. An additional option for states is having compounders perform annual compliance self-assessments, which could be useful additional documentation that states could review during or between inspections. States should also conduct facility inspections if a compounding pharmacy remodels or relocates.

Inspections of compounders should be unannounced and long enough to include direct observation of compounding activity. If a facility is not performing compounding on the day of the inspection, state inspectors should require compounders to simulate or compound for observation the sterile products that are most challenging to make. Inspectors should also review results of prior media fills simulating these most-challenging preparations, which are required under USP <797>. While states may not have the resources to regularly take samples of compounded products for testing, the committee felt it was important that states have the ability to test drugs as needed during inspections and investigations. The state should work to allocate sufficient funding and, if needed, authority to achieve this.

Inspectors should use a formalized inspection document that adequately describes what was observed and indicates the level of compliance with specific quality standards. Because regulators must assess compliance by not only compounding pharmacies within the state, but also compounders shipping into their state from other locations, the committee saw value in the development of a standard form to help states understand and rely on each other's inspections.

The committee supported allowing states to use trusted third parties to conduct inspections when needed, but emphasized that these third parties must be qualified and that inspections must assess adherence at minimum to USP standards. Auditors, whether with the state or a third party, must be competent to assess the type of activity they are inspecting, whether sterile compounding, nuclear/radiopharmaceuticals compounding, or other activities.

Best practice standards for states

Frequency

- States should inspect nonsterile compounding facilities at least every two years and sterile compounding facilities yearly. States should have sufficient staff and funding to achieve these frequencies.
- When resources are constrained, states should use a risk-based assessment to prioritize inspections, emphasizing high-risk compounding (e.g., preparing sterile drugs from nonsterile ingredients). States may also review documents to supplement in-person inspections.
- States should also conduct facility inspections if the compounding pharmacy remodels or relocates, and such changes must be reported to the state. Before sterile products can be released from a remodeled or relocated facility, a successful inspection should be required.
- Out-of-state pharmacies should be subject to the same frequency of inspections as in-state pharmacies, whether conducted by the state or a third party.

Process

- Inspections should be conducted by state regulators or by a trusted, qualified third party approved by the state.
- Inspections should include examinations specific to the compounding activity, such as sterile or high-risk compounding, with sterile compounding activities assessed for minimum core components of USP <797>. (See section on quality standards.)
- States should utilize a formalized inspection document that adequately describes what was observed on an inspection to ensure compounder adherence to appropriate quality standards for the activities being conducted.
- Inspections should be unannounced.

- Inspections should be long enough (or include return visits) to permit direct observation of the highest-risk compounding activity performed at the site. If this is not possible, states should require compounders to simulate, or compound for observation, the sterile products most challenging to make. States should also review the results of prior media fill (compounding simulations) tests that simulate the compounder's most challenging sterile product processes.
- States should have the ability to take and test samples of sterile compounded drugs when needed, such as for inspections or investigations. States should have sufficient funding and, if needed, authority to support these activities. States should have a relationship with a qualified lab to perform analyses.

Inspections by regulators in other states or by third parties

- If the state relies on another state or a third party to perform inspections, the inspection process must sufficiently assess, and the inspection report must demonstrate compliance with, USP standards at minimum. Inspection reports must describe the specific criteria reviewed and whether compliance was met.
- States should approve in advance any third parties permitted to conduct inspections and regularly confirm that these inspectors are meeting qualification criteria.
- Third-party inspectors should provide the state with timely notification of any compliance failures and with all documentation related to the inspection.

Inspector qualifications

- State and third-party inspectors should be competent to examine the type of facility they are reviewing. This includes pharmacies engaging in traditional sterile compounding or handling of nuclear/radiopharmaceuticals (knowledge of and experience inspecting for applicable USP requirements), or outsourcing facilities for states that elect to inspect them (knowledge of and experience in inspecting for relevant cGMPs). States may also choose to rely on FDA inspections of outsourcing facilities (see outsourcing facilities section).
- Inspectors should receive initial training before conducting inspections and ongoing follow-up training to stay current with updated standards. Training should include a classroom component and practical experience. States should allocate sufficient financial resources to support both initial and follow-up training for state inspectors. Third-party inspectors must be able to show proof of training.

Documentation of inspections and findings

- States should document all inspections and inspectional findings in writing, which should include an inspection report form or checklist clearly indicating the standards reviewed and observed; documentation may also include additional narrative as needed.
- States should give compounders a written description of any problems discovered during inspections and request a written response describing how problems will be addressed. States should follow up with facilities to ensure appropriate responses and actions.

Recommendations for other stakeholders: The National Association of Boards of Pharmacy (NABP), or another similar credible organization, should work with states to create a standardized inspection form to support harmonization of state oversight.

Pharmacy licensure

Pharmacy licensure is an important way for states to set both the general and activity-specific requirements that compounders must meet. States should conduct an inspection prior to initial licensure of a compounding pharmacy and before compounding activity begins at a licensed pharmacy. For out-of-state pharmacies, states may conduct their own inspection, rely on an inspection by the state where the pharmacy is located, or use a qualified third-party inspection. Given the additional quality standards necessary to safely perform sterile compounding, states should have the ability to track sterile compounding and enforce specific standards in a targeted way. Most members of the advisory committee believe this is best achieved by establishing a separate licensure category for sterile compounders. Suspending a separate sterile compounding license is simpler than restricting just the sterile compounding activity of a facility that may also conduct nonsterile compounding or have retail operations that should be allowed to continue. Licensure suspension also makes it easier for regulators in other states, where the pharmacy may ship products, to take conforming disciplinary action. Finally, separate licensure supports fees specific to sterile compounding.

Best practice standards for states

Pre-licensure inspection

- States should conduct an inspection prior to initial licensure of a traditional compounding pharmacy and before compounding activity begins at a licensed traditional pharmacy.
- States may rely on FDA licensure and inspections for outsourcing facilities. However, if the state elects to license and inspect outsourcing facilities before licensure, inspections must be to cGMP standards (see outsourcing facilities section).

Specific licensure requirements for sterile compounding

- States should have a mechanism to identify facilities that engage in sterile compounding that ship or dispense drugs in the state and must have a targeted ability to enforce standards specific to sterile compounding. The optimal way to achieve this is through separate licensure for sterile compounders.
- Licensure requirements should include quality standards for sterile compounding (i.e., USP <797>).

Out-of-state pharmacies

- States should independently license out-of-state compounding pharmacies, which should be inspected prior to initial licensure or before compounding activity begins at a licensed traditional pharmacy.
- If the state cannot conduct an inspection before initial licensure, it may rely on an inspection report by the state where the pharmacy is located or an inspection by a qualified third party. In either case, the inspection must have been performed in the previous year, and the report must sufficiently demonstrate compliance with USP standards at minimum and describe the specific criteria reviewed and whether compliance was met.

Outsourcing facilities

Outsourcing facilities, the category of FDA-regulated compounders created by the Drug Quality and Security Act of 2013, may compound drugs without prescriptions if they register with FDA and meet applicable cGMPs, the quality standards applied to drug manufacturers. The ability to compound without prescriptions enables outsourcing facilities to meet legitimate provider needs for standing supplies of compounded medicines. Congress created this new type of FDA-regulated facility to address the emergence over the past several years

of nontraditional compounding pharmacies operating without appropriate oversight. Traditional pharmacies normally compound drugs to meet individual patient needs. When compounded drugs are created in large batches and sold across the country, any contamination has the potential to affect thousands of patients. Because public exposure is increased, traditional pharmacy quality standards applied by states are not sufficient. Stricter protections are warranted.

Outsourcing facilities are not considered manufacturers or distributors under federal law, nor are they necessarily pharmacies, although they are not prevented from holding a state pharmacy license. The advisory committee considered both the optimal way in which states should recognize outsourcing facilities and what oversight states should provide.

Regarding how states recognize outsourcing facilities, a majority on the committee felt that states should incorporate a definition in harmony with federal law, though this was not an area of perfect agreement. Updating statutes and/or regulations to include an outsourcing facility category and definition is not necessarily simple for all states, although some, such as New York, have done it.¹⁰ Other states are regulating outsourcing facilities as compounding pharmacies, manufacturers, or distributors—existing categories that afford them continued control. However, because outsourcing facilities ship their products across state lines, these variations can create significant challenges and confusion. Differing licensure requirements placed on a facility by different states may even directly contradict each other.

Aligning state definitions of outsourcing facilities with federal law would help support harmonized recognition across states and would help prevent confusion about what outsourcing facilities are, what standards they must meet (e.g., cGMPs), and what they are allowed to do (e.g., compound without prescriptions). Regardless of alignment with federal law, some states may wish to require separate registration or licensure to keep track of outsourcing facilities within their borders, as many states do for pharmaceutical manufacturing companies.

Regarding oversight and inspections of outsourcing facilities, the committee said the ultimate goal is for states to rely on FDA as the primary provider of oversight, but it noted transitional oversight challenges. For example, although state inspection frequencies range widely, some states are accustomed to inspecting sterile compounding pharmacies—the category many outsourcing facilities fell into before the Drug Quality and Security Act—frequently, perhaps once a year. By comparison, FDA has historically inspected drug manufacturing sites once every two to three years. States may be reluctant to halt inspections of outsourcing facilities because they do not yet have confidence in FDA's oversight. But continued state inspections are also a challenge because outsourcing facilities must meet Good Manufacturing Practices, quality standards that state inspectors generally are not trained to know. The committee agreed that states that wish to directly inspect outsourcing facilities should be trained on cGMPs and could seek collaboration and support from FDA and the National Association of Boards of Pharmacy. Other options for states are to review inspection reports showing cGMP compliance or simply rely on FDA's oversight of these facilities.

Best practice standards for states

- States should recognize outsourcing facilities in regulation or statute and incorporate a state law definition that is aligned with federal law.
- If states wish to formally track outsourcing facilities that do business in their state via separate registration or licensure, registration with FDA should be a prerequisite.
- All production at an outsourcing facility must meet applicable cGMPs. States may:
 - Rely on FDA to conduct oversight.

- Require an inspection report demonstrating compliance with cGMPs.
- Conduct their own inspections. States that wish to inspect outsourcing facilities must ensure inspectors have the appropriate training to assess adherence to applicable cGMP standards.
- Outsourcing facilities that conduct patient-specific compounding and dispensing must also be licensed as a pharmacy with the state, but the quality standard applied to the facility must be cGMP, not USP <797>. Records of compounded products prepared based on a patient-specific prescription must be maintained separately from records of non-patient-specific compounded products, so that these distinct records are readily retrievable.

Compounding without prescriptions and other violations of federal law

Compounding is traditionally done pursuant to a patient prescription. Federal law allows compounding pharmacies to be exempt from requirements placed on drug manufacturers, such as the FDA drug approvals process, if compounding is done pursuant to a patient prescription or in limited quantities before the receipt of a patient prescription. Federal law allows compounding without a prescription only if a plant registers with FDA as an outsourcing facility and meets cGMP standards.

In contrast to federal law, some states allow compounding pharmacies to sell a certain amount of products without prescriptions for use in doctors' offices and clinics, often referred to as "office stock" or "office use" compounding. Addressing this disparity between federal and state law may be challenging, but a majority of committee members agreed that states should seek to harmonize their policies with federal law and regulations. The committee also felt that states should take a public health approach to enforcement: States should focus oversight resources on plants compounding drugs without prescriptions in larger batches, where any contamination represents a greater public health risk. The Drug Quality and Security Act brings nontraditional compounding under FDA oversight, and thus higher-quality standards, to protect patients. Continuing to allow unrestricted compounding without prescriptions outside of this system undermines the new federal oversight category because it removes the incentive to participate.

The committee considered how states should address centralized compounding services that serve a large health system network, but it did not identify a clear best practice. States, FDA, and health system stakeholders should collaborate to determine whether centralized hospital pharmacies that compound sterile products for use within their health system without receiving patient prescriptions should register with FDA as an outsourcing facility, or whether state oversight is sufficient to ensure safety. Considerations when making this decision should include the volume of output, the number of hospitals and patients served, and whether the central pharmacy compounds drugs with beyond-use dating that exceeds defaults established in USP <797>.

In addition to compounding without prescriptions, states should be vigilant for other ways pharmacies may exceed the bounds of traditional practice and violate federal law, such as compounding copies of commercially available drugs, compounding drugs on FDA's list of products that have been withdrawn or removed from the market due to safety or efficacy concerns, or compounding drugs on FDA's list of drugs too difficult to compound safely. States should communicate with FDA about any facility they think is operating outside of traditional practice. The Drug Quality and Security Act requires FDA to work with the National Association of Boards of Pharmacy to establish a mechanism for states to report these issues to the agency.

Best practice standards for states

Compounding without prescriptions

- States should align laws and regulations with federal laws and regulations on compounding and dispensing/distributing without prescriptions.
- States should prioritize enforcement oversight on higher-risk activities—such as compounding pharmacies producing products without prescriptions on a larger scale—that in the event of contamination can affect more patients.
- States should establish policies that support provider purchasing of compounded drugs without prescriptions only from FDA-registered outsourcing facilities.

Compounding in violation of federal law

- State regulators should identify any compounding entities that operate in violation of federal law and either require them to cease this activity or, if appropriate, register with FDA as an outsourcing facility. State regulators should report to FDA any facilities that refuse to either cease activities in violation of federal law or, if appropriate, register with FDA as an outsourcing facility.

Physician's office compounding

Drug compounding most commonly occurs at pharmacies, but it may also take place in a doctor's office. State pharmacy regulators manage the oversight of compounding within pharmacies but do not normally have jurisdiction over medical practices, which are regulated by state medical boards. If a doctor's office employs a pharmacist to compound, the state board of pharmacy may have a greater ability to exert control through licensure, but not always. Differing state laws on whether physicians are allowed to dispense drugs complicates matters further.

The advisory committee affirmed that quality standards must be the same wherever compounding occurs and expressed concern that compounding in doctors' offices is not always regulated or tracked well. States should have a mechanism to identify and oversee doctor's office compounding, whether done through the board of pharmacy or board of medicine. The committee recommended that this issue also be addressed through collaboration between the Federation of State Medical Boards and the National Association of Boards of Pharmacy.

The committee also acknowledged that special considerations are necessary for compounding drugs in a doctor's office that for medical reasons must be administered immediately after preparation. It also agreed that an exemption from full USP quality standards may be appropriate in this case, because a contaminant, if present, would not have time to proliferate to harmful levels when the drug is used immediately. Practitioners compounding in doctors' offices, however, must still have appropriate training and must be held to a standard of care that includes good hand hygiene and aseptic technique. States should be careful to ensure that special allowances for immediate-use compounding do not inadvertently encourage this practice outside of what is medically necessary. Some studies suggest drugs prepared outside of controlled pharmacy environments, such as in hospital wards, may be at higher risk for contamination.¹¹ Because nurses may also be asked to compound for physicians, consideration should be given to involving state boards of nursing as well.

Best practice standards for states

- Physicians' offices that compound should be held to the same standards as other compounding facilities, including quality standards (e.g., USP <797>) and reporting standards.
- The state should have a mechanism for knowing which doctors' offices are conducting sterile compounding and should inspect these offices to ensure compliance. This oversight can be done by the state medical board or the state board of pharmacy. If by the state medical board, inspectors must receive appropriate training.
- There should be an exemption for compliance by physicians' offices with full USP <797> for immediate-use drugs (which are administered within the hour as defined by USP). However, practitioners compounding in doctors' offices must still have training and be held to a standard of care that includes good hand hygiene and aseptic technique, per USP standards. The immediate-use exemption cannot apply to hazardous drugs.

Recommendations for other stakeholders: The Federation of State Medical Boards should work with the National Association of Boards of Pharmacy to address physician's office compounding and identify appropriate oversight systems, whether through state medical boards, state boards of pharmacy, or other appropriate entities.

Reporting activities and adverse events

To meaningfully regulate compounding activity within the state, regulators need complete information about what activities are occurring at which facilities. The advisory committee discussed what information would be valuable to regularly receive from compounders and what would be important to have upon request. Traditional pharmacy compounders should regularly report their intended compounding practices to the state, including sterile and high-risk compounding, as well as compounding drug products that are in short supply. This could be done through licensure and licensure renewal or through a separate reporting process.

States can also benefit from information about the volume of drugs compounded in the previous year to monitor the scale of compounding operations. Advisory committee members felt that annual reporting of production volume information was not needed, but this information should be available to state regulators upon request. States may also have interest in knowing what activities occur at the outsourcing facilities in their jurisdictions. Outsourcing facilities must submit annual reports to FDA on the volume and type of products they produce, and these facilities should also make their reports available to states upon request.

Traditional compounding pharmacies should also report adverse events and voluntary recalls to the state. States should review voluntary recalls to ensure that actions taken to carry out the recall sufficiently address any risk to patients. States that elect to license outsourcing facilities may also elect to require these facilities to report adverse events to the state. Federal law requires outsourcing facilities to report adverse events to FDA.

Best practice standards for states

Activity reporting

- States should be able to track the type of compounding activities conducted by pharmacies in the state including sterile, nonsterile, and high-risk compounding. States should require compounders to report this information to the state, whether through licensure application or renewal, or through a separate activity reporting mechanism.
- States should have the authority to request reports from traditional compounding pharmacies on the number and volume of compounded products sold or dispensed in the state and, for in-state pharmacies, outside the

state in the previous year, including the drug's active ingredients, strength, and dosage form. States should be able to request this information outside of an inspection.

- States should have the authority to request the reports outsourcing facilities give to FDA identifying the drugs compounded in the previous six months, including the drug's active ingredients, strength, and dosage form.

Adverse event and recalls reporting

- Traditional compounding pharmacies should be required to report serious adverse events (as defined by FDA)¹² to the state board of pharmacy within 24 hours.
- Traditional compounding pharmacies should be required to report voluntary recalls to the state and FDA within 24 hours. The state should review voluntary recalls to ensure that actions taken to communicate with providers and/or remove products from the market sufficiently mitigate risk to patients.
- States that elect to license outsourcing facilities may also decide to require these facilities to report serious adverse events to the state.

State authorities and sanctions

States need appropriate authorities to execute oversight of drug compounding, such as the power to seize and quarantine products and, when there is the potential for serious patient harm, to order the cessation of activity to protect the public in advance of a hearing. States should also have the ability to mandate the recall of a compounded drug when there is potential for patient harm. States should further consider appropriate administrative, civil, and criminal penalties for violations of compounding regulations. States that elect to license outsourcing facilities may also elect to clarify the authorities that apply to these facilities and the products they make.

Members of the advisory committee also underscored the importance of receiving enforcement information from other states and FDA. A central clearinghouse of publicly available enforcement actions taken against compounding pharmacies and outsourcing facilities would be a helpful resource for state regulators. In some cases, however, state law may constrain what information regulators are able to share publicly or with each other.

Best practice standards for states

State authorities

- States should have the authority to quarantine products.
- States should have the authority to seize products.
- States should have the authority to suspend activity the state believes to be in violation of applicable law or regulation in advance of a hearing when the potential for serious patient harm exists.
- States should have the authority to mandate recalls of compounded drugs when there is potential or confirmed harm to a patient.
- States should have the authority to require compounders to notify providers and patients about recalled products to protect public health.
- States should have the authority to share information with other regulators, both federal and state, to support oversight and investigations.

Sanctions and penalties

- States should post sanctions and disciplinary actions on a public website.

Recommendations for other stakeholders: An independent third party, such as the National Association of Boards of Pharmacy, should establish a central resource of public enforcement actions taken against compounding pharmacies and outsourcing facilities by state regulators, as well as product recalls. FDA enforcement actions, which the agency already posts publicly, could also be incorporated.

Conclusion

This best practices document, developed with an advisory committee of state regulators and experts (see acknowledgments), identifies the most important state practices in the regulation of compounding. Although 2013 federal legislation created a new role for FDA to oversee compounding facilities producing standing supplies of drugs without prescriptions, states remain the primary regulator of traditional pharmacy compounding. As such, states are responsible for establishing appropriate oversight systems to protect patients from the risk of contaminated or substandard compounded products. In the wake of the 2012-13 nationwide fungal meningitis outbreak linked to compounded injections, states should examine existing systems closely and address any identified gaps.

States should hold compounding pharmacies to appropriate minimum quality standards and must regularly send qualified inspectors to ensure compliance. States should have systems to track the compounding activities in their state and should set meaningful training expectations for pharmacists, especially those who compound sterile drugs. States should also communicate with each other and harmonize oversight to better address interstate movement of compounded drugs. Finally, states should ensure that their policies on compounding without a prescription are aligned with federal law. They should work with FDA to identify compounding that violates these standards or production plants that exceed traditional pharmacy practice and should be regulated by FDA as outsourcing facilities.

Appendix

Best Practices for State Oversight of Drug Compounding

Quality standards

States should require traditional compounding pharmacies to comply, at minimum, with all applicable U.S. Pharmacopeial (USP) Convention standards, including general chapters <795> and <797>, new chapter <800> when complete, and other referenced chapters.

States should hold out-of-state traditional compounding pharmacies that ship into the state to USP standards at a minimum.

States should ensure that revisions of USP standards are reflected in state requirements.

Equipment certification and lab accreditation

States should require that all sterile compounding facilities and critical air control devices be certified by a qualified individual at least every six months (as required by USP <797>) using standard testing protocols such as those endorsed by the Controlled Environment Testing Association (CETA).

States should require that sterile compounders use only external testing labs that are clinical or environmental labs with appropriate accreditation.* Labs should also meet the International Organization for Standardization and the International Electrotechnical Commission 17025:2005† quality standard, General Requirements for the Competence of Testing and Calibration Laboratories.

Pharmacist training

In addition to USP <797> training expectations, states should require pharmacists who perform or supervise sterile compounding to receive regular specialized training in the practice, whether through continuing education or certification programs.

Training must include classroom and practical components and must cover core elements of USP <797> (see section on quality standards).

States should require compounders to document that all personnel engaging in or supervising sterile compounding are qualified and have had appropriate training. Compounders should provide such documentation upon request.

Recommendation for other stakeholders: Accreditation Council for Pharmacy Education (ACPE) should adopt core curriculum standards for schools of pharmacy that include training on nonsterile and sterile compounding, in conformance with USP requirements.

* Appropriate accreditation for clinical labs could include, for example, Clinical Laboratory Improvement Amendments accreditation or College of American Pathologists accreditation. Appropriate accreditation for environmental labs could include, for example, review by the American Association for Laboratory Accreditation, American Industrial Hygiene Association's Laboratory Accredited Programs LLC, or National Environmental Laboratory Accreditation Conference accreditation.

† The nonprofit International Organization for Standardization creates standardized international specifications for numerous types of business operations and products across many industry sectors.

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Inspections

Frequency

States should inspect nonsterile compounding facilities at least every two years and sterile compounding facilities yearly. States should have sufficient staff and funding to achieve these frequencies.

When resources are constrained, states should use a risk-based assessment to prioritize inspections, emphasizing high-risk compounding (e.g., preparing sterile drugs from nonsterile ingredients). States may also review documents to supplement in-person inspections.

States should also conduct facility inspections if the compounding pharmacy remodels or relocates, and such changes must be reported to the state. Before sterile products can be released from a remodeled or relocated facility, a successful inspection should be required.

Out-of-state pharmacies should be subject to the same frequency of inspections as in-state pharmacies, whether conducted by the state or a third party.

Process

Inspections should be conducted by the state or by a trusted, qualified third party approved by the state.

Inspections should include examinations specific to the compounding activity, such as sterile or high-risk compounding, with sterile compounding activities assessed for minimum core components of USP <797> (see section on quality standards).

States should utilize a formalized inspection document that adequately describes what was observed on an inspection to ensure compounder adherence to appropriate quality standards for the activities being conducted.

Inspections should be unannounced.

Inspections should be long enough (or include return visits) to permit direct observation of the highest risk compounding activity performed at the site. If this is not possible, states should require compounders to simulate, or compound for observation, the sterile products most challenging to make. States should also review the results of prior media fill (compounding simulations) tests that simulate the compounder's most challenging sterile product processes.

States should have the ability to take and test samples of sterile compounded drugs when needed, such as for inspections or investigations. States should have sufficient funding and, if needed, authority to support these activities. States should have a relationship with a qualified lab to perform analysis.

Recommendation for other stakeholders: The National Association of Boards of Pharmacy, or other similar credible organization, should work with states to create a standardized inspection form to support harmonization of state oversight.

Inspections by regulators in other states or by third parties

If the state relies on another state or a third party to perform inspections, the inspection process must sufficiently assess, and the inspection report must demonstrate compliance with, USP standards at minimum. Inspection reports must describe the specific criteria reviewed and whether compliance was met.

States should approve in advance any third parties permitted to conduct inspections and regularly confirm that these inspectors are meeting qualification criteria.

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Third-party inspectors should provide the state with timely notification of any compliance failures and with all documentation related to the inspection.

Inspector qualifications

State and third-party inspectors should be competent to examine the type of facility they are reviewing. This includes pharmacies engaging in traditional sterile compounding or handling nuclear/radiopharmaceuticals (knowledge of and experience in inspecting for applicable USP requirements), or outsourcing facilities for those states that elect to inspect them (knowledge of and experience in inspecting for relevant current Good Manufacturing Practices). States may also choose to rely on FDA inspections of outsourcing facilities (see outsourcing facilities section).

Inspectors should receive initial training before conducting inspections and ongoing follow-up training to stay current with updated standards. Training should include a classroom component and practical experience. States should allocate sufficient financial resources to support both initial and follow-up training for state inspectors. Third-party inspectors must be able to show proof of training.

Documentation of inspections and findings

States should document all inspections and inspectional findings in writing, which should include an inspection report form or checklist clearly indicating the standards reviewed and observed; documentation may also include additional narrative as needed.

States should give compounders a written description of any problems discovered during inspections and request a written response describing how problems will be addressed. States should follow up with facilities to ensure appropriate responses and actions.

Pharmacy licensure

Pre-licensure inspection

States should conduct an inspection before initial licensure of a traditional compounding pharmacy and before compounding activity begins at a licensed traditional pharmacy.

States may rely on FDA licensure and inspections for outsourcing facilities. However, if the state elects to license and inspect outsourcing facilities before licensure, inspections must be to cGMP standards (see outsourcing facilities section).

Specific licensure requirements for sterile compounding

States should have a mechanism to identify facilities that engage in sterile compounding that ship or dispense drugs in the state and must have a targeted ability to enforce standards specific to sterile compounding. The optimal way to achieve this is through separate licensure for sterile compounders.

Licensure requirements should include quality standards for sterile compounding (i.e., USP <797>).

Out-of-state pharmacies

States should independently license out-of-state pharmacies, which should be inspected before initial licensure or before compounding activity begins at a licensed traditional pharmacy.

If the state cannot conduct an inspection before initial licensure, it may rely on an inspection report by the state where the pharmacy is located or on an inspection by a qualified third party. In either case, the inspection must have been performed in the previous year, and the report must sufficiently demonstrate compliance with USP standards at minimum and describe the specific criteria reviewed and whether compliance was met.

Outsourcing facilities

States should recognize outsourcing facilities in regulation or statute and incorporate a state law definition that is aligned with federal law.

If states wish to formally track outsourcing facilities that do business in their state via separate registration or licensure, registration with FDA should be a prerequisite.

All production at an outsourcing facility must meet applicable cGMPs. States may:

- Rely on FDA to conduct oversight.
- Require an inspection report demonstrating compliance with cGMPs.
- Conduct their own inspections. States that wish to inspect outsourcing facilities must ensure inspectors have the appropriate training to assess adherence to applicable cGMP standards.

Outsourcing facilities that conduct patient-specific compounding and dispensing must also be licensed as a pharmacy with the state, but the quality standard applied to the facility must be cGMP, not USP <797>. Records of compounded products prepared based on a patient-specific prescription must be maintained separately from records of non-patient-specific compounded products, so that these distinct records are readily retrievable.

Compounding without prescriptions, violations of federal law

Compounding without prescriptions

States should align laws and regulations with federal laws and regulations on compounding and dispensing/distributing without prescriptions.

States should prioritize enforcement oversight on higher-risk activities—such as compounding pharmacies producing products without prescriptions on a larger scale—that in the event of contamination can affect more patients.

States should establish policies that support provider purchasing of compounded drugs without prescriptions only from FDA-registered outsourcing facilities.

Compounding in violation of federal law

State regulators should identify any compounding entities that operate in violation of federal law and either require them to cease this activity or, if appropriate, register with FDA as an outsourcing facility. State regulators should report to FDA any facilities that refuse to either cease activities in violation of federal law or, if appropriate, register with FDA as an outsourcing facility.

Physician's office compounding

Physicians' offices that compound should be held to the same standards as other compounding facilities, including quality standards (e.g., USP <797>) and reporting standards.

The state should have a mechanism for knowing which doctors' offices are conducting sterile compounding and should inspect these offices to ensure compliance. This oversight can be done by the state medical board or state board of pharmacy. If by the state medical board, inspectors must receive appropriate training.

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There should be an exemption for compliance by physicians' offices with full USP <797> for immediate-use drugs (which are administered within the hour, as defined by USP). However, practitioners compounding in doctors' offices must still have training and be held to a standard of care that includes good hand hygiene and aseptic technique, per USP standards. The immediate-use exemption cannot apply to hazardous drugs.

Recommendation for other stakeholders: The Federation of State Medical Boards should work with the National Association of Boards of Pharmacy to address physician's office compounding and identify appropriate oversight systems, whether through state medical boards, state boards of pharmacy, or other appropriate entities.

Activity and adverse event reporting

Activity reporting

States should be able to track the type of compounding activities conducted by pharmacies in the state including sterile, nonsterile, and high-risk compounding. States should require compounders to report this information to the state, whether through licensure application or renewal, or through a separate activity reporting mechanism.

States should have the authority to request reports from traditional compounding pharmacies on the number and volume of compounded products sold or dispensed in the state and, for in-state pharmacies, outside the state in the previous year, including the drug's active ingredients, strength, and dosage form. States should be able to request this information outside of an inspection.

States should have the authority to request the reports outsourcing facilities give to FDA identifying the drugs compounded in the previous six months, including the drug's active ingredients, strength, and dosage form.

Adverse event and recalls reporting

Traditional compounding pharmacies should be required to report serious adverse events (as defined by FDA)[‡] to the state board of pharmacy within 24 hours.

Traditional compounding pharmacies should be required to report voluntary recalls to the state and FDA within 24 hours. The state should review voluntary recalls to ensure that actions taken to communicate with providers and/or remove products from the market sufficiently mitigate risk to patients.

States that elect to license outsourcing facilities may also decide to require these facilities to report serious adverse events to the state.

[‡] U.S. Food and Drug Administration, "What Is a Serious Adverse Event?" updated Jan. 10, 2014, <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>. FDA defines a serious adverse event associated with the use of a medical product in a patient as a death, life-threatening event, hospitalization, disability or permanent damage, congenital anomaly or birth defect, or an event that may require medical or surgical intervention to prevent one of these outcomes.

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State authorities and sanctions

State authorities

States should have the authority to quarantine products.

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States should have the authority to require compounders to notify providers and patients about recalled products to protect public health.

States should have the authority to share information with other regulators, both federal and state, to support oversight and investigations.

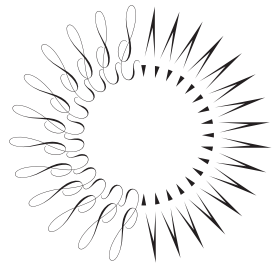
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Recommendation for other stakeholders: An independent third party, such as the National Association of Boards of Pharmacy, should establish a central resource of public enforcement actions taken against compounding pharmacies and outsourcing facilities by state regulators, as well as product recalls. FDA enforcement actions, which the agency already posts publicly, could also be incorporated.

Endnotes

- 1 U.S. Congress, H.R. 3204, Drug Quality and Security Act, <https://www.congress.gov/bill/113th-congress/house-bill/3204>.
- 2 United States Pharmacopeial Convention, "General Chapter <797> Pharmaceutical Compounding—Sterile Preparations: Notice of Intent to Revise," Sept. 25, 2015, <http://www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision>.
- 3 Controlled Environment Testing Association, "What Is CETA?" <http://www.cetainternational.org/#what>. CETA is a nonprofit trade association "devoted to promoting and developing quality assurance within the controlled environment testing industry."
- 4 Appropriate accreditation for clinical labs could include, for example, Clinical Laboratory Improvement Amendments accreditation or College of American Pathologists accreditation. Appropriate accreditation for environmental labs could include review by the American Association for Laboratory Accreditation, American Industrial Hygiene Association's Laboratory Accredited Programs LLC, or National Environmental Laboratory Accreditation Conference accreditation.
- 5 The nonprofit International Organization for Standardization creates standardized international specifications for numerous types of business operations and products across many industry sectors.
- 6 United States Pharmacopeial Convention, "General Chapter <797> Pharmaceutical Compounding—Sterile Preparations: Notice of Intent to Revise."
- 7 An Act Relative to Pharmacy Practice in the Commonwealth, Commonwealth of Massachusetts, 2014 Session Law, Chapter 159, <https://malegislature.gov/Laws/SessionLaws/Acts/2014/Chapter159>.
- 8 Continuing Education Requirements, Texas Administrative Code, Title 22, Part 15, Chapter 295, Rule Section 295.8, [http://texreg.sos.state.tx.us/public/readtac\\$ext.TacPage?sl=R&app=9&p_dir=&p_rloc=&p_tloc=&p_ploc=&pg=1&p_tac=&ti=22&pt=15&ch=295&rl=8](http://texreg.sos.state.tx.us/public/readtac$ext.TacPage?sl=R&app=9&p_dir=&p_rloc=&p_tloc=&p_ploc=&pg=1&p_tac=&ti=22&pt=15&ch=295&rl=8); and Additional Continuing Education Requirements, Texas State Board of Pharmacy (June 2015), http://www.pharmacy.texas.gov/files_pdf/Specific_CE_Requirements.pdf.
- 9 The Accreditation Council for Pharmacy Education is "the national agency for the accreditation of professional degree programs in pharmacy and providers of continuing pharmacy education" (<https://www.acpe-accredit.org/about/default.asp>).
- 10 Special Provisions Relating to Outsourcing Facilities, New York State Education Department, Education Law, Article 137, Pharmacy, Section 6831, <http://www.op.nysed.gov/prof/pharm/article137.htm>.
- 11 Cyril Stucki et al., "Microbial Contamination of Syringes During Preparation: The Direct Influence of Environmental Cleanliness and Risk Manipulations on End-Product Quality," *American Journal of Health-System Pharmacy* 66 (2009): 2032-2036.
- 12 U.S. Food and Drug Administration, "What Is a Serious Adverse Event?" last modified Jan. 10, 2014, <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>. FDA defines a serious adverse event associated with the use of a medical product in a patient as a death, life-threatening event, hospitalization, disability or permanent damage, congenital anomaly or birth defect, or an event that may require medical or surgical intervention to prevent one of these outcomes.



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