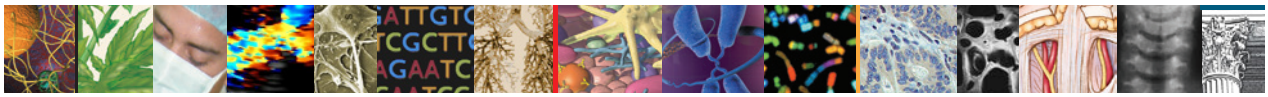

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Perspective

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Toward Better-Quality Compounded Drugs — An Update from the FDA

Janet Woodcock, M.D., and Julie Dohm, J.D., Ph.D.

Five years ago, methylprednisolone acetate and other drugs compounded by the New England Compounding Center (NECC; Framingham, Mass.) and administered to patients throughout the United States caused a fungal meningitis outbreak involving more than 750 infections and at least 64 deaths. The extent of this episode drew widespread attention, but smaller clusters of infections and other adverse events caused by contaminated or otherwise improperly made drugs compounded by various U.S. pharmacies occurred before this outbreak and continue to occur. In 2013, in the wake of the NECC case, Congress passed the Drug Quality and Security Act, which created a new category of compounder, called an "outsourcing facility," that is held to higher production standards than other compounding facilities. Our experiences at the Food and Drug Administration (FDA) with pharmacy compounding since the passage of this law reinforce the ongoing need to improve the quality of compounded drugs, particularly those intended to be sterile.

The purpose of pharmacy compounding has traditionally been to allow a licensed pharmacist to customize a medication for an individual patient whose needs cannot be met by an FDA-approved drug. For example, a patient who is allergic to a certain dye in an FDA-approved drug may need a drug compounded without that ingredient. Similarly, a liquid-compounded drug may best meet the needs of a child or elderly patient who cannot swallow an FDA-approved tablet or capsule. Such prescription-based, individualized compounding by pharmacies continues to fill a niche that mass-produced pharmaceuticals cannot fill.

However, the conventional view of pharmacy compounding as a practice limited to a local pharmacy making a product for an individual patient is clearly at odds with the realities of modern drug-compounding practices, as the NECC episode illustrates. The tragic proportions of the NECC case were largely attributable to the company's large-scale, multistate distribution of an injectable drug intended to be sterile that had been prepared under inappropriate conditions. The FDA's experience in monitoring pharmacy compounding has demonstrated the need for further improvement in compounding practices.

Table 1. Actions Related to FDA Oversight of Compounding Facilities after Passage of the Drug Quality and Security Act.*

Actions	FY 2014	FY 2015	FY 2016	FY 2017 (Q1–Q3)	Total
Inspections	92	116	135	85	428
For-cause inspections	37	35	47	17	136
Warning letters	29	30	65	38	162
State referral letters	9	10	11	31	61
Recall events	25	38	51	30	144

* A for-cause inspection is an FDA inspection to investigate a specific problem that has come to the FDA's attention, such as an adverse event or a complaint about product quality or a facility's conditions. A warning letter is a notice of an important legal violation or violations that is intended to achieve voluntary compliance. A state referral letter is the FDA's referral of inspection findings to the state for further follow-up. FY denotes fiscal year.

Since the 2012 meningitis outbreak, the agency has conducted more than 425 inspections of compounding pharmacies. We have observed problematic conditions during the vast majority of these inspections and have overseen more than 140 recalls of compounded drugs (see Table 1). Examples of observations include dead insects in compounding areas designated for sterile processing, visible mold on ceiling tiles in compounding rooms, and dog beds and dog hairs in close proximity to compounding areas.[1]

The FDA has received reports of serious adverse events, including deaths, associated with improperly compounded drugs as recently as this year. In July, for example, the agency issued a statement concerning at least 43 patients who experienced diminished visual function, such as blurred vision and loss of color perception, after receiving intraocular injections of a compounded drug containing a combination of a steroid and an antiinfective agent.[2] In August, the FDA posted a compounding risk alert about two patients who had severe hypersensitivity reactions, one of them fatal, after receiving intravenous infusions of a compounded curcumin product containing an ungraded excipient, which would be suitable for industrial use or research purposes but typically is not considered suitable for human consumption or therapeutic use.[3]

In fact, the FDA has received a steady stream of reports of serious adverse events related to compounded drugs since 2012 (see Table 2). In 2016, three infants received a compounded morphine sulfate preparation at a strength nearly 25 times that indicated on its label. In 2013, bacterial bloodstream infections developed in 15 patients, and 2 patients died, after receiving contaminated infusions that the FDA subsequently found had been compounded under inappropriate conditions. Because the vast majority of compounding facilities do not report adverse events to the FDA, our records probably include only a small proportion of the adverse events that actually occur.

These problems emphasize the need to improve the quality of compounded drugs, and efforts to raise production standards are under way. The laws that govern production standards for compounding pharmacies vary from state to state. Many states have adopted, in whole or in part, standards established by the U.S. Pharmacopeia, which are currently undergoing substantial revision. In 2015, revisions to Chapter 797 (on sterile compounding) were proposed to help ensure that sterile compounded drugs are free from contaminants. Because these revised standards are still in draft form, however, states have not yet adopted them.

In 2016, in a complementary effort, the FDA published draft guidance that describes examples of "insanitary conditions" — involving the presence of filth or other conditions that could result in an injurious product — observed in compounding facilities and actions that companies should take if they identify such conditions at their facilities.[4] The FDA issued the draft guidance to assist compounding facilities in identifying and correcting insanitary conditions and to assist state regulatory agencies in assessing whether the conditions they observe during inspections would be considered insanitary.

We are also in the process of developing standards for the new category of outsourcing facilities created by the Drug Quality and Security Act. Under federal law, outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements — the main benchmark used by the FDA for ensuring production of high-quality pharmaceuticals. Outsourcing facilities are intended to meet the needs of hospitals, freestanding outpatient surgery centers, clinics, and other health care fa-

Table 2. Examples of Adverse Events Associated with Drugs Prepared by Compounding Facilities over the Past 5 Years.

Year	Facility Location	Adverse Events
2017	Texas	At least 43 patients had adverse events, including vision loss, after receiving compounded steroid-and-antibiotic eye injections.
2017	California	Two patients had hypersensitivity reactions, and one died, after receiving an intravenous medication prepared with a compounded curcumin product.
2016	Indiana	Three infants had serious adverse events after receiving compounded morphine sulfate that was nearly 2500% as potent as it should have been.
2016	South Dakota	Seven patients had thyrotoxicosis after receiving superpotent compounded oral liothyronine products. Three patients were hospitalized in an intensive care unit.
2015	Florida	The FDA received several reports of adverse events possibly associated with compounded vitamin D_3 capsules that were approximately 300% as potent as they should have been.
2015	Texas	A patient died after using a compounded topical anesthetic cream. A court heard evidence that the cause of death was ketamine and cyclobenzaprine toxicity.
2015	Alabama	In five patients who received betamethasone sodium phosphate and betamethasone acetate, redness, swelling, and pain developed at the injection site. Three of the patients were hospitalized and had cultures that were positive for *Staphylococcus aureus*.
2014	Florida	At least 37 patients had serious adverse events after receiving intravitreal injections of repackaged Avastin (bevacizumab) or Lucentis (ranibizumab).
2014	Several states	The FDA received several reports of adverse events associated with compounded products that should have contained L-citrulline but instead contained a different active ingredient. Subpotent L-citrulline in patients with certain urea-cycle defects can lead to high ammonia levels, which is serious and potentially life-threatening.
2014	Indiana	Several neonates experienced oversedation after receiving superpotent compounded midazolam.
2014	Texas	A patient had severe flushing, stinging, and dizziness after an infusion of compounded magnesium sulfate in normal saline. The patient's blood had increased levels of magnesium.
2013	Tennessee	Twenty-six patients reported adverse events, including skin abscesses, after receiving injections of compounded methylprednisolone acetate that was contaminated.
2013	Texas	Bacterial bloodstream infections developed in 15 patients, and 2 died, after receiving infusions of compounded calcium gluconate contaminated with bacteria.
2013	Georgia	Five patients had endophthalmitis after receiving ophthalmic injections of repackaged Avastin.
2013	Texas	Six patients had adverse events, including fever and flulike symptoms, after receiving injections of compounded methylcobalamin.
2012	Massachusetts	Some 753 patients had fungal meningitis and other infections after receiving steroid injections that were contaminated with fungus. At least 64 patients died.

cilities for customized drugs and dosage forms that are not in high enough demand to be manufactured by pharmaceutical companies. Some clinicians want to keep a supply of these compounded drugs on hand so they can administer them to patients who present with an immediate need for them. At least in principle, these drugs are more safely prepared in centralized facilities subject to CGMP standards than in health care facilities. The FDA draft guidance proposes tailoring these standards to the scale and scope of outsourcing-facility operations.[5]

The outsourcing-facility sector is growing, although it is still young and must continue to adjust to tighter production standards. About 75 entities are currently registered with the FDA as outsourcing facilities, the majority of which had been compounding drugs for years before the passage of the Drug Quality and Security Act and are currently taking steps to conform to new production standards. Because outsourcing facilities are permitted to compound sterile drugs in large volumes and ship them anywhere in the United States without patient-specific prescriptions, the move toward CGMP adherence is critical. We intend to continue to work closely with key stakeholders to help outsourcing facilities throughout the country to meet CGMP standards.

Much of the patient harm

caused by compounded drugs is preventable, and the implementation of higher production standards (such as CGMP standards for outsourcing facilities and revised U.S. Pharmacopeia standards, once finalized, for other compounding pharmacies) will be essential to reducing harm associated with pharmaceutical compounding. All stakeholders have a role to play, including regulatory agencies such as the FDA and state boards of pharmacy, outsourcing facilities and other compounding pharmacies, and health care practitioners and systems that will need to make informed choices about prescribing and purchasing compounded drugs. Five years after the tragic fungal meningitis outbreak is a good time to reinvigorate efforts to ensure that the compounded drugs given to patients who need them are made in facilities that are held to appropriate production standards.

Disclosure forms provided by the authors are available at NEJM.org.

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

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Emergency Legal Authority and the Opioid Crisis

Lainie Rutkow, J.D., Ph.D., M.P.H., and Jon S. Vernick, J.D., M.P.H.

Opioid-overdose deaths in the United States have steadily increased for the past 15 years, with more than 33,000 such deaths reported in 2015.[1] The epidemic is unfolding on two fronts: use of prescription opioid pain relievers (OPRs) accounts for approximately half of opioid-overdose deaths, and deaths from heroin and synthetic opioids such as fentanyl, obtained illicitly, have increased dramatically during the past 5 years.

In the face of this public health crisis, various policies have been enacted — particularly at the state level — often to address OPR prescribing and limit opportunities for OPR diversion. For example, all 50 states have established prescription drug monitoring programs (PDMPs) that collect information about individuals' prescription-drug history in an electronic database. Eleven states have laws regulating pain-management clinics,[2] and several states have enacted laws to limit the dosage or duration of OPR prescriptions.

Recently, six states have taken the unusual step of using their legal authority to declare their opioid-overdose situation an emergency. When a government issues an emergency declaration, it can temporarily act to mitigate the emergency using powers and resources that might not otherwise be available to it. Typically, emergency declarations pertain to natural disasters or infectious disease outbreaks. The severity of the opioid-overdose crisis has led to some of the first emergency declarations for a noncommunicable health condition, though their impact remains unclear.

In July 2017, the President's Commission on Combating Drug Addiction and the Opioid Crisis called for a national declaration of emergency.[3] In its preliminary report, the commission stated that issuing such a declaration was its "first and most urgent recommendation," since doing so would potentially provide the impetus for the federal government's executive and legislative branches to respond to the crisis with additional resources and policies. On October 26, 2017, President Donald Trump directed the acting secretary of health