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Regulating Compounding Pharmacies after NECC

Kevin Outterson, J.D.

Food and Drug Administration (FDA) rules are often forged in crisis. After the 1937 sulfanilamide disaster that killed more than 100 people, Congress passed the Food, Drug, and Cosmetic Act (FDCA),

requiring drugs to be safe and properly labeled. In 1962, a requirement was introduced for proof of drug efficacy through “adequate and well-controlled investigations,” partly in response to the thalidomide tragedy. Rules protecting human-research subjects owe a debt to Tuskegee and Nuremberg. Sometimes it takes a disaster to spur the adoption of appropriate regulation.

Today, compounding pharmacies are at the center of a controversy after a rare outbreak of fungal meningitis that was traced to several lots of the injectable glucocorticoid methylprednisolone acetate compounded by the New England Compounding Center (NECC). Congress is already discussing new federal regulations.

Since 1938, the FDA has had clear authority to regulate drug manufacturing, but compound-

ing falls into a gray area between state and federal oversight. The FDA’s authority here is generally limited to reacting to problems identified by others. Traditional compounding pharmacies are not registered with the FDA as drug manufacturers, the agency doesn’t approve their prescriptions before marketing, and related adverse events need not be reported to the FDA. State law generally controls recordkeeping, certifications, and licensing for compounding pharmacies (see timeline).

Such a regulatory structure is not unusual: many U.S. health care laws embrace federalism principles, preserving substantial realms for state control. States have primary authority over the practice of both medicine and pharmacy. But over time, compounding has evolved into a busi-

ness far removed from the mortar and pestle. Once it becomes an industrial-scale national business, the arguments for federal regulation become stronger.

For more than two decades, the FDA has struggled to regulate industrial-scale compounding. In 1992, it issued a Compliance Policy Guide, attempting to police the line between traditional compounding and drug manufacturing. This guide attracted enough criticism that Congress created a safe-harbor compounding statute in 1997, amending the FDCA with a new section, 503A.

But 2 days before this law was to take effect, seven compounding pharmacies sued to block it. Section 503A(c) banned the advertising and promotion of compounded drugs; the theory was that since traditional compounding occurred in response to individual prescriptions, advertising was unnecessary. The advertising ban was the law’s Achilles’ heel. In 2002, in a 5-to-4 decision in *Thompson v. Western States Medical Center* (an early example of the

NECC Compliance with Existing FDA Compliance Policy Guide.	
Rule Violation as Listed in the 2002 Compliance Policy Guide	NECC Compliance, per FDA and Massachusetts Interim Reports
Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions	NECC did not have valid prescriptions for all compounded drugs
Compounding drugs that were withdrawn or removed from the market for safety reasons	No evidence thus far
Compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA-sanctioned Investigational New Drug Application	No evidence thus far
Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility	No evidence thus far
Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements	No evidence thus far
Using commercial-scale manufacturing or testing equipment for compounding drug products	NECC appears to have used commercial-scale manufacturing or testing equipment
Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state-licensed persons or commercial entities for resale	Unclear thus far
Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products (In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different from an FDA-approved drug that is commercially available. In these circumstances, the FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.)	NECC produced a preservative-free version of a commercially available drug, methylprednisolone acetate
Failing to operate in conformance with applicable state law regulating the practice of pharmacy	NECC appears to have violated Massachusetts law

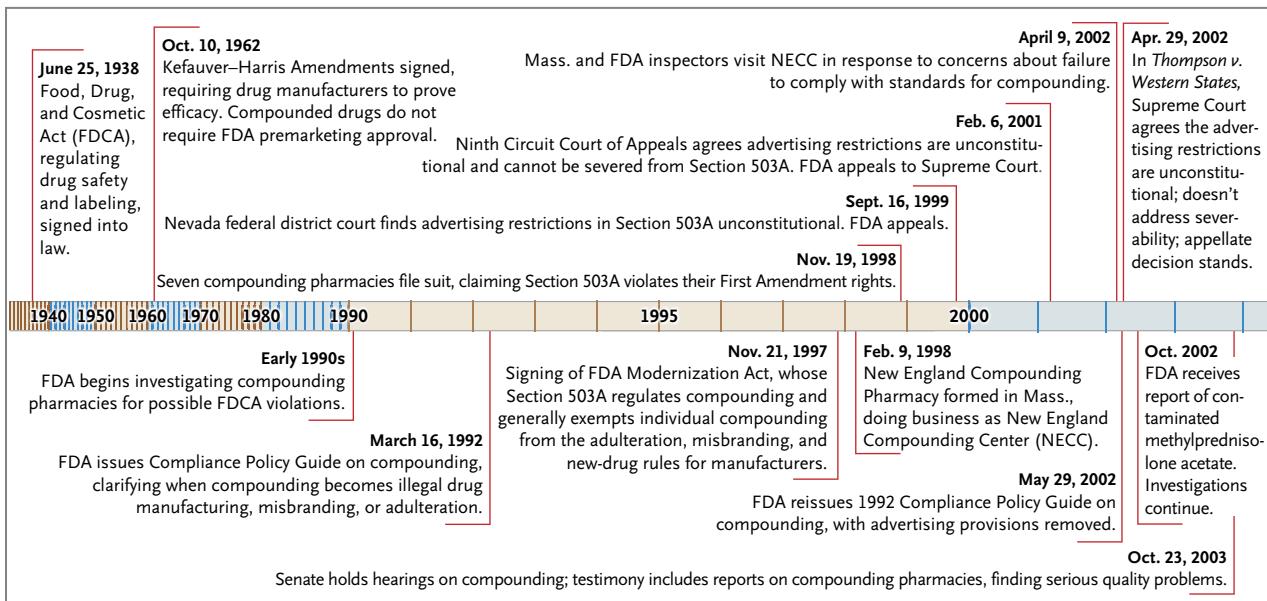
use of free speech against public health regulation),¹ the Supreme Court ruled that compounders have a constitutional right to advertise their drugs.

The FDA salvaged the Compliance Policy Guide by reissuing it without the advertising and interstate-shipment provisions, re-emphasizing the agency's author-

ity under the FDCA. The 2002 Guide articulated nine factors that the FDA would consider as relevant, including many drawn from the nonadvertising provisions of Section 503A. Several of these factors appear to have been violated by NECC (see table).

Some observers have chastised the FDA for not acting sooner

against NECC, given the agency's authority to block illegal drug manufacturing. But this critique ignores the complex regulatory history. FDA authority over compounding has never been straight-forward, and though the agency can react once a problem is obvious, it's unclear how it should proactively gather information on



History of FDA Regulation Relevant to Compounding at NECC.

potential violations before a crisis erupts. The thousands of U.S. compounding pharmacies are not registered with the FDA; they are not subject to federal recordkeeping and reporting rules for drug manufacturers; and, through litigation, the FDA can be blocked for many months from visiting them. Without information about the actual conditions in compounding pharmacies, regulators cannot act to address violations.

It's possible that if the Supreme Court hadn't struck down Section 503A, the tragedy at NECC could have been averted. Several features of that law are relevant.

First, traditional compounding was limited to a pharmacist or a physician serving a specific patient. Section 503A also permitted compounding of drugs "in limited quantities before the receipt of a valid prescription order . . . based on a history of . . . receiving valid prescription orders." According to the preliminary report from the Commonwealth of Massachusetts, NECC far exceeded these limits in preparing and shipping vials of methylprednisolone acetate.² Once

disconnected from individual patients, compounding increasingly resembles drug manufacturing.

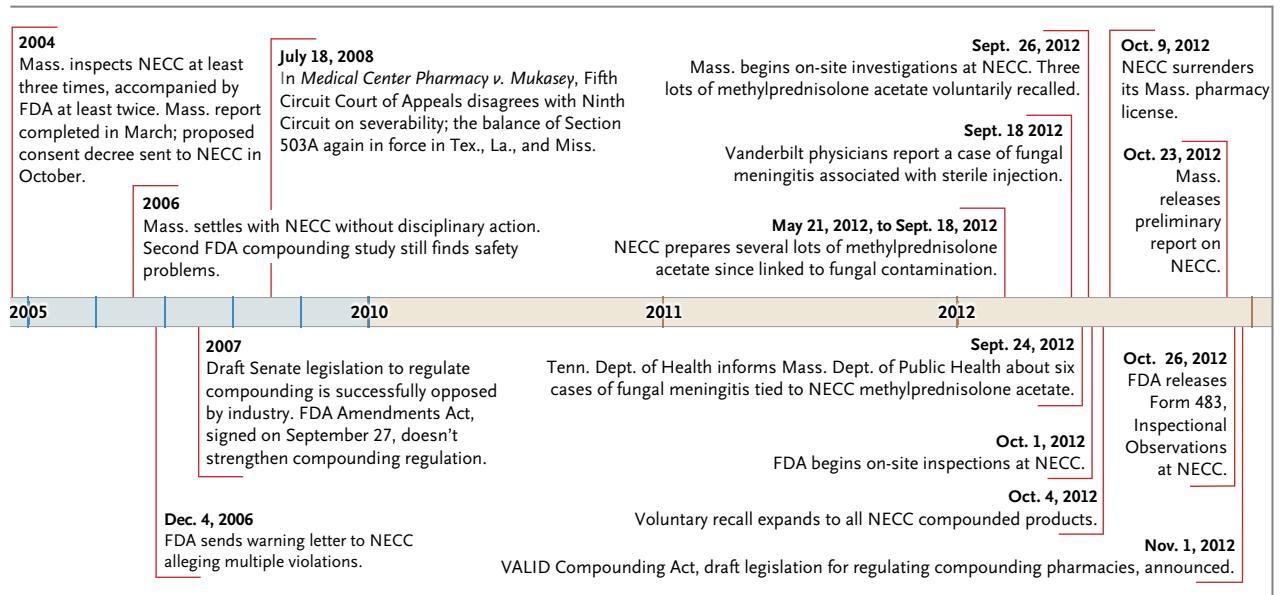
Second, compounding is not needed if a drug is commercially available from an FDA-regulated facility. Section 503A prohibited compounding "regularly or in inordinate amounts" any drugs that were "essentially copies of a commercially available drug product." FDA-approved methylprednisolone acetate is sold by Pfizer and two generics companies, but since NECC's version did not contain preservatives, it could sidestep this regulatory process — with tragic results.

Third, Congress recognized that states could effectively regulate traditional compounding pharmacies, but national-scale businesses required federal coordination. Section 503A provided a test for distinguishing between the two: it limited interstate shipments to no more than 5% of the compounder's business, unless the home state had entered into a "memorandum of understanding" with the FDA, bolstering state and federal cooperation.

NECC shipped substantial quantities of drugs to many states. If Section 503A had not been struck down, both the FDA and Massachusetts would have been more directly involved in regulating NECC for more than a decade.

Yet contamination is only one of five categories of risk associated with compounding pharmacies; the others are subpotency, superpotency, overmedication, and medication replacement.³ Other policy levers that may be needed include enhanced transparency for state-level regulation, mandatory disclosures to physicians and patients, mandatory reporting of adverse events, user fees to support oversight, clear FDA authority to register and inspect nontraditional compounding pharmacies, enhanced incentives for internal whistleblowers, and modification of reimbursement rules to blunt the economic incentives driving industrial-scale compounding.

Fungal contamination at NECC has sickened more than 400 patients and killed at least 29. But it's important to note that many patients received these sterile in-



jections for back and joint pain, a procedure that lacks high-quality evidence of efficacy.^{4,5} These problems cannot be laid entirely at the feet of compounders when clinicians persist in clinical practices despite weak evidence of efficacy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From Boston University School of Law, Boston.

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Drug Policy for an Aging Population — The European Medicines Agency's Geriatric Medicines Strategy

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In almost every country, the proportion of people over 60 years of age is growing faster than any other age group, as a result of longer life expectancy and declining fertility rates. In Europe, the median age is already the highest in the world, and in 2050 there are projected to be 88.5 million Americans 65 years old or older — more than double the 40.3 million in the 2010 census.

Although population aging is a mark of the success of public health policies, it also challenges the established way of implementing such policies. In the case of the European Medicines Agency (EMA), it has prompted an analysis of whether the regulatory system is adapted to taking the needs of older people into account in the development, approval, and use of medications.

The process started in 2006, when the EMA provided an opinion on the adequacy of guidance on the elderly regarding medicinal products. In 2011, the agency's Committee for Human Medicinal Products adopted the EMA geriatric medicines strategy,¹ marking its commitment to improving our understanding of how best to evaluate the benefit-risk

ratio for a medication in older patients.

First, the strategy recognizes that older people are the main users of medications — not a minority or special population (a fundamental difference between the geriatric and pediatric populations). Therefore, legislative and regulatory frameworks must be designed to ensure that the use of newly approved medicines in the intended population is supported by relevant data on the benefit-risk balance. The strategy's second aim is to improve the availability of information to patients and prescribers, to support safer use of medications.

Analysis of the data submitted in support of recent applications for marketing authorization shows that the current regulatory environment has ensured reasonable representation of “younger old” patients, but drug-usage patterns reveal a high prevalence of use in “older old” patients (see graph). Patients who are 75 years old or older often present a complex picture involving coexisting conditions and frailty: they are the fastest-growing demographic group but are largely underrepresented in clinical trials given

their disproportionately high actual use of drugs. This imbalance will make it increasingly difficult and potentially inappropriate to extrapolate data to these patients.² Though trials are less likely to set unjustified age limits than they were a few decades ago, this improvement must be considered in the context of a rapidly aging population and the continued widespread use of exclusion criteria based on coexisting conditions. Corrective efforts must be maintained to ensure that a representative population of patients covering the entire age range is studied in the preauthorization phase, in accordance with international guidelines.³

Chronologic age alone is inadequate for characterizing the population enrolled in a clinical trial. Frailty is a predictor of clinical outcomes,⁴ and the reduction of frailty has benefits for individuals and society. The EMA is exploring the possibility of reaching a consensus on an operational definition of frailty and tools for evaluating it that could be used for clinical research and to guide therapeutic decisions.

Medications commonly prescribed to treat other conditions