How gaps in regulation of compounding pharmacy set the stage for a multistate fungal meningitis outbreak

Besu F. Teshome, Kelly R. Reveles, Grace C. Lee, Laurajo Ryan, and Christopher R. Frei

Abstract

Objective: To provide an overview of the regulation issues surrounding compounding pharmacy that allowed the United States fungal meningitis outbreak to occur and the changes in regulation that ensued.

Summary: In September 2012, a single case report sparked an investigation into a nationwide outbreak of fungal meningitis due to contaminated injectable drugs. The source of the contamination, New England Compounding Center (NECC), was in violation of several state and federal laws and had a history of such violations. The regulation of compounding pharmacies has historically been left to the states, while manufacturing fell under the jurisdiction of the Food and Drug Administration. However, as more compounders took part in large-scale interstate distribution of drugs, the current state-based regulatory system became less equipped to provide oversight. The lack of a clear definition of "compounding pharmacy" further obscures proper oversight and regulation. Congress and several states have taken steps to build safeguards against large-scale compounding by increasing inspections, adopting stricter licensing requirements, and enacting the Drug Quality and Security Act of 2013.

Conclusion: While the current compounding regulation changes are a necessary step forward, it remains to be seen how effective they will be in safeguarding the public.

Keywords: Compounding, regulations, laws, patient safety, microbiology, quality assurance.

J Am Pharm Assoc. 2014; 54:441–445.
doi: 10.1331/JAPhA.2014.14011

Received January 16, 2014, and in revised form April 8, 2014. Accepted for publication April 20, 2014.

Besu F. Teshome, PharmD; Kelly R. Reveles, PharmD, BCPS; and **Grace C. Lee, PharmD, BCPS,** are graduate students. **Laurajo Ryan, PharmD, MSc, BCPS,** is Clinical Associate Professor. **Christopher R. Frei, PharmD, MSc, FCCP, BCPS,** is Associate Professor, University of Texas at Austin, Austin, and University of Texas Health Science Center at San Antonio, San Antonio.

Correspondence: Christopher R. Frei, PharmD, MSc, FCCP, BCPS, University of Texas Health Science Center at San Antonio, Pharmacotherapy Education and Research Center, 7703 Floyd Curl Dr., MSC-6220, San Antonio, TX 78229-3900. E-mail: freic@uthscsa.edu

Disclosure: Dr. Frei has received research grants and/or served as a scientific consultant/advisor for the National Institutes of Health, AstraZeneca, Bristol-Myers Squibb, Elan, Forest, Ortho-McNeil-Janssen Pharmaceuticals, and Pfizer. The other authors declare no conflicts of interest or financial interests in any product or service mentioned in this article, including grants, employment, gifts, stock, holdings, or honoraria.

In September 2012, a single case report sparked an investigation that uncovered the most devastating drug-related tragedy in recent history. An estimated 14,000 people in 23 states were exposed to contaminated, preservative-free methylprednisolone acetate (MPA) for injection, leading to 751 cases and 64 deaths from fungal infections.[1,2] The source of this widespread tragedy was not a large multinational drug manufacturer. Instead, the contaminated MPA originated from a single compounding pharmacy in Massachusetts—New England Compounding Center (NECC). Other compounding contaminations have been reported previously, but the magnitude of the NECC case brought this issue into the national spotlight.[3–5]

The goal of this commentary is to provide a brief overview of the history of compounding regulation, the NECC tragedy, and the regulatory issues that allowed it to occur. We then provide a more comprehensive look at the new compounding law and discuss its potential limitations in preventing another compounding tragedy.

Fungal meningitis outbreak

NECC, based in Framingham, MA, was a compounding pharmacy that distributed medications to more than 3,000 facilities in all 50 states.[6] In 1998, NECC became licensed to produce compounded pharmaceutical products in accordance with Massachusetts state law. The law required them to have an individual patient prescription for each compounded product and follow the U.S. Pharmacopeia (USP) <797> standards for compounding sterile products.[7] USP <797> establishes provisions that include proper garbing, training of personnel, environmental control, quality assurance, preparation, handling, and storage of compounded products to maintain sterility. A complete description of USP <797> requirements can be found on its website.[8]

NECC was found to be in violation of both aspects of the law during a joint inspection by the Food and Drug Administration (FDA) and the Massachusetts State Board of Pharmacy on October 1, 2012.

This was not the first time NECC had been in the spotlight; the company had been the target of several state and federal investigations between 1999 and 2011. Health professionals and state boards of pharmacy from at least seven other states had issued complaints to the Massachusetts State Board of Pharmacy regarding NECC's practices. The allegations included illegal solicitation, production of non-FDA approved drugs, and distribution of compounded products without a prescription.[9]

The most recent complaint was filed in April 2011, when a routine Colorado State Board of Pharmacy inspection identified NECC products without patient-specific prescriptions in a Colorado facility. This violated both Massachusetts and Colorado laws and resulted in the Colorado Board issuing a cease-and-desist order stating NECC was no longer allowed to ship products into Colorado.[9,10] However, as with previous complaints filed against NECC, the Massachusetts State Board of Pharmacy did not take formal disciplinary action against NECC, and a year after the cease-and-desist order was filed, more nonpatient-specific drugs were found in Colorado facilities during inspections.[9]

FDA investigated NECC on three separate occasions between 2002 and 2006, including twice for reports of adverse events linked to epidural steroid injections produced by NECC.[9] The inspectors found violations of sterility procedures, but their investigation was impeded when NECC challenged FDA's jurisdiction over the pharmacy and refused to cooperate. FDA issued written warnings to NECC on three separate occasions, but again, jurisdictional issues and the lack of proper oversight by the state officials allowed NECC to continue to operate.[9]

Compounding versus manufacturing

The regulation of compounding pharmacy has historically been left to individual states, while manufacturing falls under the jurisdiction of FDA. A major regulatory distinction is that manufacturers must adhere to a more stringent set of procedures and requirements, such as good manufacturing practices, national reporting of ad-

At a Glance

Synopsis: In this Commentary, the events leading up to and surrounding the multistate outbreak of fungal meningitis in the fall of 2012 are reviewed and subsequent actions analyzed. The New England Compounding Center (NECC), a Massachusetts-based compounding operation, had a decade-long history of citations from the Food and Drug Administration (FDA) and complaints to the Massachusetts State Board Pharmacy when the fungal outbreak began. A total of 751 cases and 64 deaths were associated with the use of NECC's preservative-free methylprednisolone acetate (MPA) for injection. The federal legislative response was passage of the Drug Quality and Security Act of 2013. It leaves jurisdiction of traditional compounding pharmacies with the states, but gives compounders the option to register as an "outsourcing facility."

Analysis: *While the United States Congress acted relatively quickly to pass legislation following the NECC tragedy, it remains to be seen whether the law will be sufficient to prevent similar tragedies in the future. Large-scale compounders are not required to register as "outsourcing facilities," and without FDA oversight that accompanies registration, past history suggests that the state boards of pharmacy are not adequately trained and staffed to oversee such operations.*