The Regulation of Compounding Pharmacies

The recent outbreak of fungal meningitis emphasizes the need for more efficient oversight.

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Pharmaceutical compounding is a method of preparing customized medications to meet the specific needs of physicians and patients. Examples of commonly used ophthalmic medications that must be created by a compounding pharmacy are fortified antibiotics, preservative-free formulations, discontinued medications, and specialty items such as bevacizumab (Avastin; Genentech) for intravitreal injection. Compounding pharmacies play an important role in ophthalmology by allowing physicians to prescribe individualized regimens. An improved therapeutic outcome may be achieved by the use of a compounded ophthalmic treatment, and, as is the case with bevacizumab, the compounded agent is often more cost-effective than a commercially available alternative.

Despite the advantages of pharmaceutical compounding, there are risks associated with this method of drug preparation. Poor practices can result in contamination or in products that do not possess the required sterility and quality. Unfortunately, compounding pharmacies are regulated by the states and are therefore not subject to the same regulations as large-scale drug manufacturers. Contaminated compounded drugs have been linked to outbreaks of infections such as endophthalmitis and, more recently, have caused a fatal outbreak of fungal meningitis. The adverse events associated with compounded drugs have caused patients, physicians, and lawmakers to question the safety of these pharmacies and the potential need for federal regulation of their practices.

REGULATIONS

In the United States, compounding pharmacies are licensed and regulated by their respective states. Most state boards of pharmacy use the United States Pharmacopeia's (USP) Chapter 797 guidelines in the development of regulations for compounding sterile preparations.

National standards have been created by the Pharmacy Compounding Accreditation Board (PCAB), which assesses pharmacies and awards the PCAB Seal of Accreditation to those that meet or exceed the PCAB requirements and comply with the terms of the PCAB program.

"The state boards of pharmacy that license pharmacies and pharmacists oversee their day-to-day operations," Sarah Clark-Lynn, of the US Food and Drug Administration (FDA) Office of Public Affairs, told *Retina Today*. "FDA also has some authority over drugs made by compounding pharmacies. The Agency can initiate enforcement action against a compounded drug if it is adulterated or misbranded in certain ways (eg, if the drug is contaminated or falsely labeled)."

Ms. Clark-Lynn explained that the law exempts some pharmacy compounding from certain requirements that are otherwise applicable to drugs manufactured for use in the United States. "For example, compounded drugs are not approved by the FDA and therefore do not undergo premarket review for safety and effectiveness," she said.

Unlike commercial drug manufacturers, compounding pharmacies are not required to report adverse events associated with compounded drugs, and unless a complaint is filed or a patient is harmed, drugs made by compounders are seldom tested. Only 2 states—Texas and Missouri—perform random testing of compounded drugs. The FDA therefore learns of adverse events only through voluntary reporting, the media, and other sources.[1] In turn, the FDA refers complaints to the states, provides support if requested, and cooperates in investigations and follow-up actions. If the states are unable to act, however, the FDA will proceed without them.

"When the Agency becomes aware of potentially contaminated or otherwise adulterated or misbranded compounded drug products, FDA investigates and works with its state counterparts to take appropriate action as quickly as possible," Ms. Clark-Lynn said.

RECENT OUTBREAKS

In October 2012, the Centers for Disease Control and Prevention (CDC) traced an outbreak of fungal meningitis to fungal contamination in 3 lots of preservative-free methylprednisolone acetate used for epidural steroid injections. The medication was packaged and marketed by the New England Compounding Center (NECC), a compounding pharmacy in Framingham, MA. Doses from these lots had been distributed to 75 medical facilities in 23 states. As of November 14, 19 states had reported cases, in which 461 people were diagnosed with meningitis and other infections associated with epidural injection, and 32 of these individuals had died.

In response to the outbreak, the Massachusetts Department of Public Health issued a recall of all NECC medications, and NECC announced that it was suspending all operations and voluntarily surrendering its licenses. On October 9, members of the US House of Representatives and US Senate requested that federal health officials provide them with briefings on the outbreak as a first step toward possible legislative action to strengthen federal drug safety regulation.

Adverse events caused by contaminated lots of compounded ophthalmic drugs have been reported as well. Last year, patients in at least 3 US states developed severe eye infections—some resulting in permanent blindness—after receiving bevacizumab injections. The FDA issued a statement alerting health care professionals that repackaged bevacizumab had caused the cluster of *Streptococcus* endophthalmitis infections that were reported by the Florida Department of Health. Investigators traced the infections back to a single compounding pharmacy in Hollywood, FL. This incident prompted the US Department of Veterans Affairs to temporarily halt its use of the drug and garnered great attention from the public and the media.

CONGRESSIONAL COMMITTEE

On November 14, the House Energy and Commerce Committee's investigations subcommittee held the first hearing on the outbreak of fungal meningitis tied to contaminated steroids from the NECC. At the hearing, lawmakers questioned FDA Commissioner Margaret A. Hamburg, MD, and accused the agency of failing to prevent the crisis by moving too slowly against NECC. The FDA and Massachusetts officials inspected the NECC more than 10 years ago after patients were hospitalized with meningitis-like symptoms, and they identified contamination of methylprednisolone acetate, the same drug at issue in the current outbreak, as the source. The Massachusetts Board of Registration in Pharmacy, which oversees the NECC, reportedly failed to carry out sanctions against the compounding pharmacy.[2]

In defense, Dr. Hamburg argued that new laws must be passed to give the FDA clearer authority to regulate compounding pharmacies as it does larger commercial drug manufacturers. "This isn't, sadly, an isolated incident," she said.[2] "This is the worst and most tragic. It should be the last wakeup call for us. We really need a strong, clear, and appropriate legislation. We cannot have a crazy quilt where different parts of the country are subject to different legal frameworks."

Dr. Hamburg suggested that traditional pharmacies stay largely under state control, with the FDA being able to have greater inspection authority. Nontraditional pharmacies and those that prepare drugs on a large scale in anticipation of prescriptions, rather than adhering to the traditional role of responding to individual physician's orders, should register with the FDA. Dr. Hamburg confirmed that the FDA is pursuing a criminal investigation into the NECC, and the Justice Department is investigating the company as well. The FDA plans to hold a meeting on December 19 with state officials to determine how best to regulate compounding pharmacies.[3]

CONCLUSION

While the regulation of compounding pharmacies continues to be debated, there are ways in which physicians can better ensure the quality and safety of compounded drugs. The type, quality, and quantity of the pharmacy's customers, as well as how many years the pharmacy has been in business, can be clues to its expertise. Pharmacies that are used largely by health maintenance organizations and universities have likely undergone extensive audits and selection procedures.[4] Physicians can take an active role in trying to guarantee that the drugs they deliver to their patients come from reputable sources until a more efficient surveillance system at the state and federal levels is in place. ■

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