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Quality Standards for Stock Supplies of Compounded Drugs Keep Patients Safe

Federal law ensures that compounders meet requirements to reduce public health risks

Overview

Medical providers may at times treat patients whose needs cannot be met by commercially available, Food and Drug Administration-approved products, such as a child who requires a liquid form of a medicine approved only as a pill. In these situations, providers can instead prescribe compounded drugs, which are made by pharmacists or physicians instead of drug manufacturers. To protect patient safety, compounded drugs must be made under quality standards appropriate to their risk.

Recognizing the serious harm that Americans face when compounding errors occur, Congress passed the bipartisan Drug Quality and Security Act of 2013 (DQSA) to ensure that facilities making these drugs operate under appropriate quality standards and oversight. Compounding for a single patient is a traditional part of pharmacy practice; states oversee patient-specific compounding and mandate quality standards for it. Bulk supplies of compounded drugs present greater risks because of their typically longer shelf life and larger batch sizes, so for compounders of non-patient-specific batches of drugs, the DQSA requires FDA to apply quality standards similar to those for drug manufacturers. Robust implementation and enforcement of the DQSA is necessary to make certain that patients who need compounded drugs have access to products made under quality standards that suit their risk.

Clinicians need office stock

In many cases, after a compounded drug is prescribed, it is compounded and dispensed to the patient, who then self-administers the custom-made drug. In other situations, clinicians need supplies of ready-made compounded products—office stock—to administer in a practice or hospital setting. Waiting for a pharmacy to fill a prescription may not be practical or possible if, for instance, a patient needs a drug sooner than a compounder could make or deliver it. Many hospitals maintain stocks of compounded injections for pain, for example.

Congress provided for clinicians' office stock needs in the DQSA by authorizing its production in compounding businesses called outsourcing facilities. These facilities must follow more stringent manufacturing practices than pharmacies dispensing compounded drugs for individual patients. They must register with FDA, and are subject to the agency's specific requirements and inspections, which vary in rigor and frequency depending on the potential risk posed by the type of compounding done in the facility.

Higher quality standards mitigate office stock's increased risks

Office stock products carry distinct risks for patients. They are often stored before use, which increases the opportunity for any contaminants such as bacteria and fungus to grow to dangerous levels.[1] Also, because they are not tailored to specific patients, these drugs are frequently produced in bulk—sometimes at significant scale—so more patients are potentially exposed to any lot of contaminated or substandard product.[2] In these ways, stock supplies of compounded drugs pose similar risks to FDA-approved drugs, which are also produced in larger batches with the expectation that it may be some time before they are used.

To mitigate these risks, Congress included a provision in the DQSA requiring FDA to establish quality standards—requirements for how to make and store drugs to prevent contamination or other potentially dangerous problems—for outsourcing facilities that are similar to those that apply to FDA-approved drugs made by pharmaceutical companies. The quality standards FDA applies to outsourcing facilities are called Current Good Manufacturing Practices (CGMP).

Compounders that do not make stock supplies of drugs—such as community pharmacies, hospitals, and physicians' offices that compound upon receipt of, or in anticipation of,[3] a prescription—are subject to different quality standards, established by the laws of the state in which they are located. Most states use standards established by the U.S. Pharmacopeial Convention (USP) to guide pharmacists on how to minimize risk when creating compounded drugs. These standards describe conditions and procedures that, if followed, help ensure compounded drugs' quality and prevent them from harming patients.

Prescription requirement helps ensure quality, accountability, and appropriate incentives

To ensure that all drugs are compounded under suitable quality standards and with appropriate oversight, it is essential that the two categories of business engaged in this practice—traditional compounders and outsourcing facilities—be clearly delineated and defined. Under the DQSA, the dividing line is the prescription requirement that federal law applies to state-licensed, traditional compounders. Delineating compounders in this way is critical to ensuring that all drugs are produced under suitable quality standards and with appropriate oversight, and that businesses that invest in quality are remunerated for that investment.

Quality

Even if a few doses of office stock product could be safely made under state standards, history shows that without a clear limitation, such as the prescription requirement, facilities that produce a few doses of product could grow to producing a few dozen, a few hundred, or a few thousand. Ultimately there would be no inherent check on their production scale. The prescription requirement ensures that stock supplies of drugs, which pose a greater safety risk because of their typically longer shelf life and larger batch sizes, are subject to the quality standards appropriate to bulk production and longer shelf life.

Safety concerns arising from bulk drug production at an unchecked scale in a facility regulated as a traditional pharmacy are not hypothetical. The federal DQSA was passed in response to an outbreak of fungal meningitis in 2012 and 2013, in which roughly 750 people became ill and more than 60 died after fungus-contaminated compounded drugs were injected into their spines and joints. Many surviving victims still struggle with chronic—and in some cases disabling—health problems, including pain and mobility challenges caused by the meningitis, and impaired memory and concentration, which are side effects of the antifungal medication that saved their lives from the infection. These people had all received injections from a compounding facility that had started as a small-scale pharmacy, and grew over time. Doses from just three contaminated lots were administered to more than 13,000 patients across the country.[4]

Accountability

The prescription requirement also creates clarity regarding whether FDA or the state in which a compounder is located is primarily responsible for overseeing compounding operations. States have primary authority when a product is dispensed or distributed for a particular patient. FDA is primarily responsible for oversight of office stock. Unlike other ways Congress considered to delineate traditional compounders and outsourcing facilities, the prescription requirement does not compel FDA or any state to search through pharmacy records or calculate geographic distances to determine which facilities are under its respective jurisdiction. The regulator merely determines whether the drug has a patient name on it. If the prescription requirement were eliminated (or if the prescription could be sent after the product was dispensed or administered), that clear line would be lost.

Incentives

Moreover, the prescription requirement preserves the incentive for outsourcing facilities to invest in the costly equipment, training, and specialized personnel necessary to comply with CGMP—all of which lead to safer drugs for patients. Current law is a market-based system. Substantial investments in quality give outsourcers access to a market in which they cannot otherwise participate: office stock. If the prescription requirement were compromised, the market incentive would also be compromised.

Conclusion

Federal policies around compounded office stock were designed by Congress in the DQSA to both preserve access to a category of medications that providers need to treat their patients, and to protect those patients from the risks of drugs produced under dangerous conditions.

Patient safety depends on whether compounders are required to follow quality standards appropriate to their level of risk. The law's dividing line between the two types of compounders—the prescription requirement for traditional compounders—is the only enforceable way to ensure that stock supplies of drugs are subject to the quality standards appropriate to longer shelf life and generally higher production volume. For these policies to serve public health and protect patient safety, the law's prescription requirement for traditional compounders must be preserved.

Endnotes

1 Reforming the Drug Compounding Regulatory Framework: House Hearing, Before the Subcomm. on Health of the Comm. on Energy and Commerce, 113th Cong. First Session (2013), (statement of Allan Coukell, senior director, drug and medical devices, The Pew Charitable Trusts), https://www.gpo.gov/fdsys/pkg/CHRG-113hhrg86394/html/CHRG-113hhrg86394.htm.

2 Eric S. Kastango and Katherine H. Douglass, "Quality Standards for Large-Scale Sterile Compounding Facilities" (2014), http://www.clinicaliq.com/images/stories/clinicaliq_compounding%20quality%20standards.pdf.

3 In circumstances where a pharmacist can anticipate receiving repeated prescriptions for the same compounded drug (e.g., if the pharmacist has an established relationship with a practitioner who commonly prescribes a particular product), the pharmacist can compound a supply of that drug in anticipation of that need, and then dispense or distribute it as prescription orders come in. This is known as anticipatory compounding.

4 U.S. Centers for Disease Control and Prevention, "Multistate Outbreak of Fungal Meningitis and Other Infections," accessed Oct. 17, 2017, https://www.cdc.gov/hai/outbreaks/meningitis.html; Rachel M. Smith et al., "Fungal Infections Associated With Contaminated Methylprednisolone Injections," *New England Journal of Medicine* 369, no. 17 (2013): 1598–1609, http://www.nejm.org/doi/full/10.1056/NEJMoa1213978.

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