Compounding Law Five Years Later
FDA Implementation Slow, Industry Criticism Significant
Stephen Barlas

It has been five years since the passage of the Drug Quality and Security Act (DQSA) meant to address safety concerns about compounded drugs.1 The Food and Drug Administration (FDA) is still laboring to fulfill the law’s provisions, which were intended to allow the agency to walk the fine line between assuring public safety while ensuring access to legitimately and safely compounded drugs. It is a tough balancing act, especially given the FDA’s chronic funding shortage, which impedes regulation development, inspections, and enforcement. At hearings in front of the House Energy and Commerce Committee on January 30, FDA Commissioner Scott Gottlieb, MD, admitted that the FDA’s compounding regulatory program “is a program where we do operate by, in some cases, begging, borrowing, and stealing from other aspects of the agency.”2

That said, under Dr. Gottlieb, the agency appears to be moving marginally more aggressively to meet substantial challenges than the FDA did under the Obama administration. But that hasn’t stopped industry groups from complaining about FDA inaction in numerous other cases. In an effort to calm the criticism, the FDA issued the multipart 2018 Compounding Policy Priorities Plan in mid-January, which specifically details how the agency will:

- Address manufacturing standards for outsourcing facilities;
- Regulate compounding from bulk drug substances;
- Restrict compounding of drugs that are essentially copies of FDA-approved drugs;
- Solidify the FDA’s partnership with state regulatory authorities; and
- Provide guidance on other activities that compounders undertake.3

The plan includes elements meant to both upgrade safety for purchasers and provide some flexibility for sellers of compounded drugs. In the latter category are what are referred to as traditional pharmacies, generally neighborhood drugstores doing compounding, and 503B “outsourcing facilities,” a new category of compounders created by the 2013 DQSA that are allowed to sell bulk quantities of compounded drugs across state lines without individual prescriptions. They are federally regulated and subject to current good manufacturing practices (cGMPs), which the FDA has struggled to establish.

Controversies Bedevil FDA Regulatory Program

The traditional pharmacies, called 503As, complain that the FDA does not allow them to provide more than a single prescription at a time to one purchaser, such as a physician who wants to keep a small stock on hand for patients who might need an immediate injection. The 503B outsourcing facilities say the FDA’s inspections are based on the cGMPs used to monitor the big drug manufacturers and are not targeted at 503Bs, which is what the DQSA required.

The 503Bs are supposed to be the main supply line for hospitals, but their numbers are much fewer than anticipated, in part because of the cost of registration with the FDA and in part because of what are viewed as unfair inspection standards. “I think many of us, when this law was first implemented, envisioned that that sector would grow much more quickly than it has,” Dr. Gottlieb said at the House hearings.2

Even for the 75 or so 503Bs that have registered, they have run into criticism because they can manufacture drugs from 200 “bulk substances” for which safety cannot be ensured, posing a potential problem to hospital patients who are the end users of 503B-produced compounds. These bulk substances, known as active pharmaceutical ingredients (APIs), are not FDA-approved and are only supposed to be used by 503B facilities when an FDA-approved version of the drug is not available.

The use of these compounds may put some 503B facilities that don’t use APIs at a disadvantage in terms of cost. “PharMEDium has seen a dramatic marketplace shift toward purchasing bulk-compounded versions of several critical drugs since these policies were issued,” said Jenn Adams, President of PharMEDium, when she testified before the House committee. “This trend threatens to undermine the federal drug approval system and adds additional safety risks for patients. Hospitals and other providers are not necessarily aware that they are receiving products compounded from bulk API rather than from approved drugs.”2 PharMEDiun, which has a 503B facility, is a subsidiary of AmerisourceBergen and serves thousands of hospitals across all 50 states.

Physicians and consumers buy compounded drugs from 503A pharmacies, which have existed since before the DQSA was passed. These traditional compounding pharmacies sell directly to physicians, dentists, and veterinarians, who pass along the drugs to patients. Sometimes patients buy the drugs from the pharmacy and bring them to the physicians for infusion or injection. The 503A pharmacies are regulated and inspected by the states based on individual practice statutes in a state, although the FDA can inspect them when allegations arise that a 503A is “manufacturing” drugs by providing them to physicians without first receiving a specific prescription. That would ostensibly make them liable as 503B facilities.

Shawn Hodges, PharmD, Vice President of the International Academy of Compounding Pharmacists (IACP), argued that the 503A section established in 1999 allows limited bulk compounding by traditional 503A pharmacies without first receiving an individual prescription, a contention buttressed by repeated

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Compounding Law Five Years Later

language from Congress in several recent appropriations bills, which the FDA has ignored. “Unfortunately, we have yet to see any significant movement away from the policies of the last Administration, nor have we seen a willingness to work with stakeholders towards improving the FDA’s compounding policies to better reflect the practice of medicine and pharmacy in the real world and the state laws and regulations that regulate those professions,” Dr. Hodges said.

The IACP is part of the DQSA Coalition, an organization backing the Preserving Patient Access to Compounded Medications Act of 2017, which was introduced by U.S. Representatives Morgan Griffith (R-Virginia) and Henry Cuellar (D-Texas) in June of last year. The legislation would clarify some of the outstanding issues about the DQSA in a way that is supported by pharmacy groups. But there has been no vote on the bill.

Gottlieb Argues “Great Strides” Have Been Made

At the contentious hearing in the House committee on January 30, Dr. Gottlieb argued the FDA had made “great strides” since 2013 when the DQSA was passed and, as the agency had announced earlier in the month, is committed to “taking a robust series of policy steps to continue to properly implement DQSA consistent with our public health mission mandated by Congress.” However, he added, “Unfortunately, there remain compounders whose practices present significant risks to patients.”

Congress passed the DQSA in 2013 after the 2012 fungal meningitis outbreak that resulted from a compounding pharmacy sending contaminated compounded drugs throughout the country, leading to more than 750 cases of illness and 60 deaths in 20 states. The bill set up the new DQSA program but didn’t resolve some of the conflicts over where state board of pharmacy regulations and state inspection end and FDA regulation and enforcement begins, especially with regard to 503A pharmacies. The FDA has been slow to clarify that dividing line having not finalized a draft memorandum of understanding (MOU) issued in 2015 that sought to clarify some of the state/federal confusion.

Safety Issues Remain

While pharmacy groups have criticized the FDA over state/federal uncertainties with regard to inspections, FDA inspections have been moving forward and have uncovered numerous instances of unsafe compounding conditions and practices. The federal agency has conducted nearly 500 inspections of 503A and 503B facilities between the passage of DQSA in 2013 and the end of fiscal year (FY) 2017. Dr. Gottlieb said inspectors have observed problematic conditions during the vast majority of these inspections and have overseen more than 150 recalls of compounded drugs and issued more than 180 warning letters. The FDA has issued more than 70 referral letters to state regulatory authorities for follow up on certain inspectional findings and is working with the Department of Justice on civil and criminal enforcement actions.

The risks are greater when it comes to sterile drugs. In some of its initial inspections, the agency found vermin, such as cockroaches, in the area where employees prepare for sterile processing; employees processing sterile drugs with exposed skin that sheds particles and bacteria; contamination, including bacteria and mold, in the environment where sterile drugs are produced; and much more. In some cases, pharmacies that produce drugs under these conditions ship them to health care facilities and patients nationwide. “While we have seen problematic conditions at both 503A and 503B facilities, the majority of the most concerning findings were associated with those regulated under section 503A,” Dr. Gottlieb explained. Though there has not been a public health disaster equal to the 2012 fungal meningitis outbreak, there have been some serious public safety breaches. In 2017, 23 patients in Texas had adverse reactions and vision loss due to steroid-and-antibiotic eye injections. Three infants in Indiana had serious adverse reactions after receiving compounded morphine sulfate that was nearly 2,500% more potent than it should have been.

Inspection Conundrums

But who is to inspect and against what standard? When 503B outsourcing facilities register with the FDA, it is clear they will be inspected by the FDA. But the FDA has never issued a regulation establishing cGMPs for 503B facilities and has basically adopted the cGMPs it uses for conventional drug manufacturers. Dr. Gottlieb acknowledged that the agency has to do a better job of targeting cGMPs based on the facility it is inspecting.

The FDA appears to be heading toward adopting a risk-based standard based on what the facility is compounding; the size of the facility; how many drugs it is developing; how they are shipped; and whether the drugs are oral or parenteral drugs that are going to be injected, which would be sterile drugs with a higher risk profile. “The idea is that, by trying to adjust the level of the regulatory oversight to the level of risk, we could potentially allow more 503A facilities to make the conversion into being 503B facilities,” Dr. Gottlieb said.

The agency estimated that the cost of becoming a 503B outsourcing facility for a large manufacturer under the current inflexible cGMP regime is about $1 million. For a medium-sized pharmacy, the cost is about $600,000. The shift to a “risk-based” inspection mindset with tailored cGMP requirements would ostensibly lower those costs substantially so that the pool of 503B outsourcing facilities would deepen.

But even after being registered and cleared of any inspection problems, a 503B outsourcing facility faces confusing post-inspection regulatory requirements regarding what ingredients it can and cannot use. Conceptually, 503B facilities are supposed to use sterile ingredients from FDA-approved drugs and packaging systems. They can deviate from that, based on a provision in the DQSA, when a drug is in short supply or the FDA determines that there is a “clinical need” that is not being met by approved products and includes the substance on a list of such ingredients. The FDA currently has a list of 200 of these APIs that 503B facilities can use and has a list of 65 for 503A pharmacies. However, the substances on those lists may not be sterile. The FDA is supposed to winnow down both lists, but has moved very slowly on the 503B list and not at all on the 503A list.

The FDA issued draft guidance in March 2018 that laid out how the agency intends to evaluate the 200 substances, which in fairness were all allowed to be used by compounding pharmacies before the DQSA was passed. Each evaluation of each API is between 20 and 80 pages long. Dr. Gottlieb said...
that he hopes to have decisions on the first five by this fall, but acknowledged that many of the bulk substances now on the list of 200 will be removed from the list eventually. What the FDA doesn’t want to do is pull too many bulk substances off the list too quickly for fear of creating access issues, especially with respect to the outsourcers because the numbers of 503B facilities are disappointingly small already.

PharmMEDiun’s Adams told the House committee that rather than starting with an FDA-approved finished vial of a particular drug, an entity can prepare simple dilutions or reconstructions from bulk APIs, enabling them to undercut the approved drugs and the drugs prepared by outsourcing facilities from approved drugs. The implication is that PharmMEDiun is being hurt financially. “In the above example of pain management epidurals, some compounders are substituting the FDA-approved finished drugs, such as a vial of fentanyl, with nonsterile API powders, despite the absence of a clinical rationale for doing so,” she said.2

According to PharmMEDiun, nonsterile APIs introduce risks into the compounding process that simply cannot be justified when a sterile finished drug can be used to meet patients’ clinical needs. For example, because current policies do not specify that outsourcing facilities must use a particular grade of API and testing is often limited to identity/potency, the resulting impurity profile is unknown and, therefore, uncharacterized. Furthermore, the company said terminal sterilization introduces additional complexities (e.g., endotoxins and pyrogens) that would not be expected in aseptic processing of already sterile finished drugs and components.

Traditional Pharmacies Want More Latitude

Whatever the level of concern about impure or unsafe drugs coming from 503B facilities, those concerns are apparently elevated with regard to 503A traditional pharmacies, which typically prepare prescriptions for physicians. In some cases, for example, physicians compound in their office. Physicians prepare allergens as part of immunotherapy, a process in which allergenic extracts or “concentrates” are combined in a sterile vial using sterile syringes.

The problem arises when a physician asks a 503A pharmacy to send over a number of batches of a particular compounded drug so the physician will have them on hand as needed. This is called “in-office” use and has been among the most controversial aspects of post-DQSA compounding. The law says that a 503A pharmacy needs to receive a specific prescription for each patient a physician wants to treat. The exception is where a state has signed an aforementioned MOU with the FDA committing to do certain things.

The FDA has argued that if a physician wants to get 10 prescriptions for a drug and store them in his or her office until a future patient needs an infusion or injection, he or she should purchase the 10 from a 503B pharmacy. But others argue that the 503B pharmacies won’t make shipments that are so small. When the FDA is alerted that a 503A pharmacy is shipping multiple drugs in a shipment without getting individual prescriptions, the agency then inspects that pharmacy as a 503B pharmacy (meaning against cGMPs), which no 503A pharmacy can measure up to.

However, a 503A pharmacy would not have to comply with cGMPs and still be able to dispense bulk amounts across state lines if it is in a state that has signed a MOU with the FDA. The requirement to establish an MOU was included in the 1997 Food and Drug Modernization Act that established Section 503A of the Food, Drug, and Cosmetic Act. The FDA produced an initial draft MOU in 1999 but never proceeded with it. The 2015 draft says unless a pharmacy is in a state that has signed an MOU with the FDA, it could not distribute more than 5% of the total prescription orders dispensed or distributed by that pharmacy or physician across state lines. This whole MOU issue is important only in the context of pharmacies with customers close by but on the other side of a state line.

For purposes of the MOU, a pharmacist, pharmacy, or physician would be considered to have distributed an inordinate amount of compounded human drug products interstate if the number of units during any calendar month is equal to or greater than 30% of the number of units of compounded and noncompounded drug products distributed or dispensed both intrastate and interstate by the pharmacist, pharmacy, or physician.

At the House hearings, Dr. Hodges of the IACP took the members of the committee through a lawyerly discussion of the language of the 1997 law setting up 503A, which he argued refers to “distribution” of compounded products, not “dispensing,” which is an important distinction the FDA has muddied in its 2015 draft MOU in which it defines “distribution” to include “dispensing.” That turbidity would end up disadvantaging pharmacies. The FDA conflated the two terms again when it published its Final Guidance for Industry (GFI) entitled “Prescription Requirement under 503A of the Federal Food, Drug, and Cosmetic Act” in December 2016.

Congress has, through multiple letters to the FDA and in report language in the last two FDA appropriations bills (FY16 and FY17), told the FDA their redefining of these terms in a sample MOU and in a GFI is an “overreach” and is “unprecedented” and inconsistent with congressional intent of the statute. “However, FDA continues to move forward with implementing compounding policies in a way that is inconsistent with the statutory language of this section of the Food, Drug, and Cosmetic Act and the definitions of these terms throughout federal and state law and congressional intent, which will threaten patient access to critical compounded medications,” Dr. Hodges said.

The FDA has been slow to fully implement the DQSA, although it always has to be underlined that the FDA is already overburdened and underfunded and lags with implementation of a number of laws, such as the multipronged CURES Act. Fortunately, the FDA’s lackadaisical approach on the DQSA hasn’t allowed any compounding tragedies to occur. But that may be more a matter of luck than anything else because it seems that quality is lacking within both 503A and 503B facilities in many instances.

REFERENCES

Vol. 43 No. 5 • May 2018 • P&T® 273
Compounding Law Five Years Later

continued from page 273


