WHITE PAPER

A Primer on Compounding Pharmacy Requirements

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By Lee H. Rosebush, JD

Traditionally, compounding pharmacies were small, had minimal federal oversight, and focused on making unique drug formulations to fill a local physician's request for a specific patient. The goal might be to eliminate an ingredient to which the patient was allergic, for example, or compound a high-dose formulation for an unusual case.

Over time, some compounding pharmacies began mass-producing larger supplies that were sold nationwide. In some cases, these were designed to fill unmet needs; in others, to offer consumer-friendly variations, such as a liquid format of a common pill, or a medication with added flavoring.

In 2013, the Drug Quality and Security Act (DQSA) changed how compounding pharmacies were regulated. The DQSA was enacted to improve drug supply chain security and to give the Food and Drug Administration (FDA) more authority to regulate and monitor the manufacturing of compounded drugs. The DQSA specifically cites the need for compounding to fill drug shortages and to provide customized products that are "essentially different" from what is commercially available.

Under the DQSA, there are now 503A and 503B pharmacies (see Table 1). The 503A category is similar to traditional compounding pharmacies. They remain primarily state-regulated and can only make formulations for an individual patient prescription. 503B pharmacies, however, are mainly FDA-regulated outsourcing facilities that must follow stringent quality and Current Good Manufacturing Practices (CGMP) requirements. In return, the 503Bs can make formulations to meet the needs of a clinic, hospital, or surgery center and provide them directly to the facilities and providers to help treat their patients.

The CGMP standards are the same standards to which large commercial pharmaceutical manufacturers are held. These ensure the identity, strength, quality, and purity of drug products and help to prevent drug contamination and errors. Although registration as a 503B facility is "voluntary," the CGMP standards are not. In other words, if a company wants to sell compounded products for office or facility use (without an individual patient prescription), it must follow CGMP.

CGMP standards ensure the identity, strength, quality, and purity of drug products and help to prevent drug contamination and errors.

It is also important to know that compounded medications (whether made by a 503A or 503B) that meet these specific standards are exempt from the FDA approval process by law. The standards include using approved substances when compounding and ensuring that the compounded product is not an exact copy of an approved drug product, with some limited exceptions.

TABLE 1: 503A AND 503B: WHAT'S THE DIFFERENCE?

	503A COMPOUNDING PHARMACY	503B OUTSOURCING FACILITY
Intended use of medication	Patient specific	Patient specific or stocked by health care facility
Main regulatory body	State pharmacy board	Food & Drug Administration
Regulatory standards	U.S. Pharmacopeia (USP) standards such as 795 and 797	Certain USP standards and Current Good Manufacturing Practices (CGMP) (21 CFR Part 210 and 211 and related FDA Guidance)
Reporting	Varies by state	Must report product list and adverse events to FDA
Inspection	State inspections	Mandatory FDA inspections and state inspections
Requirement for environmental monitoring	Based on USP	CGMP standards such as every production shift in primary compounding areas; weekly in secondary compounding areas

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What Surgeons Need to Know about Compounded Medications

By William F. Wiley, MD

I've been a longtime proponent of compounded medications, for many reasons. In most cases, compounded medications cost the patient less and are more convenient, because we can deliver them at the point of service. I don't have to worry that patients haven't filled the prescription, or the pharmacy has substituted a different drug from their formulary. More importantly, a combination drop in a single bottle (with or without an injected compounded medication at the time of surgery) eliminates all the confusion about what drop to use when. By controlling the medication and dispensing it at the surgery center, I'm more confident that patients will be compliant with their postoperative regimen.

Physicians rightfully have questions about the quality and legality of compounded pharmaceuticals, and it is important to know that not all compounded medications are the same. Here are answers to some of the questions I get asked regularly.

Benefits of Compounded Medications

- Lower cost to patient
- Eliminate pharmacy call-backs
- Eliminate pharmacy substitution
- More convenient dosing
- Avoid or reduce compliance problems

Q: Aren't compounded drugs riskier than branded pharmaceuticals?
A: Not necessarily. The FDA doesn't classify them as higher risk. Intraocular drugs (compounded or not) do carry a higher degree of risk than topical drugs. We can mitigate that risk by relying on suppliers with strict quality standards and long track records.

Q: How can I be sure that I'm using high quality compounded drugs?
A: As surgeons, we need to understand where the drugs we use or prescribe are being manufactured and what type of manufacturing standards they are held to. In the sidebar (page 6), I provide a list of 10 questions to ask a compounded pharmaceutical supplier. But the most important thing to know is whether you are purchasing from an FDA-registered 503B facility. 503B outsourcing facilities (such as ImprimisRx®) are FDA inspected and have to follow the same high manufacturing standards as commercial pharmaceutical companies. The FDA does have authority to inspect 503B facilities to verify that they comply with applicable good manufacturing practice regulations. In fact, the oversight of 503B facilities is in many ways more stringent than oversight of generic drug products, many of which are manufactured outside the U.S.

Q: Compounded drugs aren't FDA approved. How can I use them?
A: The FDA has specifically established standards and regulations for compounded pharmaceuticals, so it is well aware of the need for them. It is true that compounded combination products haven't gone through the FDA approval process in their combination form and compounded medications are not FDA approved, however, the individual ingredients have been evaluated through an FDA approval process and the agency has determined that the benefits outweigh the known risks for the intended use for the individual active ingredients. In ophthalmology, we routinely use medications outside of their FDA indications. For example, no antibiotic has been approved for endophthalmitis prophylaxis in cataract surgery, but most of us wouldn't operate without them.

Q: Is it complicated to use a compounding pharmacy?

A: For a new and unique need, it might be a little complicated to find a company to make exactly what you want. However, many useful products are already well established and available from compounding pharmacies. 503B outsourcing facilities are very easy to use.

Q: Should I be worried if a facility has gotten a Form 483 warning letter? Should I choose companies that have never gotten one?

A: Companies subject to FDA oversight are inspected and may occasionally get warning letters from the FDA about resolvable violations of Current Good Manufacturing Practices. Such letters are routinely sent to large pharmaceutical manufacturer, as well. Often, they address process violations that are easily corrected. Local 503A compounding pharmacies are not inspected or held to the CGMP standards so they would not be subject to warning letters. The fact that they haven't received one tells you very little.

Q: Will using compounded drugs jeopardize my ASC certification?

A: No. Self-compounding has been an issue for ASCs going through AAAHC certification, and many have had to stop making their own lidocaine or epinephrine preparations in house. However, certifying bodies should have no problems with the use of certified 503B compounded pharmaceutical products.

Q: Will using compounded drugs jeopardize reimbursement?

A: No. Physicians should check with their own third-party payer agreements, but in many cases pharmacy benefit managers and insurance plans would prefer drugs to be made under CGMP conditions, both from a drug wastage perspective and for pricing reasons.

Compounded medications cost the patient less and are more convenient.

Compounded medications have an important role to play in contemporary ophthalmic surgery. They offer more choices for physicians, compliance benefits, and good value for patients. But not all compounded medications are created equal. It behooves physicians to spend a little time investigating how long a compounding pharmacy has been around and what standards it adheres to. Registration as a 503B facility is the clearest indication of high-quality manufacturing standards and federal oversight of the facility.

WILLIAM F. WILEY, MD

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10 Questions to Ask When Choosing a Compounded Pharmaceutical Supplier

1	Where are your formulations made? Does your company own and manage these facilities?
2	How long has your pharmacy been making these formulations?
3	Are all of the formulations tested in an FDA-registered laboratory?
4	Is the laboratory testing every batch of your formulations for potency, sterility and endotoxins?
5	Is the "beyond use date" (BUD) determined using validated, stability-indicating methods and data from an FDA-registered laboratory?
6	Do you test the active pharmaceutical ingredient (API) raw material for potency before making new batches?
7	Is your supplier using validated warehouses to store finished product?
8	Can I order and store inventory of your product on my shelf to use as needed?
9	Does your supplier follow CGMP requirements when making and testing formulations?
10	Does your pharmacy participate in MedWatch, the FDA safety information and adverse event reporting program?

Why ImprimisRx®?

ImprimisRx is the nation's leading ophthalmic-focused outsourcing facility and pharmaceutical compounding business dedicated to delivering high-quality and innovative medicines at affordable prices. The state-of-the-art FDA-registered 503B outsourcing facility utilizes sophisticated equipment designed for sterile drug manufacturing to complete the compounding, filling, sealing, capping, weighing, labeling and inspection of each formulation, all meant to reduce the risk of human error.

All active pharmaceutical ingredients and raw materials are sourced from FDA-registered and inspected manufacturers. The materials are quarantined and undergo strict internal testing procedures by independent laboratories to verify critical product characteristics have been completely met before they are dispensed. There is a high degree of confidence in the equipment, facilities, certified staff, and the quality release requirements utilized in providing customers with unique, high-quality formulations.

The efficiency of the ImprimisRx business model allows the company to quickly innovate and deliver needed medications directly to patients at a low cost without the hassles of coupons, prior authorizations and pharmacy callbacks. ImprimisRx is patient focused; the company's mission is to partner with healthcare providers to ensure high quality medications are delivered at affordable prices.

Click here to learn more about the products offered at ImprimisRx.

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