Alliance for Pharmacy Compounding
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ISSUE BRIEF SEPTEMBER, 2024

Anticipating and Alleviating Drug Shortages

A 503A pharmacy is a traditional pharmacy that dispenses compounded medications **one patient at a time** (and only when those patients have prescriptions for a specific compounded medication).

503B outsourcing facilities operate on a larger scale, and are also required to follow federal sterility and manufacturing regulations. They typically **distribute larger quantities** of medications for use in healthcare facilities including hospitals, clinics, and veterinary offices.

When the supply chain fails, pharmacy compounders are there…

We've seen how fragile the pharmaceutical supply chain can be for so many reasons, causing FDA-approved drugs to disappear from hospital and pharmacy inventory. 503B outsourcing facilities were created in part to help provide a reliable and high quality alternative when FDA approved drugs — always the first choice for treatment — are "currently in shortage."

503Bs were established by federal law in 2013 to allow (highly regulated) bulk compounding for hospitals and healthcare facilities and to supply needed medications when there is no FDA-approved alternative. The 80 or so in the country are registered directly with the FDA and adhere to robust production standards similar to those required of major drug manufacturers.

That's why, when the FDA determines that the supply of a drug can't meet demand, the law allows 503B compounding facilities to prepare a copy. They are able to — and expected to — fill gaps in the supply chain.

You don't have to look far for a perfect example: In 2023, compounding pharmacies and outsourcing facilities literally saved children's lives by compounding amoxicillin suspension when it was in severe shortage and parents were frantic.

Point is, we have at our fingertips a way to reduce the impact of drug shortages, whether caused by manufacturing issues, supply-chain bottlenecks, or even tornadoes.

… but they need time, and incentive, to prepare

As critical as outsourcing facilities are to alleviating shortages, they can't turn-on production of a drug at the drop of a hat.

Just like drug manufacturers, outsourcing facilities must adhere to FDA's Current Good Manufacturing Practice (cGMP) regulations. But that means it can take 3 to 9 months for a 503B to accomplish the necessary testing and other requirements that will allow them to begin production of a drug that goes into shortage. And that's not taking into account the lag between when hospitals notice a shortage and drug makers report it to the FDA.

Worse, too often there's little financial incentive for a 503B to put in the time and expense to prepare a shortage drug if it may come back into supply the moment it begins distribution.

The bottom line is that there's a gap between when hospitals are hit by a shortage and when 503Bs can step in to help. In the meantime, patients may have to be administered a second-choice drug or even postpone treatment.

We can — we must — do better for patients. Here are two relatively easy policy changes that would go a long way to ensure patients' access to necessary medications:

1. **Better anticipate drug shortages.** Equip the FDA to take into account more and better information about shortages will allow it to recruit and prepare outsourcing facilities to produce shortage drugs.

2. **Reduce risk.** Incentivize 503Bs to produce shortage drugs by reducing their risk of losing a large investment if those drugs come off shortage sooner than expected.

Two easy fixes

Ensuring continuity of care while maintaining quality and safety isn't difficult when we take advantage of the nimble, flexible nature of compounding pharmacies and outsourcing facilities. Here are two ways to mitigate the effect of drug shortages, no matter what the cause:

Anticipating the shortages

The first people to notice drug shortages are often pharmacies and prescribers. Unfortunately, when determining whether a drug is actually accessible to patients, the FDA is limited by federal law to a single source of information: the drug manufacturers themselves. The result is an FDA drug shortage list that lags the market. Shortages seen by pharmacists and prescribers may not be noted by the FDA for months.

A more realistic process would include feedback from health systems, providers, pharmacists, and other stakeholders. By including that information, the FDA can better forecast when a drug will no longer be accessible to patients, allowing it to mobilize 503Bs to begin their production ramp-up. The lag may not be eliminated, but it's certainly reduced.

Reducing 503Bs' risk

Today, even after a potentially huge investment in production, once a drug comes off the FDA's shortage list, 503B outsourcing facilities must stop distributing the drug within 60 days. That short cut-off is one reason some outsourcers are reluctant to fill shortage gaps. Further, even when a drug is officially off the shortage list, it can take more than 60 days to actually reach hospitals and patients.

The solution is simple: **Extend that "tail" from 60 days to 180 days.** That will give 503Bs more incentive to step in, knowing they're guaranteed at least six months to recoup their investment, while also ensuring continuity of care for patients.

Of course there is still that gap between when a drug goes into shortage and when 503Bs can begin production. But by getting ahead of the curve — and providing an incentive to compounders — that gap can be reduced and the effect on patients reduced without introducing any additional expense or risk.

What we're asking

Senator Tim Kaine of Virginia's soon-to-be-introduced bi-partisan bill, the End Drug Shortages Act, would go a long way toward solving these issues by helping the FDA anticipate shortages sooner. He's working to identify a Republican co-sponsor, and is expecting to introduce a bill this session. With the current record number of drug shortages, we urge Senators to join in co-sponsoring and supporting it. Contact Samantha Koehler in Sen. Kaine's office (samantha_koehler@kaine.senate.gov) office for details.

In the House, Rep. Abigail Spanberger (D) of Virginia and Rep Adrian Smith (R plan to introduce an identical companion bill. For details, contact Lucy Schwartz on Rep. Spanberger's staff (Lucy.Schwartz@mail.house.gov) or Joel Keralis (joel.keralis@mail.house.gov) in Rep. Smith's office.

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BACKGROUNDER SEPTEMBER, 2024

5 Things You Need to Know About Compounded GLP-1 Drugs

1. Compounding pharmacies and outsourcing facilities are permitted to prepare copies of FDA-approved drugs, including GLP-1 weight loss drugs, when the drug appears as "currently in shortage" on the FDA Drug Shortage List — and it's not a loophole.

It doesn't matter that Eli Lilly says Zepbound is "available." Available doesn't mean accessible. Just because Taylor Swift tickets are "available" doesn't mean you have a good chance of getting one.

FDA's "Essentially a Copy" guidance is simple and clear. Copies of a drug listed as "currently in shortage" may be compounded, even if certain dosages are listed as "available." Both semaglutide and tirzepatide injection have been listed as "currently in shortage" since 2022. Notably, FDA's guidance doesn't make an exception for patented drugs. That's intentional — the agency wants to ensure patients have access to the medications they need even when the supply chain breaks down.

2. Fake and counterfeit drugs aren't the same as compounded medications.

Don't confuse legitimate, state-licensed compounding pharmacies with those fake online 'pop-up shops' offering what they say are GLP-1 drugs. *State-licensed* is the key — legitimate compounders are not only licensed by individual states, they're closely monitored, regularly inspected, and must adhere to the strict standards of the U.S. Pharmacopeia.

The problem of fake online pharmacies is so bad that a recent USC study found that as many as 40% of online "pharmacies" might be fake.

Two obvious red flags:

1. When a company claims to sell prescription medications online without requiring a prescription. It's not a licensed compounding pharmacy — and it's breaking the law.
2. If a store advertises a compounded drug by using a brand name (e.g., "Compounded Ozempic"), or says a compounded drug is FDA-approved. *Those are illegal claims, and legitimate compounding pharmacies know better than to make them*.

The easiest way to see if a pharmacy is a legitimate business is to look it up on the state's board of pharmacy website. ***(APC has links to all those sites at a4pc.org/isitlegit.)***

3. By definition, compounded drugs aren't FDA-approved.

They exist to fill the gaps when FDA-approved drugs aren't right for a patient or when commercial drugs simply aren't accessible.

Millions of patients use compounded therapies every day — drugs that are prepared especially for them. How do you approve a drug that's customized for a single patient? You can't. But it's a leap to suggest that because they're not FDA-approved, they are unsafe. In fact, federal and state law (and the compounding standards of the US Pharmacopeia) represent a rigorous quality and compliance framework in which state-licensed compounding pharmacies operate.

Want examples of "non-approved" compounded drugs?

- Compounding amoxicillin suspension for children when the drug was in severe shortage in 2023
- Preparing a mouthwash for cancer patients to help alleviate mouth sores resulting from chemotherapy
- Compounding post-op eye drops for cataract patients, combining multiple meds into a single, convenient bottle
- Medications for animals: Veterinary medicine relies on compounding because of the wide range of animal species they treat, from mice to elephants

While *an FDA-approved drug should always be the first-line therapy*, compounding is about ensuring patients have access to the exact medication their prescriber says they need — when they need it.

4. Compounders must source their ingredients from the same sort of FDA-registered manufacturers many pharma companies do.

When a company like Novo Nordisk says it doesn't sell its ingredients to compounding pharmacies, that's true. But it answers an unasked question. Currently there are more than 20 FDA-registered manufacturers of semaglutide listed on the FDA website. So why would a pharmacy need to buy it from Novo?

Under federal law, compounding pharmacies must source their active pharmaceutical ingredients from FDA-registered wholesalers who source API from the same kind of FDA-registered manufacturers that many pharma companies do — and the active ingredient (we call it the API) comes with a valid certificate of analysis and, often, third-party testing data.

You don't need to buy chocolate chips from Hershey to make a chocolate chip cookie. And compounders don't need to buy their ingredients from Novo Nordisk or Eli Lilly — not according to federal law. And besides, as they've stated repeatedly: Novo and Lilly aren't selling it.

5. FDA's July 2024 risk alert about GLP-1 dosing errors were about *prescribing*.

The "adverse events" the agency reported weren't about the quality of compounded drugs. They were about dosing errors — e.g., doctors starting patients at too high a dose, or patients ramping up dosage levels too rapidly. These errors happen with both compounded and FDA-approved versions of the drugs. (Want proof? Read how people are breaking open their Mounjaro pens to customize their doses. Quick link: a4pc.org/atlantic.)

Both pharmacists and providers are required to offer patient counseling when a drug is prescribed or dispensed, but patients often elect to forgo that counseling, and no doubt that has contributed to the problem FDA has pointed out.

What we're asking

No action required. With so much misinformation in the news, we want to make sure members of Congress have accurate information about compounded drugs. To assist pharmacy compounders in keeping patient safety front and center, we've created a document, "Best Practices When Compounding FDA-Approved Drugs Listed in Shortage." **It's available to anyone via a4pc.org.**

We've also created a 'one-stop shop' for anyone to verify that a pharmacy is licensed in their state so they can avoid being scammed — or worse — by bad actors. It's at a4pc.org/isitlegit.

Don't take our word for it. We're happy to help arrange a tour of a compounding pharmacy near you so you can see the care and compliance measures that protect patients. That invitation is open to both members of Congress and their healthcare staffers.
Contact info@a4pc.org to request a tour.

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ISSUE BRIEF SEPTEMBER, 2024

FDA's Proposed "Demonstrably Difficult to Compound" rule exceeds its authority and puts essential therapies at risk.

Proposal may set-up framework for future restriction of compounded hormones and other therapies that are used by millions of patients.

Background

The Food, Drug & Cosmetic Act provides authority to FDA to restrict compounding of drugs that are deemed to be "Demonstrably Difficult to Compound (DDC)." DDC drugs are those that may exceed the current capabilities of 503A pharmacies and/or 503B outsourcing facilities.

- **503A pharmacies** are traditional pharmacies that prepare and dispense compounded medications to individual patients based on a valid prescription. They're regulated and inspected by state boards of pharmacy.

- **503B outsourcing** are regulated by the FDA directly. 503Bs must adhere to current good manufacturing practices and are authorized to distribute compounded medications in bulk directly to hospitals or clinics, and in some states to 503A pharmacies, without a prescription.

Federal law requires FDA to have a list of specific DDC *drug products* for 503A pharmacies *and a separate list* of DDC drugs *and categories of drugs* for 503B Outsourcing Facilities.

APC's Concerns

1. ***The FDA has proposed a rule that would allow it to add entire categories of drugs to both the 503A and 503B DDC lists***. The FD&C Act states that the agency is allowed to add drug categories to the 503B DDC list. Only specific drug *products* can be added to the 503A DDC list. By adding categories of drugs to both lists, FDA exceeds its authority and sets up a pathway for restricting entire therapies — say, all compounded hormones or compounded GLP1 drugs — instead of an individual drug product itself. It's a distinction that matters both in law and to millions of patients who benefit from certain categories of compounded medications. FDA has long had its sights on compounded hormones, for instance – drugs that are widely prescribed to millions of patients and which have been safely compounded for a half century or more.

2. ***FDA's proposed rule uses the undefined terms "complex" and "complexity" without linking them***. Federal law requires that a DDC drug have a "reasonable likelihood that such difficulty will lead to an adverse event." Yet FDA does not establish the link between their use of complex/complexity and the potential for an adverse event.

3. ***The FDA is trying to do two things at once***. The proposed rule creates both the criteria for the DDC lists and looks to add three categories of drugs. These should be handled in two separate proposed rules. Notably, the 3 categories of drugs FDA is attempting to add are not being compounded at all to our knowledge.

4. ***FDA has not proposed any mechanism to make changes to the DDC list.*** Technology in compounding continues to evolve and what may be difficult today is not guaranteed to be difficult in the future.

What we're asking

The proposed rule's comment period ended June 18, 2024. APC and many other stakeholders have written to FDA to raise concerns about the agency's proposal and the overreach it represents. As FDA considers how to proceed, we urge members of Congress to reach out to the FDA to express concern and urge the agency to address these issues before releasing a final rule. For convenience, a sample letter accompanies this brief.

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FDA's Center for Veterinary Medicine is tightening the noose on animal drug compounding from bulk substances

Until recently, veterinarians kept a variety of compounded medications in stock for office use which allowed them to begin treatment immediately and reduce animal suffering. These medications also allowed veterinarians to have access to appropriate dosage forms or flavors that could be critical for driving patient and pet owner compliance. Recent action by the FDA is jeopardizing care and may result in additional patient harm.

FDA Guidance for Industry #256

- In April 2023, FDA's Guidance for Industry #256 (GFI#256) became effective.
- GFI #256 places new restrictions on compounding medications from bulk drug substances for office stock by dividing these medications among listed, not-listed, and under-review lists.
- Compounding pharmacies are only permitted to sell for office stock those drugs which are either on the "listed" or "under review" lists.
- To date, FDA has rejected 93% of the dosage forms and strengths of drugs that have been nominated. FDA's rejection essentially substitutes their medical judgment for that of the veterinarian and makes it non-compliant for pharmacies to sell to veterinarians as office stock many drugs that veterinarians have used as office stock for decades.
- If standard-of-care drugs are not able to be stocked in veterinarian's offices, pets and animals will be harmed.

- **503B Outsourcing Facilities**
  - FDA has recently announced that it is working on draft Guidance for Industry #256B (GFI #256B), for 503B outsourcing facilities.
  - While this guidance has not yet been published, the "listed, not-listed and under-review lists" procedure should not apply to animal drugs produced at 503Bs because 503Bs are not permitted to sell patient-specific drugs. If the principals of GFI #256 are applied to 503Bs, it is likely to eliminate the production of animal drugs in a 503B, further compromising access.

- **Inspections and "Untitled Letters"**
  - FDA is issuing and publishing "Untitled Letters" that are sent to compounding pharmacies following an inspection. The issues cited in the letters are not brought up during the inspection, discussed in the closeout session, or noted on a Form 483.
  - FDA threatens that failure to correct the issues noted in the untitled letter will cause the pharmacy to be inspected under cGMP.

What are we asking?

We're asking members of Congress to contact FDA's Center for Veterinary Medicine to express concerns about these restrictions – including the slowness in developing a robust set of "listed" drugs and the arbitrary nature of drugs they decline to add to the list. Specifically, ask CVM to:

- Place on the "listed list" nine critical drugs that veterinarians say are needed for office stock.
- Reduce the administrative burdens FDA has placed on veterinarians and pharmacies through it's GFI #256 Question and Answer documents.
- Ensure that GFI #256B does not apply the listing review and decision process of GFI #256 to 503B facilities.
- Maintain transparency with pharmacies during the inspection process and to adhere to broad interpretation of GFI#256 guidelines rather than a severely restricted one that will result in reduced access to medications and increased patient suffering.

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