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Dispensing Compounded Drugs from a 503B Outsourcing Facility and the Prohibition on Wholesaling Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Lee Rosebush (BakerHostetler)
Marc Wagner (BakerHostetler)

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The Federal Food, Drug and Cosmetic Act (FD&C Act) provides for a bifurcated compounding framework: Section 503A and Section 503B. Separating the types of compounders, quality standards, federal oversight, and activities each compounder may perform is a complementary system because patients should have access to compounded drug products when necessary. As a policy consideration, drugs approved by the Food and Drug Administration (FDA) should be used whenever available and appropriate for a given patient based on a prescriber's clinical judgment. However, there are many scenarios where a compounded drug may be necessary—for example, if the FDA-approved drug is in shortage and therefore unavailable, as patients benefit from compounded drugs over no drug at all. Additionally, patients may have allergies to certain components found in FDA-approved drugs and the compounder can formulate a drug product that does not contain the allergen. Patients may also need a different dosage form or strength than is available in an FDA-approved drug product. These are just three examples of when a compounded drug may be indicated as determined by a prescriber.

Section 503A

Compounding pharmacies that engage only in patient-specific compounding are likely operating under Section 503A of the FD&C Act.[1] Section 503A applies to all state-licensed pharmacies engaged in compounding drugs including retail pharmacies, hospital pharmacies, and pharmacies specializing in drug compounding that compound and dispense products based on a prescription or order for an identified individual patient (and in some limited instances, based on a history of receiving valid prescription orders). Compounders operating under Section 503A, in theory, should be compounding smaller quantities of drugs than those operating as Section 503B outsourcing facilities because the 503A compounders should be compounding pursuant to patient-specific prescriptions. Because of the patient-specific limitation, 503A compounders are exempt from following current good manufacturing practices (CGMPs)—the quality standard that both FDA-approved drug manufacturers and outsourcing facilities adhere to. In lieu of the CGMPs, most states have adopted USP compounding standards for Section 503A compounders. Other differences include that Section 503A compounders are not registered with the FDA and do not report the products that the 503A pharmacy compounds to the FDA. The 503A pharmacies have

less federal regulatory oversight than Section 503B outsourcing facilities. Therefore, Section 503A pharmacies are primarily regulated by the state boards of pharmacy.

Section 503B

Congress created "outsourcing facilities" in Section 503B of the Drug Quality and Security Act of 2013 (DQSA). The law was designed to protect the safety of compounded medications after deadly contamination occurred at the New England Compounding Center (NECC). Previously, there were questions about whether large compounders, like NECC, were subject to federal regulation and oversight. But, since the passage of the DQSA more than a decade ago, 503B outsourcing facilities have been required by law to register with the FDA, undergo periodic risk-based FDA inspections, and meet the same robust CGMP manufacturing safety and quality standards as prescription drug manufacturers.

Outsourcing facilities work to tailor prescription drugs to patients' unique medical needs in a variety of ways—for example, producing a drug without an allergen that an FDA-approved product might typically contain, formulating a different dosage, or an alternative form of administration. When a drug is listed on FDA's drug shortage list, 503B outsourcing facilities are statutorily permitted to compound from bulk drug substances, also known as active pharmaceutical ingredients or APIs. As such, outsourcing facilities are a tool to address clinical need during drug shortages.

Generally, Section 503B of the FD&C Act prohibits 503Bs from wholesaling compounded human drug products.[2] However, the statute plainly excludes administration in a health care setting and *dispensing* pursuant to a patient prescription from this prohibition.[3] Because "dispensing" is not included in the prohibition on wholesaling, under federal law, the FDA has recognized that a 503B entity could sell a compounded human drug product to a state-licensed pharmacy or physician, as long as the state-licensed pharmacy or physician then dispenses the product to a patient pursuant to a prescription. This activity is distinguished from the prohibited act of a 503B entity selling to a state-licensed distributor, or pharmacy, which would then transfer, sell for office use, or wholesale the compounded product to another pharmacy or dispensor. One transaction between the 503B entity and purchaser before dispensing is permissible because it is exactly what occurs when a hospital purchases compounded drug product from a 503B pharmacy and then the hospital pharmacy subsequently fills a medication order for the compounded product to a patient. The wholesaling prohibition operates to prohibit any further distribution of compounded products to downstream entities.[4]

Under the FD&C Act, drug products that are compounded by 503B entities are eligible for certain exemptions from the statutory requirements including submission of new drug applications and labeling products with adequate directions for use, as long as the 503B entity meets certain criteria.[5] Under Section 503B of the FD&C Act, one such criterion is the prohibition of 503B facilities from wholesaling the compounded product. Specifically, the DQSA states that a drug compounded by a 503B entity can qualify for the aforementioned exemptions if "[t]he drug will not be *sold* or *transferred* by an entity other than the outsourcing facility that compounded such drug."[6] The statute then clarifies that the aforementioned restriction "does not prohibit administration of a drug in a health care setting or *dispensing* a drug pursuant to a prescription executed in accordance with section 503(b)(1)."[7] Section 503(b)(1) of the FD&C Act requires that certain products be dispensed pursuant only to a prescription. Specifically, the statute states that "[a] drug intended for use in man . . . shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug. . . ."[8] Further, the statute also requires that the compounded product be labeled with certain information prohibiting *resale*, specifically the phrase "not for resale."[9] To "dispense," however, is distinct from resale. The resale of a compounded drug that is labeled "not for resale" in accordance with Section 503B is a prohibited act.[10] Dispensing to patients, however, is permitted.

Despite what appears to be clear statutory authority for a pharmacy to dispense drug product compounded by an outsourcing facility, further clarification was needed because historically many state boards of pharmacy would not allow pharmacies to dispense drugs compounded by 503B outsourcing facilities. The most common rationale for this contradictory view held by certain state boards of pharmacy was that the labeling "not for resale" meant that the compounded product could not be sold. However, taking this interpretation to the extreme—no hospital would then be able to use compounded drugs from outsourcing facilities if the hospital charged for the drug because, based on this reading of the statute, charging for a drug would be a "resale." Nonetheless, certain state boards maintain restrictive views on the prohibition on wholesaling.

FDA's Draft Guidance

On June 27, 2023, the FDA published a guidance document called: *Prohibition on Wholesaling Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry.*[11] In this draft guidance, the FDA provides examples of activities prohibited by the wholesaling provision and also activities *not* prohibited by the wholesaling provision.

Section 503B prohibits outsourcing facilities from wholesaling their products as one mechanism to preserve the integrity of the drug approval process.

> One of the conditions that must be met for a drug compounded by an outsourcing facility to qualify for the exemptions in section 503B of the FD&C Act is that the drug "will not be sold or transferred by an entity other than the outsourcing facility that compounded such drug." However, this provision "does not prohibit administration of a drug in a health care setting or dispensing a drug pursuant to a prescription executed in accordance with section 503(b)(1)."

Until this draft guidance, the FDA has never clarified its interpretation of the second clause in the prohibition on wholesaling: "does not prohibit administration of a drug in a health care setting or dispensing a drug pursuant to a prescription executed in accordance with section 503(b)(1)."

As is expected, the FDA confirms that an outsourcing facility may not sell a drug it compounded to a wholesale distributor, manufacturer, repacker, or relabeler that sells or otherwise transfers the compounded drug. Additionally, the FDA explains that an outsourcing facility runs afoul of the prohibition on wholesaling when a third party (e.g., a marketing firm or operator of a website that is not a pharmacy) sells a drug compounded by the outsourcing facility, even though the third party does not take physical possession of the drug, by providing services (e.g., training, billing, advertising) to the physicians that prescribe the drug and then bundling the cost of those physician services with the cost of the drug.

Outsourcing facilities may, however, engage in several activities that are not prohibited by the wholesaling prohibition. For example, according to the FDA's guidance, the following activities are not subject to the wholesaling prohibition:

1. moving a drug it compounded to another location (e.g., a warehouse) that is part of the same outsourcing facility (i.e., at the same address or geographic location) for subsequent distribution;
2. distributing a drug it compounded (without obtaining a patient-specific prescription) to a health care professional, hospital, or health system who administers it in a health care setting (e.g., in a hospital or the physician's office);
3. distributing a drug it compounded (without obtaining a patient- specific prescription) to a health care professional, hospital, or health system who dispenses that drug to patients pursuant to prescriptions;
4. distributing a drug it compounded to a state-licensed pharmacy, federal facility, or licensed physician, which subsequently dispenses the drug pursuant to a prescription; or distributing a drug it compounded

> to an entity that provides health care services (e.g., a hospital or health system, health clinic, or physician's office) for administration in that specific health care setting based on pricing agreements the outsourcing facility negotiated with a third party (e.g., group purchasing organization (GPO)) acting on behalf of the health care services entity.

FDA's guidance has been anticipated by industry for years. This draft guidance should clarify what constitutes federally permissible activities to state regulators.

State Board of Pharmacy Reactions

State board of pharmacy reactions to the FDA's draft guidance have been mixed.

Some state legislatures expressly provide for pharmacy dispensing of 503B compounded drugs since the issuance of the FDA's draft guidance. For example, the Nevada Governor signed SB 161[12] into law adopting the principles set out in the FDA's guidance. Likewise, the South Carolina legislature amended the Pharmacy Practice Act to clarify that any person or entity authorized to dispense drugs including, but not limited to, a pharmacy, institutional pharmacy, or practitioner, may purchase or otherwise acquire drugs compounded or repackaged by an outsourcing facility directly from the outsourcing facility without an order from a practitioner other than, when applicable, the practitioner purchasing or acquiring the drug; and administer and dispense drugs purchased or acquired from an outsourcing facility.

Alabama and Mississippi, however, have rejected FDA's interpretation of the wholesaling prohibition.

In its August 2024 newsletter, in a section on compounding semaglutide, the Alabama Board of Pharmacy stated: "At this time, 503B outsourcers may not supply medications to pharmacies for delivery to patients. In June 2023, FDA released draft guidance to remove the prohibition on wholesaling under 503B. However, this is a draft only and specifically states the draft contains nonbinding recommendations and is not for implementation." The newsletter did not distinguish or clarify whether an outsourcing facility may supply medications to hospital pharmacies for administration. Additionally, even final FDA guidance contains the statement: "Contains Nonbinding Recommendations." Outsourcing facilities, pharmacies, and prescribers should take note of Alabama's restrictive stance, which will limit patient access to medications.

Similarly, in its July 2024 newsletter, the Mississippi Board of Pharmacy stated:

> Mississippi Pharmacy Practice Regulation, Article XXXI Compounding Guidelines does not permit pharmacies to offer compounded human drug products to practitioners or other pharmacies for resale or dispensing. We believe this regulation is consistent with the original intent of 503B outsourcing pharmacies supplying products only to hospitals and clinics for administration by a clinician. In Mississippi, products compounded by a 503B outsourcing pharmacy may not be dispensed to a patient unless the 503B directly dispenses the product to the patient. Outsourcing facilities, hospitals, health systems, prescribers and state-licensed pharmacies should take note of the opportunities presented in this guidance as the supply chain for quality compounded drugs and mitigation efforts for drug shortages is shaped by this consequential policy.

While Mississippi did clarify that hospitals may administer drugs compounded by outsourcing facilities to patients, Mississippi's restrictive stance will limit patient access to medications compounded under current good manufacturing practices.

Conclusion

The prohibition on wholesaling under Section 503B of the FD&C Act prohibits FDA-registered outsourcing facilities from wholesaling compounded drugs. Yet, the text does not prohibit administration of a drug in a health care setting or *dispensing* a drug pursuant to a prescription. Thus, the wholesaling prohibition operates to prohibit any further distribution of compounded product to downstream entities but allows for downstream entities to dispense to patients. This interpretation was recently confirmed in FDA's draft guidance. From a policy perspective, allowing pharmacies to dispense drugs compounded by outsourcing facilities increases the availability of drugs that are compounded at the CGMP level, which is the same quality standard that conventional drug manufacturers follow. This is extremely important for patient access, especially for those drugs in shortage. Encouraging compounding at this robust quality standard ensures that the highest quality compounded drugs will reach patients. For instances where CGMP compounding is not feasible, compounders compounding under Section 503A pursuant to a patient-specific prescription can meet the clinical need for compounded drugs. Because FDA-registered outsourcing facilities are regulated at both the federal and state level, outsourcing facilities and pharmacies must know and understand the state landscape for the regulation of compounded drugs. Certain states defer to the FDA on the interpretation of the wholesaling prohibition; other states have expressly codified FDA's interpretation in state law, and still other states are resistant to new entrants in the pharmacy space and instituted restrictive interpretations that could potentially harm patients and limit access to drugs compounded under CGMP.

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[1] 21 U.S.C. § 353a.

[2] FD&C Act 503B(a)(8).

[3] *Id.*

[4] For example, a 503B entity may not sell compounded human drug product to a wholesaler who then sells the compounded human drug product to a hospital, pharmacy, or physician. This activity is expressly prohibited under Section 503B. *See* FD&C Act 503B(a)(8).

[5] FD&C Act Section 503B(a).

[6] FD&C Act 503B(a)(8) (emphasis added).

[7] *Id.* (emphasis added).

[8] FD&C Act 503B(b)(1).

[9] FD&C Act 503B(b)(10)(A)(iii)(IX).

[10] FD&C Act 301(ccc)(1).

[11] FDA, Prohibition on Wholesaling Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry (June 2023), https://www.fda.gov/media/169838/download.

[12] https://www.leg.state.nv.us/App/NELIS/REL/82nd2023/Bill/9870/Overview.

