



Market for Compounded Drugs Needs Greater Transparency and Regulatory Certainty

FDA, states, and hospitals can help improve access to customized medications

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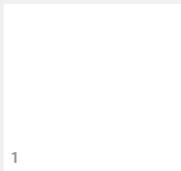
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This report benefited from the insights and expertise of Jane Axelrad, principal at Axelrad Solutions LLC, and Erin Fox, senior director, Drug Information and Support Services, University of Utah. Although they have reviewed the report, neither they nor their organizations necessarily endorse its findings or conclusions.

Acknowledgments

The authors are grateful to Kalah Auchincloss of Greenleaf Health, who provided significant assistance in the drafting of the final report, and Brian Williamson and Greg Rockers of the Williamson Rockers Group, who consulted on the project and offered input on the interview guide and on the identification of interview subjects. Although they have reviewed the report, neither they nor their organizations necessarily endorse its findings or conclusions.

We also thank former Pew staff member Kate Barker, who managed a significant portion of the data collection process and performed the initial analysis of the findings.



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The Pew Charitable Trusts is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public, and invigorate civic life.

Overview

Many hospitals and medical practices rely on compounding pharmacies to produce drugs that meet patients' clinical needs when available medications approved by the U.S. Food and Drug Administration (FDA) cannot. For example, compounders can make liquid formulations of products for people unable to swallow pills; combine pharmaceuticals to simplify their administration in trauma care; or dilute medications to strengths not offered by commercial manufacturers. While these compounded drugs can pose serious risks—they have not been reviewed for safety and efficacy and are typically not subject to the same quality standards as FDA-approved products—they are essential for some patients.

Health care providers can write prescriptions for compounded products that patients can fill at pharmacies. Clinics and hospitals can also procure larger amounts of certain compounded medications—known as “office stock”—directly from compounders to keep on-site and administer to patients as needed. Only businesses registered with FDA as outsourcing facilities may compound office stock; these facilities can also compound products that are listed on FDA's Drug Shortages List, which the agency updates on a regular basis.

Some hospitals and health systems have anecdotally reported trouble acquiring office stock. The American Society of Health-System Pharmacists (ASHP) surveyed members on this topic in 2019, and respondents named several specific compounded medications that had been difficult to procure in the previous six months.

The Pew Charitable Trusts conducted interviews with representatives from six outsourcing facilities to understand what may be driving these market challenges. Participants received a list of 20 office stock products deemed hard to acquire by some ASHP survey respondents. (See Table 1.) Interviewees were then asked to identify key factors that could make obtaining the products difficult.

Four themes emerged from these interviews:

1. Product-specific challenges can drive up the manufacturing cost of certain drugs, making them less attractive investments for compounders.
2. A lack of market transparency can lead office stock purchasers to experience access challenges even when adequate supplies are available from outsourcing facilities.
3. Regulatory uncertainty may deter companies from compounding certain products.
4. The often short-term, unpredictable nature of FDA-declared drug shortages can disincentivize compounding of office stock to help health systems manage these situations.

Addressing these challenges will require a range of interventions, some of which have been previously proposed or are already underway. Some examples:

1. FDA can improve management of its drug shortages process to give outsourcing facilities more certainty about the expected duration and severity of shortages. This information would help compounders better assess the business feasibility of producing drugs in times of shortage.
2. Outsourcing facilities and trade groups can enhance transparency with additional outreach to health care providers about their products and capacity. Hospitals and other providers could also participate in group purchasing organizations that negotiate collective agreements between medical product suppliers and multiple collaborating health systems that include smaller hospitals that may have more challenges procuring office stock products on their own.
3. Health care systems and providers can standardize their orders of office stock formulations rather than ordering multiple different formulations, which would create incentives for outsourcing facilities to increase the supply of these products.

4. FDA can continue to support the development of a robust compounding market by finalizing its guidances for industry and continuing to conduct regular inspections of outsourcing facilities.
5. States can ensure that their laws and regulations for compounders are clear, consistent, and in alignment with federal law. For instance, as of 2018, 11 states still had policies allowing compounders other than outsourcing facilities to make office stock products, which conflicts with FDA regulations.

These actions could significantly improve access to high-quality compounded office stock for hospitals and other medical facilities across the nation.

Table 1

List of Compounded Office Stock Drugs Discussed in Outsourcing Facility Interviews

Product	Category
Buffered lidocaine (any form)	Local anesthetic
Bupivacaine and epinephrine injection	Local anesthetic
Calcium chloride injection	Fluids and electrolytes
Calcium gluconate injection	Fluids and electrolytes
Cardioplegia solutions	Critical care-cardiovascular
Cefazolin in 0.9% NaCl (sodium) bottle	Critical care-anti-infective and other surgery
Dexmedetomidine	Trauma/Emergency department
Epinephrine	Critical care-cardiovascular
Fentanyl syringe	Pain management
Heparin	Critical care-cardiovascular
Hydromorphone PCA	Pain management
Lidocaine with epinephrine	Local anesthetic
Lidocaine, epinephrine, and tetracaine (LET or LAT) gel/solution	Local anesthetic
Morphine syringe	Pain management
Nicardipine	Critical care-cardiovascular

Continued on next page

Phenylephrine in 0.9% NaCl bag	Critical care-cardiovascular
Phenylephrine syringe	Trauma/Emergency department
Ropivacaine 0.2% with epinephrine	Local anesthetic
Sodium bicarbonate injection	Fluids and electrolytes
Sufentanil	Pain management

Source: Unpublished data shared by the American Society of Health-System Pharmacists

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Federal action creates safeguards for compounded office stock

In 2012, contaminated compounded injections sold as office stock by a single pharmacy caused a fungal meningitis outbreak that killed more than 100 people and sickened an additional 793 people in at least 20 states.¹ The tragedy helped expose lagging federal and state oversight of compounders, particularly those that produced large quantities of drugs without appropriate manufacturing quality standards. In response, Congress passed the Drug Quality and Security Act (DQSA) of 2013 to strengthen oversight of the compounded drug market.² The law reinforced that traditional compounding pharmacies—also known as 503A pharmacies, after the section of the Food, Drug, and Cosmetic (FD&C) Act that outlines the basic requirements they must meet—can compound a product only in response to a patient prescription.³ Provided certain conditions are met, these products are exempt from FDA approval, certain labeling requirements, and stringent manufacturing standards known as current good manufacturing practices (CGMP).

The law also established a separate category of compounder known as an outsourcing facility or 503B facility (again, after the relevant section of the FD&C Act). Unlike 503A pharmacies, outsourcing facilities may supply drugs without first obtaining a patient-specific prescription, but they are held to CGMP standards, and must register with and submit to regular inspections by FDA. Outsourcing facilities may compound office stock using FDA-approved products—for example, diluting a drug into a less concentrated form. They may also make medications from bulk drug substances—the active ingredients in approved drugs—if FDA determines a drug is in shortage or if there is a clinical need for such a product. (See Appendix 1 for a more detailed comparison of the regulatory requirements applicable to 503A pharmacies and 503B facilities.)

The requirements and restrictions placed on outsourcing facilities are intended to mitigate the distinct risks associated with office stock products, which are often stored before use—increasing the time for bacteria or fungus to grow—and may be administered to a large number of patients in many states.

FDA has taken a range of actions to implement the DQSA and to further define the regulatory framework for compounded pharmaceutical products, including office stock. Among other efforts, it has issued draft guidances on CGMPs applicable to outsourcing facilities, held a public meeting on these standards, and is working to establish a Compounding Quality Center of Excellence that will include training for outsourcing facilities on CGMP requirements and how to identify and address insanitary conditions that can lead to patient harm.⁴ FDA is also developing a list of bulk drug substances for which there is a clinical need to compound, known as the 503B Bulks List, that outsourcing facilities may use in their compounded products.⁵

However, the regulatory framework for 503B facilities is still under development, and the outsourcing facility industry is relatively nascent. Some pharmacy groups have questioned whether outsourcing facilities can meet the demands of health care providers and have argued that 503A pharmacies should also be permitted to supply office stock, despite the statutory requirement that they must first obtain a patient-specific prescription.⁶ In response to anecdotal reports that health care providers are experiencing difficulty in accessing certain office stock products, Pew conducted interviews with representatives from six outsourcing facilities to better understand the factors that may be contributing to these challenges and to identify potential policy solutions that could help to address them. In advance of the interviews, each participant received a list of 20 office stock products that had been previously identified as challenging to acquire within the previous six months by providers who responded to a member survey fielded by the American Society of Health-System Pharmacists in the summer of 2019. For a more detailed description of the study methodology, see Appendix 2.

Barriers in an evolving office stock market

During the interviews, the outsourcing facility representatives highlighted a range of issues that might contribute to office stock access challenges, which varied depending on the product in question.

Product-specific business challenges

Interviewees at all six outsourcing facilities frequently cited business concerns that contributed to access challenges. Interviewees explained that their companies must take into account the cost of production versus the potential revenue stream from each product. In some cases, the investment may not seem worthwhile. This can be an issue for low-priced drugs that require high volume production and sales to generate revenue; medications that require large upfront capital investments in facilities or equipment; or those that are technically challenging—and therefore expensive—to compound.

For example, four of the 20 drugs discussed—hydromorphone, morphine, fentanyl, and sufentanil—are controlled substances. A 503B facility seeking to manufacture these products from bulk drug substances must obtain a quota allocation for those ingredients from the Drug Enforcement Administration (DEA), which can be difficult.⁷ The facility must also comply with additional requirements, such as registering with DEA and complying with certain labeling, packaging, and record-keeping requirements established by FDA.⁸ Only one business among the six interviewed reported compounding controlled substances.

Beta-lactam antibiotics such as cefazolin also require significant capital investments. These products can cause severe allergic reactions and must be compounded in a separate room or facility to prevent contamination of other compounded medications.⁹ For that reason, some interviewees said their companies choose not to compound these antibiotics.

Other compounded products do not require expensive investments in facilities or equipment but are nonetheless technically challenging and therefore less attractive business investments. For example, one interviewee explained that lidocaine is acidic and can cause patients pain when injected. If compounded with a buffer, typically sodium bicarbonate, such discomfort is reduced. However, the buffered solution is unstable and therefore has a short shelf life or “beyond use date” (BUD). In addition, 503B facilities must test their products before distribution, shrinking the brief time available for sale and use of the office stock before it expires. Compounders may have difficulty finding buyers for such drugs. Interviewees noted that anesthetics with epinephrine, such as the lidocaine-epinephrine-tetracaine (LET) gel or solution, also have short BUDs.

Still other products are requested in such a variety of formulations that office stock compounding may become impractical. Compounding a standard formulation of a product in large batches supports increased quality and

efficiency, which better enables an outsourcing facility to make the product.¹⁰ Interviewees noted that there is no established industry standard for some compounded products, including hydromorphone, phenylephrine in 0.9% NaCl, and cardioplegia solutions. The formulations sought may vary between hospitals and other customers,¹¹ making it difficult for a 503B facility to compound every variation or produce any particular one in a large enough quantity to justify the investment.

Finally, some products are difficult to compound because the active ingredients or other component parts such as packaging are in short supply, or because the mechanism of administration is complicated. For example, interviewees reported shortages of heparin derived from pigs following a swine flu outbreak, as well as sodium chloride (NaCl) and IV bags, which has affected production of compounded drugs such as phenylephrine in 0.9% NaCl (bag) and cefazolin in 0.9% NaCl (bottle). According to interviewees, products in IV bags also require manual rather than automated filling, making their manufacture more time-consuming. This reduces the volume of product that 503B facilities can make and sell, further deterring compounding of such medications. Similarly, ropivacaine with epinephrine is administered via an elastomeric pump, which complicates and increases the expense of the manufacturing process.

In short, products that require significant upfront investments in facilities or equipment or that are technically challenging or otherwise difficult to compound may not be attractive candidates for outsourcing facilities, contributing to provider access challenges.

Lack of market transparency

Interviewees were surprised to see some products on the list, including phenylephrine (syringe) and phenylephrine in 0.9% NaCl solution (bag); calcium chloride; calcium gluconate; and the LET gel/solution. They noted that these drugs were among those offered by their businesses. This incongruence may be related to the issues discussed above, such as low margins discouraging investment, provider preferences, and a lack of standardization, but it may also be an indication of poor transparency in the marketplace. Health care providers may not know that a 503B facility has a product they need, and 503B facilities may not know of unmet demand for their product.¹²

Almost all interviewees said that there is no central list or database of products compounded by 503B outsourcing facilities, and the facilities do not engage in extensive advertising or promotion of their products.¹³ They instead rely on established relationships with customers. Moreover, a facility's product list may frequently change, as it is tied in part to FDA's Drug Shortages List and the 503B Bulks List (discussed in more detail below). As a result, hospitals and clinics may not be aware that a difficult-to-obtain product is produced by an outsourcing facility, or even that outsourcing facilities are a supplier option at all.

Furthermore, outsourcing facilities are prohibited by statute from selling their products to wholesalers. As a result, customers must acquire each drug directly from its compounder. Potential purchasers may not have the time to identify and contact multiple 503B facilities to find one that makes, or is willing to produce, the office stock they need.

Regulatory uncertainty

Interviewees also cited regulatory uncertainty as a potential source of access challenges. Though FDA is supportive of creating a robust outsourcing industry, developing and implementing clear regulatory guidelines is a slow, deliberative process. Outsourcing facilities are therefore operating in a somewhat uncertain regulatory environment, which can affect business decisions about product offerings or even whether to enter this emerging industry.

For example, FDA is still developing the 503B Bulks List, which is a key mechanism governing the bulk drug substances that outsourcing facilities may use. FDA has solicited nominations for the list several times, and in March 2019, it issued final guidance describing the factors the agency intends to consider when determining whether there is a clinical need to compound from certain substances.¹⁴ Until the list is finalized, FDA issued an interim policy,¹⁵ which created three categories of ingredients: Category 1 (substances nominated and currently under evaluation); Category 2 (substances nominated that raise significant safety issues); and Category 3 (substances nominated without adequate evidentiary support). While the 503B Bulks List is being developed, outsourcing facilities may compound from products in Category 1, but not Categories 2 or 3.

FDA is evaluating substances on a rolling basis. This creates a level of uncertainty for outsourcing facilities, as products may be removed from Category 1 or 2 and added to or excluded from the Bulks List at any time. For example, one product that was discussed with interviewees, nicardipine, was excluded from the 503B Bulks List in March 2019.¹⁶ As of that date, outsourcing facilities were no longer permitted to compound starting from bulk nicardipine. The absence of a finalized 503B Bulks List—in combination with a changing FDA Drug Shortages List—means that many 503Bs do not have a stable product list, which contributes to the lack of market transparency.

Interviewees also cited the challenges and expense associated with CGMP compliance as a factor in access issues. At the time of the interviews, FDA had issued a revised draft guidance on CGMPs applicable to outsourcing facilities and had recently held a public meeting to solicit input.¹⁷ However, some of the interviewees reported that the CGMP guidance is a source of frustration, and many outsourcing facilities have received the FDA Form 483 (a list of potential violations issued after an inspection) and/or warning letters from the agency for failure to comply with CGMPs.¹⁸ FDA posts online Form 483s received by outsourcing facilities as a measure of public transparency, but the agency does not have a clear mechanism for removing a 483 or otherwise indicating that a facility has fixed the findings identified. This may deter potential customers from doing business with certain 503B compounders, even during a shortage.¹⁹

In addition to FDA regulations, interviewees noted that compliance with state regulations may also contribute to difficulties in acquiring compounded office stock. For example, many of the interviewees do not operate in all 50 states, in part because some states have not adapted their current licensing and registration laws to accommodate outsourcing facilities. These businesses do not fit neatly into most state pharmacy, manufacturer, or wholesaler licensing requirements.²⁰

Variations in state licensure or registration categories for outsourcing facilities can impede a facility's ability to distribute drug products in certain states and also impose additional operating costs in the form of licensing fees, both of which could create access challenges. For example, an outsourcing facility may locate in a state that prohibits licensing such businesses as pharmacies, while a pharmacy license may be required before a neighboring state allows the facility to ship compounded products across its borders. This would effectively prevent the outsourcing facility from doing business in both states.²¹

Finally, although not directly related to regulatory uncertainty, many of the interviewees noted difficulties in finding, training, and retaining qualified staff to compound products.

Drug shortage uncertainties

Each of the six interviewees cited the uncertainty associated with compounding a product when it is in shortage as a potential deterrent to compounding most of the 20 products on the list. Before a drug appears on the Drug Shortages List, FDA must confirm any reports of supply problems with information from individual manufacturers and distributors, as well as market-share data from sources such as IMS Health, which can take time.²² However,

interviewees reported that they have heard about potential or impending shortages through their relationships with hospitals and other customers, sometimes weeks before the product makes it to the FDA Drug Shortages List. In these instances, providers may not be able to acquire the FDA-approved product because it is in shortage, but 503B facilities are not yet permitted to make a compounded alternative from a bulk drug substance until FDA formally places it on the Drug Shortages List.

Even after a product appears on the list, outsourcing facilities must still evaluate the business rationale for making it. This includes consideration of production cost, revenue returns, technical feasibility, and facility capacity. Moreover, FDA's list frequently changes as shortages are confirmed or resolved. Once resolved, a 503B facility can no longer compound the product, and may sell remaining inventory for only 60 days after the drug's removal from the list.²³ Several interviewees noted that during this period they may face rising competition from manufacturers of the FDA-approved product previously in shortage, increasing the possibility that outsourcing facilities could be left with office stock they cannot sell. Many 503B facilities may therefore decide not to compound some drugs in shortage.

If a facility does move forward with compounding a drug in shortage, it must develop the product formulation, source the ingredients, compound the product, and test for sterility and stability before it can finally distribute the drug to hospitals and other customers. One interviewee estimated that it can take three to four months from the time a drug appears on FDA's list to the point when an outsourcing facility can distribute a compounded product. Another interviewee stated that it has built capabilities around some products in chronic shortage, allowing the facility to respond more quickly to demand, but not all outsourcing facilities have taken such measures.

Inexpensive drugs in shortage may be even less attractive products for 503B compounders. One interviewee explained that for these low-price drugs, a facility needs high-volume sales to generate enough revenue to justify the investment. However, the duration of any shortage is difficult to predict, and the original manufacturer could re-enter the market at any time.²⁴

Many older sterile injectable products, including those from the product list provided to interviewees, fall into this category.²⁵ For example, interviewees stated that sodium bicarbonate, calcium chloride injection, and the injectable local anesthetics (lidocaine with epinephrine; bupivacaine with epinephrine; lidocaine, epinephrine, and tetracaine [LET] gel or solution; and ropivocaine with epinephrine) would all fall into the category of products that are sometimes in shortage, but generate limited profits and are therefore unlikely candidates for a 503B facility to compound.

Potential solutions

The interviews suggest that the outsourcing facility industry is still maturing and underscore the importance of FDA's efforts to support a robust, well-regulated market for compounded office stock products that meet the agency's rigorous standards for safety and quality. These include taking steps to enhance the ability of 503B outsourcing facilities to compound drugs in shortage, improve market transparency, and continue supporting the development of a robust outsourcing industry.

Enhance the ability of 503B outsourcing facilities to compound drugs in shortage

Outsourcing facilities can meet a critical public health need by compounding drugs in shortage. FDA could further support this effort by improving the process for creating the Drug Shortage List and by requiring manufacturers to provide more information about anticipated time to resolution of the shortage.

Hospitals and pharmacists, for example, may predict shortages much earlier than FDA because they are on the front line of product use and distribution. The ASHP relies on these earlier signals—such as product substitutions, use of alternative products, or delayed treatment at the point of care—when creating its shortage list and will include products that are experiencing short-term regional shortages, not just nationwide shortages. FDA could consider amending its process to more closely follow the ASHP model, but this would require an amendment to the statutory definition of a shortage.²⁶ Alternatively, it could establish a separate process that would allow the agency to update the Drug Shortage List in a timelier manner, reducing the gap between when a shortage is identified by providers and when an outsourcing facility may legally compound the drug in shortage.

In addition, the agency could provide more information on the anticipated length and severity of a shortage, and the level of demand during the shortage. This would help 503B facilities make more realistic production plans. Until recently, this was a challenge, because traditional manufacturers were only required to notify FDA when there was an interruption in manufacturing or they were discontinuing a particular product.²⁷ However, the Coronavirus Aid, Relief, and Economic Security Act, which was enacted in March 2020, contained several provisions intended to address drug shortages.²⁸ As part of these changes, manufacturers will now be required to report more detailed information on pharmaceutical supply disruptions to FDA, including any events that may have led to the shortage, its likely extent and duration, and the expected impact. They must also report any disruptions to the supply of a product's active ingredient and whether any medical device used to administer the drug might be in shortage. With this information, FDA may be able to update the Drug Shortages List more quickly, and compounders may in turn be able to make more informed decisions about whether to compound from that list.

As part of its broader response to the coronavirus public health emergency, FDA has also taken additional steps to ensure adequate supplies of drugs needed to treat COVID-19 patients. In April 2020 the agency released guidance that temporarily loosened certain requirements for outsourcing facilities. Provided specific circumstances were met, the agency said it did not “intend to take action against an outsourcing facility for compounding a drug product that is essentially a copy of an approved drug, for using a bulk drug substance that is not on FDA’s 503B Bulks List, or for not meeting CGMP requirements with regard to product stability testing and the establishment of an expiration date.”²⁹ After the public health emergency subsides, the agency should evaluate to what extent its policy change affected production decisions by 503B compounders or health care systems’ access to these drugs to determine whether these changes offered meaningful benefits for patients while not creating unnecessary risks.

Improve market transparency

Although the DQSA was enacted in 2013, many providers may not be knowledgeable about the outsourcing facility industry, the products they compound, or how to purchase from them. To close this knowledge gap, trade groups such as the Outsourcing Facility Association (OFA) along with other organizations could conduct additional outreach and develop educational materials about 503B facilities and the niche they can fill during a drug shortage. As part of this effort, OFA and others could also encourage providers to review the information that is available on FDA’s website to understand what products 503B facilities make and the standards they are held to, and to develop established relationships with high-quality 503B facilities to source products.

Finally, broader use of group purchasing strategies could help to address some of the market transparency challenges identified. Some larger 503B facilities have contracted with group purchasing organizations (GPOs),³⁰ which are entities that allow health care organizations such as hospitals to negotiate collective purchasing agreements with medical product vendors. These GPOs act as intermediaries with the health system and allow for small providers to obtain volume-related discounts on their purchases. However, this type of arrangement does not appear to be common.

Continue to support development of a robust outsourcing industry

Though FDA and other key stakeholders have made significant progress in establishing a robust outsourcing facility market, some challenges persist. For example, several 503B facilities indicated that a lack of standardization across product formulations is a deterrent to manufacturing certain products, due primarily to challenges in scaling production and earning return on investment. In some cases, these individualized variations in orders are driven more by provider preferences than by clinical need.³¹ In recognition of this challenge, ASHP launched the Standardize 4 Safety Initiative “to standardize medication concentrations in order to reduce errors and improve transitions of care.”³² Provider associations could also play a role in establishing these standards and promoting their adoption. This would require hospitals and health systems to accept and implement these formulations, which may in turn necessitate updates to their internal ordering systems and retraining of personnel. Greater standardization will require collaboration across the health care system but could yield benefits in the form of a more secure supply of products.

FDA should also continue to support a robust outsourcing industry by finalizing and implementing guidance documents and regulations to provide additional regulatory certainty. The revised draft CGMP guidance for outsourcing facilities issued in January 2020 is an important step toward that goal, but it will likely take several years for the agency to finalize the related regulations. In the interim, outsourcing facilities should at a minimum follow the practices outlined in the guidance in order to ensure a safe supply of compounded office stock. This will build credibility with provider customers and work in tandem with efforts to better educate providers about the outsourcing facility industry. For its part, FDA should continue to inspect and enforce quality standards, but it should also adopt a process to “close” or otherwise indicate to the public when 483 findings of violations from an inspection have been remedied. This would address concerns that although FDA regularly inspects 503B facilities and publicly shares 483s and warning letters, it is not evident when an incident has been resolved, or how severe the warning was. A quality rating system that accounts for these factors and others may also help hospitals and pharmacists identify preferred partners for their business.

Finally, states should implement clear and consistent licensing requirements for outsourcing facilities. As of 2018, 11 states still had office stock policies and regulations that were not aligned with federal law.³³ Aligning these policies will help to reduce regulatory uncertainty in those remaining states.

Conclusion

FDA has made significant progress in implementing the DQSA and has taken important steps to ensure the safety and quality of compounded drug products on the market. However, there are ongoing issues that will need to be addressed in order to facilitate the development of a robust outsourcing facility industry. These challenges include business uncertainties related to the Drug Shortages and Bulks lists, technical challenges that disincentivize investment in certain products, and a lack of market transparency that contributes to access challenges for providers. Some of these issues can be addressed through direct FDA action, while others will require the involvement of additional stakeholders, such as industry associations and provider groups. However, given the additional risks associated with compounded drugs, it will be important for FDA to continue to hold outsourcing facilities to a high standard for safety and quality.

Appendix 1: Key Differences Between 503A Compounding Pharmacies and 503B Outsourcing Facilities

	503A compounding pharmacies	503B outsourcing facilities
Primary regulatory body	State boards of pharmacy, but FDA may inspect to determine whether conditions of Section 503A are met.	FDA
Who may compound?	<ul style="list-style-type: none"> Licensed physician; or Licensed pharmacist in a state-licensed pharmacy or federal facility. May compound sterile and nonsterile drugs. FD&C Act § 503A(a)(1).	<ul style="list-style-type: none"> Drugs must be compounded “under the supervision” of a licensed pharmacist in a facility registered with FDA as an “outsourcing facility.” Must compound at least some sterile drugs but can also compound nonsterile drugs FD&C Act § 503B(a) and (d).
Prescription required?	<p>Yes. “Valid prescription” required for an “identified individual patient” noting that a compounded product is needed for the patient.</p> <p>BUT, “anticipatory compounding” is permissible: Pharmacist may compound products “in limited quantities” before receiving a prescription but may not dispense the compounded product until a prescription is received.</p> FD&C Act § 503A(a).	<p>No. May compound products for office stock without patient-specific prescriptions.</p> FD&C Act § 503B(d)(4)(C). <p>BUT, significant limitations on the active ingredients that 503B facilities may compound (see “Other requirements”).</p>
Applicable quality and manufacturing standards	<ul style="list-style-type: none"> May not compound under “insanitary conditions.” Must comply with certain standards established by the U.S. Pharmacopeia (USP), an independent body that establishes safety and quality standards. Current good manufacturing practices (CGMP) do not apply, but pharmacies are subject to FDA inspection to ensure conditions of Section 503A are met and that there are no insanitary conditions. FD&C Act § 503A(a) and (b)(1)(A), (B).	<ul style="list-style-type: none"> May not compound under “insanitary conditions.” Must comply with certain standards established by the U.S. Pharmacopeia. Must meet CGMPs. Are subject to risk-based inspections. FD&C Act § 503B(b)(4) [risk-based inspections].
Compounding “copies”	May not compound “regularly or in inordinate amounts” products that are “essentially a copy” of a commercially available drug, as defined under Sections 503A(b)(1)(D) and 503A(b)(2) of the FD&C Act.	May not compound “essentially a copy” of one or more approved drugs, as defined under Sections 503B(a)(5) and 503B(d)(2) of the FD&C Act.

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Interstate distribution

Subject to limits on volume of drugs dispensed or distributed interstate depending on whether there exists a signed memorandum of understanding between the state and FDA that addresses the distribution of inordinate amounts of drugs interstate and the investigation of complaints.

No limits on interstate dispensing or distribution.

FD&C Act § 503A(b)(3)(B).

Other requirements

- May not compound products on the “Difficult to Compound” list or that were withdrawn or removed for reasons of safety or effectiveness.
- May compound from bulk drug substances only if substance is:
 - Subject of a USP monograph.
 - A component of an FDA-approved drug.
 - Included on FDA’s list of bulk drug substances that may be compounded (see [FDA’s Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A](#)).

FD&C Act § 503A(b)(1)(C)

FD&C Act § 503A(b)(3)(A).

FD&C Act § 503A(b)(1)(A).

- May not compound products on the “Difficult to Compound” list or that were withdrawn or removed for reasons of safety or effectiveness.
- May compound from bulk drug substances only if substance:
 - Appears on a list developed by FDA of bulk drug substances for which there is a “clinical need” (see [FDA’s Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B](#)); or
 - Appears on FDA’s drug shortage list
- Limitations on compounding drugs subject to formal Risk Evaluation and Mitigation Strategies established by FDA.
- Prohibited from wholesaling compounded drugs.
- Subject to user fees, adverse event reporting, labeling provisions, registration and listing, and certain other requirements.

FD&C Act § 503B(d)(4)(A)(i)

FD&C Act § 503B(a)(2), (4), (6), (7), (8), (10)

FD&C Act § 503B(b)(5)

Appendix 2: Methodology and Interview Guide

Pew conducted hour-long telephone interviews with a convenience sample of seven representatives from six different outsourcing facilities, identified through the recommendations of existing contacts in the compounding industry. These facilities ranged in size and were located across the U.S. (including sites in Kansas, California, Florida, Texas, New Jersey, Colorado, and Nevada). They are licensed in multiple states (between 20 and 50), and collectively service roughly 5,800 clinical centers. Interviews occurred between July 31 and Sept. 23, 2019, and were recorded and transcribed for analysis. In advance of each interview, respondents were provided with a list of 20 products that had been identified as challenging to acquire within the previous six months by 339 providers who responded to a nonprobability member survey fielded by the American Society of Health-System Pharmacists (ASHP). For each product on that list, the interviewee was asked a series of questions intended to understand the factors that might contribute to those reported access challenges. A copy of the interview guide and the list of office stock products are provided below.

This research is subject to several limitations. Though we attempted to include a broad range of facilities, we spoke with representatives from just six of the 74 registered outsourcing facilities, and thus our results may not be generalizable to all facilities. Additionally, the list of drugs focused on just 20 products identified from a survey of ASHP members, and thus does not provide a comprehensive picture of the market or of product availability. This may have affected our findings by focusing the conversation around a certain subset of products, thus missing additional barriers that may affect product availability.

Interview guide

The list of products we will review today was provided by the American Society of Health-System Pharmacists (ASHP), who recently surveyed their members on access issues with certain office stock products from 503B outsourcing facilities. The products are listed from most to least respondents reporting access issues.

When reviewing this list as a whole:

1. Are there any products you would add?
2. Are there any products that you are surprised to see?

Reference #	Category	Product
1	Pain management	Hydromorphone PCA
2	Fluids and electrolytes	Sodium bicarbonate injection
3	Pain management	Morphine syringe
4	Local anesthetic	Lidocaine with epinephrine
5	Critical care-cardiovascular	Epinephrine
6	Local anesthetic	Bupivacaine and epinephrine injection
7	Pain management	Fentanyl syringe

continued on next page

8	Trauma/ED	Phenylephrine syringe
9	Fluids and electrolytes	Calcium gluconate injection
10	Local anesthetic	Buffered lidocaine (any form)
11	Fluids and electrolytes	Calcium chloride injection
12	Local anesthetic	Lidocaine, epinephrine, and tetracaine (LET or LAT) gel/solution
13	Critical care-cardiovascular	Heparin
14	Critical care-cardiovascular	Phenylephrine in 0.9% NaCl bag
15	Local anesthetic	Ropivacaine 0.2% with epinephrine 1:200,000 units
16	Critical care-cardiovascular	Nicardipine
17	Trauma/ED	Dexmedetomidine
18	Critical care-cardiovascular	Cardioplegia solutions
19	Pain management	Sufentanil
20	Critical care-anti-infective and other surgery	Cefazolin in 0.9% NaCl bottle

Now we would like to discuss each product on this list. Let's start with the first drug, [Product].

3. Based on your experience, why are health systems indicating that they are facing access issues to this product?
 - a. Business Issues
 - i. Low order volume (i.e. inadequate/infrequent demand)
 - ii. Product falls outside of the specialty
 - iii. Cannot make the product for a competitive price because of the cost of testing products at CGMP level
 - iv. Not interested in making the product
 - v. Unaware of market demand for product
 - b. Technical Issues
 - i. Active bulk substance is not available
 - ii. Active bulk substance is not a permissible ingredient for compounding under FDA guidance
 - iii. Product requires specialized equipment or facility design that the business does not have
 - iv. The product requires specialized knowledge or skill the business does not have

- c. Standardization
 - i. The business creates a similar or equivalent product
 - d. Product characteristics
 - i. The product is nonsterile, and we only make sterile product
 - ii. Product is unstable and cannot get adequate shelf life
4. Are there any products on this list that are related to [Product] or that have similar access challenges for similar reasons? Could you please explain this relation?
- a. Other
 - i. Do you think the opioid crisis has affected drug supplies?
 - ii. Can you tell me about the DEA application process?
 - 1. Was there anything particularly challenging or cumbersome?
 - 2. How did this affect your ability to manufacture and distribute pain management drugs?

Now we will discuss the next product on the list.

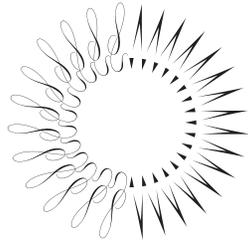
(Repeat Question 3 & 4 until product list has been completed or there are five minutes remaining.)

5. Are there any changes occurring within the industry that you envision impacting the level of access to certain products in the near-term? Could you please describe these changes?
- Probe:
- a. New technologies coming to market
 - b. Changes in population demand
 - c. Alternatives coming to market

Endnotes

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