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COMMENTARY

Outsourcing facilities and their place in the U.S. drug supply chain

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A B S T R A C T
The purpose of this commentary is to describe the ideal role of 503B outsourcing facilities in the U.S. drug supply chain. We also address the challenges that 503B outsourcing facilities are facing that limit their utilization and offer possible solutions. Section 503B outsourcing facilities are emerging contributors in compounding owing to their ability to compound large quantities of medication without requiring patient-specific prescriptions. As such, they play a valuable role in the U.S. drug supply chain. The use of outsourcing facilities to compound ready-to-use drug products is gaining traction in hospitals and other health care systems. Outsourcing facilities help hospitals that are facing time and cost constraints owing to the evolving regulatory landscape around compounding. Although outsourcing facilities are assets to the drug supply chain, there are several challenges to their use. The lack of a finalized 503B Bulks List has led to outsourcing facilities being overly cautious in compounding products using bulk drug substances. In addition, the time between Food and Drug Administration (FDA) inspections is undefined, and a lack of follow-up information regarding concerns identified during an inspection may result in uncertainties about the current state of the outsourcing facility. Health care providers, outsourcing facilities, and FDA need to work together to ensure that patients are provided the drugs they need in a safe and effective way.

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The U.S. drug supply chain includes a variety of participants who ensure that the drug reaches the patient, while maintaining safety and efficacy. Although it is preferable for providers to use Food and Drug Administration (FDA)—approved, commercially available drug products, there are times when drug products need to be compounded to meet a patient-specific need. In 2012, a meningitis outbreak linked to compounded steroid injections led to the passage of the Drug Quality and Security Act, which established 2 distinct types of pharmaceutical compounders for human patients: 503A and 503B.1

Compounding under section 503A is performed by a physician or a pharmacist in a state-licensed pharmacy or federal facility, pursuant to a patient-specific prescription. Limited quantities may be compounded in anticipation of a prescription if the facility has an established relationship with the patient or the prescriber.2

Outsourcing facilities, established under section 503B, may register with FDA, and compounding is supervised by a pharmacist. Outsourcing facilities are not required to receive a patient-specific prescription before compounding and therefore are able to compound drug products in larger quantities than 503A facilities.3 As a requirement, all drug products must be compounded following current good manufacturing practices, must be reported to FDA every 6 months, and a portion of these must be sterile preparations.1 Any drug product that an outsourcing facility intends to compound from a bulk drug substance (or a pure active pharmaceutical ingredient) must be on the 503B Bulks List that FDA is currently developing; a list of substances for which there is a demonstrated clinical need. While the list is being developed, bulk drug substances

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In a January 2014 letter, FDA encouraged hospitals to purchase compounded sterile drug products from FDA-registered outsourcing facilities because these facilities are under increased federal oversight. The use of outsourcing facilities has gained traction, on the basis of a recent report from the Office of Inspector General, which surveyed a stratified random sample of 601 Medicare-participating hospitals. Of the 564 hospitals that responded, 89% exclusively obtained non-patient specific compounded drug products from FDA-registered outsourcing facilities, 9% obtained some drug products from outsourcing facilities, and 2% exclusively obtained drug products from unregistered compounders.

Another role of outsourcing facilities is to ensure continued availability of drug products and to provide a bridge in the event of manufacturer discontinuation or other scenarios in which there is a shortage of a commercial drug product. In the event of a commercial manufacturer electing to withdraw a drug product from the market for reasons not relating to safety or efficacy, a provider may use an outsourcing facility to obtain the withdrawn drug products. The same holds true for drug shortage events; outsourcing facilities can bridge the gap until the commercial product becomes accessible again or until the provider can find another therapy that works for the patient.

Finally, outsourcing facilities can provide stock for providers to use for in-office procedures in specialties such as dentistry, ophthalmology, and podiatry. Having drug products readily available in their office is more efficient for some providers than the process of using a 503A compounding pharmacy, in which the patient must take the prescription to the pharmacy, have it compounded, and then bring it back to the prescriber before it can be used. By keeping the drug product stocked in their offices, providers have control of the storage conditions, assuring the providers of drug product quality and safety, which is especially important when using sterile drug products.

The ideal role of outsourcing facilities in the U.S. drug supply chain

We believe the ideal role for outsourcing facilities is to produce ready-to-use sterile drug products for hospitals. For some hospitals, implementing best practices guidelines such as United States Pharmacopeia (USP) <797> standards can be time-consuming and costly, as addressed in the 2019 public comments for the recent revision of the USP <797>.

Commenters on the USP revision felt that identifying microorganisms when the sampling level exceeds a certain threshold, changing filters during batch processing, and Compounding Record requirements would be burdensome. Hospitals can avoid these requirements if products are supplied by outsourcing facilities. Another benefit of using outsourcing facilities for hospital supply is that they can provide aseptic drug products with longer beyond-use dates, which can help decrease waste, turnover, and cost for hospital pharmacies. In these scenarios, outsourcing facilities may end up a permanent part of the hospital’s drug supply chain.

Outsourcing facilities can also be temporary suppliers for hospitals that require a longer implementation time to adhere to regulatory standards. In the summary of public comments received for the revised USP <797>, there was a concern of not
having enough time to implement changes, with several commenters requesting at least 18–24 months.\(^{11}\) There were also commenters who expressed concerns about remediation plans that involved closing the pharmacy, which would lead to the hospital not being able to continue compounding.\(^{11}\) Although this revised chapter is on hold, there may still be delays in implementing future revisions.

During states of emergency, hospitals in need of sterile drug products that are in high demand could consider using outsourcing facilities. For the coronavirus disease pandemic, FDA has implemented a temporary policy for compounding facilities that allow them to take a more active role in compounding certain drug products for hospitalized patients.\(^{12,13}\)

### Challenges and potential solutions to participation in the U.S. drug supply chain

Despite the opportunities that outsourcing facilities have in the U.S. drug supply chain, there are multiple challenges that currently limit their use.

Although the 503B Bulks List is in development, outsourcing facilities can compound using category 1 nominated substances. However, there is no guarantee that these substances will be included on the final list, so resources invested in compounding them may be wasted. Because the 503B Bulks List is not finalized, outsourcing facilities remain concerned about using nominated drug substances still under review, especially because no nominated drug substance has been added to the list thus far.\(^{14-16}\) In a recent comment to FDA, the Outsourcing Facilities Association (OFA), the trade organization that represents outsourcing facilities, detailed their concerns about how the 503B Bulks List is being developed. They suggested additional questions FDA should consider when making decisions for the 503B Bulks List and recommended consistent updates to the interim list and more transparency of the review process.\(^{14}\) Similar challenges with using outsourcing facilities to provide compounded drug products were identified in a recent report from the Pew Charitable Trusts.\(^{17}\)

Another challenge to the use of outsourcing facilities is inconsistencies in the inspection process. After an initial inspection, outsourcing facilities are inspected on a risk-based schedule. There is no specific time interval in which subsequent inspections take place, which can lead to a facility being left uninspected for a prolonged period of time. In OFA’s 2019 comment to FDA, the organization expressed concerns about the “pace at which inspections are classified and closed, [creating] an inconsistent enforcement environment.”\(^{14}\) They noted that at some facilities, inspections remain open for years, with some of these facilities operating under a warning letter or other actions.\(^{14}\) OFA called for a clear distinction between outsourcing facilities that are compliant and those that are not.\(^{14}\)

At the end of an inspection, the facility may be issued an FDA Form 483, which describes the investigator’s concerns for conditions that the facility may be violating.\(^{18}\) The FDA Form 483 is publicly available on the FDA’s website along with information on the dates of initial and most recent registration, the last FDA inspection, and whether any FDA action was taken on the basis of the inspection.\(^{19}\) However, the publicly available information does not mention whether the observed conditions have been resolved. Moreover, the form may not provide a complete picture of the facility because it “does not include observations of questionable or unknown significance at the time of the inspection.”\(^{18}\) These observations can include anything from lack of written procedures for production and process controls to deficiencies in aseptic processing areas, quality control units, and employee training. Therefore, the observed objectionable conditions are important for potential buyers because they could affect product quality.

For outsourcing facilities to be part of the U.S. supply chain, they need to proactively respond to the concerns outlined in FDA Form 483 in a transparent and publicly accessible manner. This may include resolving the problems quickly and posting a notice about their action on their website so potential buyers can verify facility status. In addition, FDA should provide the current compliance status of facilities on their website, along with a definitive time frame in which actions will next be taken by them. This will allow health professionals to know the status of an outsourcing facility before selecting one for use.

When selecting an outsourcing facility for compounded drugs, buyers should first check the FDA’s list of registered outsourcing facilities, which is available on the FDA website. Most hospitals look at FDA registration and the facility’s history of federal enforcement actions, including product seizures or injunctions, when choosing an outsourcing facility.\(^{18}\) Buyers should also review the outsourcing facility’s inspection history and most recent results from FDA and the state board of pharmacy. The FDA website also has a list of products that outsourcing facilities have reported making in the past year. For more information about what products are available, buyers should review the outsourcing facility’s website or reach out to the contact person provided on the FDA’s list of registered facilities. Buyers can also use the American Society of Health System Pharmacists contractor assessment tool to evaluate a facility’s compliance with USP <797>.\(^{20}\) Although it may be logistically challenging, buyers should try to visit potential outsourcing facilities themselves whenever possible to assess if they meet their needs.\(^{20}\) Buyers can also speak to other buyers who have previously ordered from the facility to have a better understanding of the environment and their compounding capabilities.

### Conclusion

Outsourcing facilities can play an important role, especially for hospital supply of ready-to-use sterile drug products. However, health care providers should recognize that drug products from outsourcing facilities are not held to the same regulatory standards as commercially available drug products and thoroughly research a facility before deciding to use it for their compounded drug needs. FDA and outsourcing facilities should consider being more transparent about compliance status. FDA could also provide more frequent updates about the substance list and the outsourcing facilities’ status on the FDA webpage. Health care providers, outsourcing facilities, and FDA need to work together to ensure that patients are provided the drugs they need in a safe and effective way.
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