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RESEARCH NOTES

The role of outsourcing facilities in overcoming drug shortages

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ABSTRACT

Background: The Drug Quality and Security Act passed in 2013 created a new voluntary category of compounders, referred to as outsourcing facilities. The regulatory landscape allows these facilities to compound on a larger scale in comparison with the typical compounding pharmacies, which positions them to potentially serve a role in overcoming drug shortages.

Objective: The purpose of this article is to identify the number of drug products on shortage as reported by the Food and Drug Administration (FDA) that were also compounded by outsourcing facilities.

Methods: All current and resolved drug shortages through January 27, 2020, as reported by FDA, were compared with the 503B product reports from July 2018 through June 2019 submitted to FDA by outsourcing facilities. The active pharmaceutical ingredient (API) and dosage form for each product on shortage were compared with the 503B product reports to identify similarities.

Results: There were 344 unique APIs on the FDA drug shortage list and 774 unique APIs on the 503B product reports. After comparison of the APIs on the drug shortage list with those on the product reports, 27% of unique APIs (74 of 272) were included on both lists, and of these, 18% (50 of 272) of the APIs on the drug shortage list were compounded by outsourcing facilities in the same dosage form as what was on shortage.

Conclusion: The regulatory landscape positions outsourcing facilities to play an important role in providing access to medications while on shortage. However, when comparing the drugs on shortage as reported by FDA with the 503B product reports, there was minimal overlap. Additional research into why outsourcing facilities are not taking on a larger role in overcoming drug shortages should be explored.

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Background

The Food and Drug Administration (FDA) defines a drug shortage as “a period of time when the demand for the drug within the United States exceeds the supply of the drug.”¹ There are various reasons that may lead to a drug being on shortage, with manufacturing issues, production delays, and issues surrounding the raw materials needed to manufacture

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the product being the most common.² In 2018, at the request of senators and members of the House of Representatives, FDA convened an interagency Drug Shortages Task Force to study the problem, determine the root cause of drug shortages, and to make recommendations for solutions.³ This task force identified 3 major causes of drug shortages: lack of incentives to produce less profitable drugs, the market does not recognize and reward manufacturers for mature quality management systems, and logistical and regulatory challenges that make it difficult for the market to recover after a disruption.³ Drugs on shortage are typically sterile injectable products or those in which a generic product is commercially available.³ The peak of the drug shortage crisis was in 2011 when more than 250 shortages were reported to FDA.⁴ Although the number of new drug shortages has decreased since then, there has been an increase in the number of drugs on shortage, and the shortages are lasting longer than in the past.³

Drug shortages have had a major impact on the drug supply chain and patient access to medications. In 2017, the Institute for Safe Medication Practices surveyed pharmacy directors,

managers, and purchasing agents to understand their experiences with drug shortages. From the nearly 300 respondents, 71% reported that they were unable to provide patients with the recommended drug or treatment. This resulted in patients receiving a less effective drug to treat their condition or treatments were delayed altogether.⁵ Medication errors of patients receiving the wrong dose or concentration have also been linked to drug shortages.^{5,6} As a result, drug shortages continue to pose a challenge to public health and continue to remain a top priority for FDA with efforts focused on medically necessary products that have a significant effect on public health.^{1,4}

Although FDA works to mitigate drugs shortages and has helped prevent hundreds of drug shortages each year, there is a need to explore alternative strategies to help reduce the impact on patient care while a drug is on shortage.⁴ Pharmacy compounding describes the act of combining, mixing, or altering of the ingredients of a drug to create a new medication tailored to the needs of an individual patient.⁷ Compounding of a product is generally done pursuant to a patient-specific prescription when a commercially available product is not available to treat that patient. This could be due to a patient allergy to an ingredient in the commercially available product or the need for a different concentration, route of administration, or dosage from that which is available. Section 503A of the Federal Food, Drug, and Cosmetic (FD&C) Act grants compounded products various exemptions, including the need to undergo FDA approval, certain labeling requirements, and the need to follow current good manufacturing practices (CGMP) in the preparation of the product.⁸ Compounding under section 503A is done by a pharmacist in a state-licensed pharmacy or federal facility or by a licensed physician.⁸

With the passage of the Drug Quality and Security Act (DQSA) in 2013, the FD&C Act was amended to include a new section, 503B.⁹ Compounding under section 503B is done under the supervision of a pharmacist in a new category of voluntary compounding facilities, referred to as outsourcing facilities. These facilities are not required to be state-licensed pharmacies but register directly with FDA and are, therefore, predominately regulated and inspected by FDA.¹⁰ Compounded products prepared in an outsourcing facility are granted similar exemptions regarding the need for FDA approval and labeling, but 1 major difference is that outsourcing facilities are required to follow CGMP.¹⁰ In addition, outsourcing facilities are required to report to FDA every 6 months the drugs compounded during the previous 6 month period, must compound at least 1 sterile product, and are not restricted to compounding pursuant to a patient-specific prescription.¹⁰ Outsourcing facilities are able to compound using a bulk drug substance, or pure active pharmaceutical ingredient (API), if the drug appears on a list that has been created by FDA, the 503B Bulks List, or if it appears on the shortage list maintained by FDA.¹⁰ To protect the drug application process, regulations prohibit outsourcing facilities from compounding a product that is essentially a copy of a commercially available product.¹¹ However, if the drug appears on the FDA drug shortage list at the time of compounding, distribution, and dispensing, this restriction is waived.¹¹ Although FDA prefers to address drug shortages by working through the global supply chain to restore supplies of

FDA-approved drugs, compounding could serve as an interim solution to help manage the shortage in real time.¹²

When a drug is on the shortage list, the ability to compound without receipt of a patient-specific prescription and the additional leniencies granted to outsourcing facilities, including the use of a bulk drug substance and the waiver of the essentially a copy provision, outlines a framework to allow these facilities to serve a role in providing drug products currently on shortage.

Objective

The purpose of this article is to identify the number of drug products on shortage as reported by FDA that were also compounded by outsourcing facilities.

Methods

Using the FDA website, all current and resolved shortages through January 27, 2020 and all available product reports were downloaded into Excel spreadsheets.^{13,14} Only the product reports from July 2018 through June 2019 were publicly available and included in the analysis. Shortages with an initial posting date after June 2019 and shortages that were resolved before July 2018 were excluded. The drug shortage and 503B product reports were sorted to determine the API, dosage form, and strength. For any products on the drug shortage list in which this information was not provided in the report, the national drug code (NDC) was used to search the NDC directory to collect this information.¹⁵

One author reviewed both reports to identify APIs that were present on both reports. The APIs present on both reports were included for further review, and those that were not present on both reports were excluded. Next, the dosage forms of the APIs included were reviewed. The APIs with the same dosage form on both reports were considered a match and included for analysis. The APIs with dosage forms that differed were excluded. Drug strength was not required for a match to be determined owing to outsourcing facilities potentially compounding ready-to-use products (i.e., diltiazem 25-mg/5-mL solution for injection was on shortage, and diltiazem 125-mg/100-mL solution for injection was compounded by an outsourcing facility). Matches were combined into 1 Excel spreadsheet, and descriptive statistics were used to analyze the data.

Results

A total of 2307 entries were included on the drug shortage list, which included initial posting dates from February 2012 to January 27, 2020. On review of the report, an additional 14 entries were included because 1 entry included multiple products. There was 1 shortage that was resolved before July 2018, and 344 shortages with an initial posting date after June 2019 were excluded. A total of 1976 drugs were included for analysis. These products represented the same drug at the same strength in different package sizes (i.e., amitriptyline 10-mg tablets in a 100-count bottle and amitriptyline 10-mg tablets in a 1000-count bottle were included as separate entries) as well as the same drug at the same strength in the same package size with different manufacturers (i.e., allogliptin

Table 1
Active pharmaceutical ingredients and dosage form on shortage and compounded by a 503B facility

Active pharmaceutical ingredient	Dosage form
Amino acids	Solution for injection
Atropine	Injection, sterile
Bupivacaine	Injection, sterile
Bupivacaine hydrochloride and epinephrine	Injection, sterile
Calcium chloride	Injection, sterile
Cefazolin	Injection, sterile
Cefepime	Injection, sterile
Ceftazidime	Injection, sterile
Cefuroxime	Injection, sterile
Dexamethasone sodium phosphate	Injection, sterile
Dextrose	Injection, sterile
Diazepam	Injection, sterile
Diltiazem hydrochloride	Capsule, injection, sterile
Diphenhydramine	Injection, sterile
Epinephrine	Injection, sterile
Erythromycin lactobionate	Injection, sterile
Fentanyl citrate	Injection, sterile
Fludrocortisone acetate	Tablet
Fluoxetine	Capsule
Heparin sodium	Injection, sterile
Hydromorphone	Injection, sterile
Hydroxyprogesterone caproate	Injection, sterile
Hydroxyzine pamoate	Capsule
Ketamine	Injection, sterile
Ketorolac tromethamine	Injection, sterile
Labetalol hydrochloride	Injection, sterile
Lidocaine	Injection, sterile
Lidocaine premixed bag	Injection, sterile
Lidocaine hydrochloride and epinephrine	Injection, sterile
Methadone hydrochloride	Injection, sterile
Methotrexate	Injection, sterile
Morphine sulfate	Injection, sterile
Nicardipine hydrochloride	Injection, sterile
Ondansetron	Injection, sterile
Orphenadrine citrate	Injection, sterile
Piperacillin and tazobactam	Injection, sterile
Polyethylene glycol 3350	Oral solution
Potassium chloride	Injection, sterile
Potassium phosphate	Injection, sterile
Progesterone	Injection, sterile
Remifentanyl	Injection, sterile
Rocuronium bromide	Injection, sterile
Ropivacaine hydrochloride	Injection, sterile
Sodium bicarbonate	Injection, sterile
Sodium chloride	Injection, sterile
Sodium phosphate	Injection, sterile
Tacrolimus	Suspension
Testosterone	Gel
Triamcinolone acetonide	Cream
Water, sterile	Injection, sterile

6.25-mg tablets in a 30-count bottle manufactured by Perrigo Company PLC and alogliptin 6.25-mg tablets in a 30-count bottle manufactured by Takeda Pharmaceuticals USA Inc were included as separate entries). After sorting by the API, 272 unique APIs were identified.

Product reports were available from July 2018 to December 2019, representing 64 outsourcing facilities, included a total of 6391 entries. The same drug at the same strength in a different package size were included as separate entries (i.e., atropine 0.4-mg/mL solution for injection in a 1-mL syringe and atropine 0.4-mg/mL solution for injection in a 5-mL syringe were 2

Table 2
Comparison of products on the 503B product report and the Food and Drug Administration drug shortage list

Variable	503B product report	FDA drug shortage list
No. products	6391	1976
No. unique API	774	272
No. matching API (%)	74 (27)	
No. matching API and dosage form (%)	50 (18)	

Abbreviations used: API, active pharmaceutical ingredient; FDA, Food and Drug Administration.

separate entries on the report). After sorting by the API, 774 unique API were identified.

After reviewing the APIs that were present on both the drug shortage list and the product reports, 27% of unique APIs (74 of 272) were included on both lists. These 74 APIs represented 1926 products on the product reports and 969 products on the shortage list. Of these 74 APIs, 32% (24 of 74) were excluded owing to the product listed on the product report not being in the same dosage form as the drug on shortage (i.e., amitriptyline was compounded in various concentrations as a cream, but amitriptyline tablets were on shortage). As a result, 18% (50 of 272) of the APIs on the drug shortage list were compounded by outsourcing facilities (Tables 1 and 2). These APIs were compounded by 48 outsourcing facilities. Of the 50 APIs that were included on both lists, 86% (43 of 50) represented sterile injectable products.

Discussion

The regulatory structure of outsourcing facilities creates a framework that outlines a role for outsourcing facilities to provide access to drugs while they are on shortage. If a drug is on shortage and unavailable from the manufacturer, the outsourcing facility would likely be forced to compound the drug using the bulk drug substance. Pursuant to the DQSA, outsourcing facilities are only able to compound using a bulk drug substance if it is on a list that has been established by FDA, the 503B Bulks List, or if the compounding, dispensing, and distribution of the product occurs while the drug is on the shortage list, defined as 60 days of the drug appearing on the shortage list.^{10,16} In addition, if the drug is on the shortage list, the restriction prohibiting outsourcing facilities from compounding essential copies of commercially available products is waived.¹¹ Outsourcing facilities are also required to compound sterile products, the most common type of drug on shortage, and are required to follow CGMP. This indicates that these facilities have implemented minimum requirements for the methods, facilities, and controls used in their compounding process ensuring that the product is safe and contains the right drug in the right strength.^{17,18} When this is combined with the ability of outsourcing facilities to compound in large quantities and to provide compounded products for use in another health care setting, such as a hospital or practitioner's office, there is a clear guide for the role that outsourcing facilities can play in providing drugs that are on shortage. However, when comparing the drugs on shortage as reported by FDA with the 503B product reports, there is minimal overlap.

This preliminary evaluation suggests that the role of outsourcing facilities could be increased to alleviate the burden that shortages have on the drug supply chain, and it is important to understand why outsourcing facilities are not playing a larger role. The American Society of Health System Pharmacists held a roundtable in 2017 to discuss avenues to minimize the impact of drug shortages on patient care, and 1 potential solution was the use of outsourcing facilities.¹⁹ However, several challenges were identified that could serve as barriers to this solution. One challenge was the unpredictable nature of drug shortages.¹⁹ When taking into consideration the length of time in which a product will be on shortage compared with the time needed to increase production of the drug, some facilities may deem this endeavor to not be financially viable.

If a drug is on shortage, the outsourcing facility would likely need to compound using the bulk drug substance. While the 503B Bulks List is in development, FDA divided the bulk drug substances nominated for inclusion on the list into 3 categories. Bulk drug substances that were added to category 1 were submitted with sufficient information for evaluation, and while the list is in development, outsourcing facilities can compound using substances in category 1 regardless of whether the drug is on shortage.¹⁶ Although not every drug was nominated for inclusion on this list, the nominations can serve as a guide for the drugs that outsourcing facilities are interested in compounding. Of the category 1 substances, 72 were on the shortage list during the reported time; however, only 32 were reported as being compounded by outsourcing facilities. Compounding using a bulk drug substance in category 1 would not be affected by the time to increase production as the compounding, dispensing, and distribution is not restricted to the time in which the substance is on shortage. Therefore, an outsourcing facility had the ability to compound using an additional 40 bulk drug substances that were on shortage without concern for the time in which the drug was on shortage.

Another challenge discussed was whether facilities were equipped to compound starting from a bulk drug substance.¹⁹ The product reports from July 2018 to June 2019 included 64 outsourcing facilities, of which 53 are still currently registered as outsourcing facilities. Of these 53 facilities, 46 indicated that they intend to compound from bulk drug substances; because the remaining 11 are no longer registered, information regarding these facilities is not available. In addition, of the 74 currently registered outsourcing facilities, 63 have identified that they intend to compound sterile products from bulk drug substances.¹⁴ With a large percentage of outsourcing facilities indicating an intention to compound from bulk, this may not be as much of a barrier as stated.

With the recent coronavirus disease (COVID-19) pandemic, FDA granted additional leniencies regarding compounding of an essential copy, use of a bulk drug substance that is not on the 503B Bulks List, and certain CGMP requirements specific to stability and expiration date testing to outsourcing facilities when compounding drugs for hospitalized patients with COVID-19.¹² Outsourcing facilities are required to report weekly to FDA the products compounded under this guidance.¹² Extending the time in which the drug must be dispensed and distributed beyond 60 days coupled with a similar approach used during the COVID-19 pandemic may reduce the financial barriers needed to initiate production as well as allow for FDA oversight through increased reporting.

One limitation to this analysis is related to how the product information is reported to FDA and made publicly available. Outsourcing facilities report to FDA in January and June of each year all products compounded within the previous 6-month period.²⁰ These reports do not indicate the specific date in which a product was compounded; therefore, a direct connection between the compounding of a product and a drug going on shortage cannot be made. In addition, the reports do not indicate whether the product was compounded using the bulk drug substance or a commercially available product, which also limits the ability to connect compounding to a drug shortage. Another limitation is an analysis of the decision-making process a health care institution uses when developing strategies to overcome drug shortages. If there is not a demand for an outsourcing facility to compound a drug on shortage, then the role of the outsourcing facility in overcoming that shortage will be limited.

Conclusion

With one of the major root causes of a drug shortage being a lack of incentives for manufacturers to produce less profitable drugs and the impact shortages have on patient care, all potential avenues should be explored to identify solutions.^{3,5,6} The regulatory structure of outsourcing facilities outlines a framework in which these facilities are able provide access to drugs currently on shortage. However, this preliminary research identified that they are not necessarily filling this role. Additional research into why outsourcing facilities are not taking on a larger role in overcoming drug shortages should be explored.

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