Quantifying drivers of supply chain resilience in pediatric oncology medications

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Introduction

Critical pediatric oncology drugs have a 90% higher likelihood of a shortage event[1] than the average drug product. While use of multiagent combination chemotherapy and supportive care reagents (CASCAs) have driven five-year survival rates for children with cancer to near 85%,[2] effective therapies are often hindered by frequent, long-lasting drug shortages. These older, mainly sterile injectable, CASCAs have few, if any, therapeutic alternatives. While the COVID-19 pandemic exposed additional underlying vulnerabilities in the pharmaceutical supply chain, issues with availability and access to critical drugs, including essential pediatric oncology medications, have persisted for decades. Drug shortages can result in significant harm, including increased medication errors, delayed administration of lifesaving therapies, inferior outcomes, and patient deaths. Pediatric oncology patients, lacking autonomy and decision-making capacity for their own treatment plans, constitute one of our most vulnerable patient populations. To ensure supply chain issues don't impede access to these lifesaving treatments, a cross-industry team analyzed potential indicators and drivers of supply chain fragility for a select group of CASCA drugs.

The U.S. Pharmacopeia (USP),[3] Vizient,[4] and Angels for Change[5] collaborated to better characterize drug shortages through machine learning and advanced analytics. Each of these organizations independently leads efforts to strengthen the resiliency of the pharmaceutical supply chain. By combining USP's Medicine Supply Map,[6] Angels for Change's network of clinical and market experts, and Vizient's strategic sourcing and analytics expertise for essential medications, the collective team has the capability and data to explore novel drug shortage insights in the pediatric oncology space.

> ***Pediatric oncology patients, lacking autonomy and decision-making capacity for their own treatment plans, constitute one of our most vulnerable patient populations.***

Angels for Change consulted with clinical experts who prioritized 19 CASCA drugs, including both injectable and oral products, from a list of CASCA essential medicines published by the *Journal of the American Medical Association* in 2019. The collective team then examined the underlying factors driving supply chain weakness in these essential CASCA drugs.

Of the 19 essential pediatric oncology drugs, 14 (74%) have experienced one or more shortages[7,8] since 2016 (Figure 1), compared to 18% for the universe of all drug products in USP's Medicine Supply Map. The average duration of the shortage is also longer–over 40 months compared to under 30 months for the average drug shortage (Figure 2).

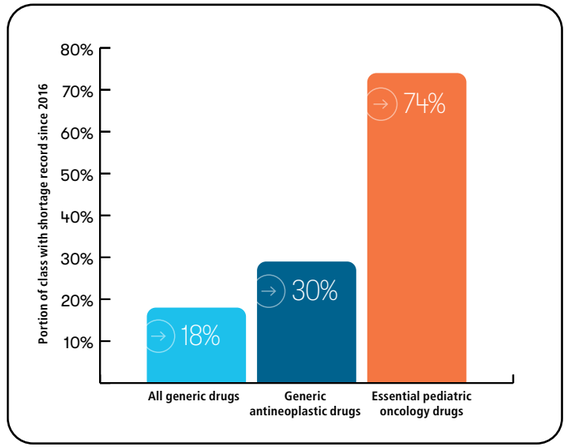

Figure 1 – *Frequency of drug shortages by class, USP's Medicine Supply Map*

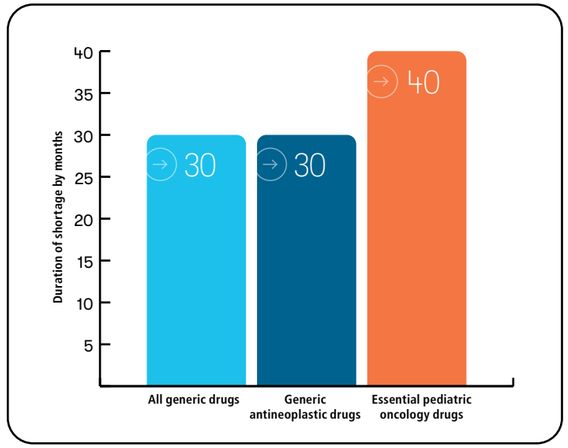

Figure 2 – *Duration of drug shortages by class, USP's Medicine Supply Map*

Essential pediatric oncology drugs
Arsenic Trioxide Injection
Asparaginase Erwinia Chrysanthemi Injection
Bleomycin Injection
Cisplatin Injection
Cytarabine Injection
Dactinomycin Injection
Doxorubicin Hydrochloride Injection
Etoposide Injection
Fludarabine Phosphate Injection
Ifosfamide Injection
Isotretinoin Capsules
Leucovorin Calcium Injection
Lomustine Capsules
Mercaptopurine Tablets
Mesna Injection
Methotrexate Injection
Thiotepa for Injection
Tretinoin Capsules
Vincristine Sulfate Injection

Methodology and model description

USP leveraged the capabilities of its Medicine Supply Map to develop the USP Drug Supply Chain Resiliency Model, incorporating data on supply-side drivers of risk, namely the location of ingredient and fill-finish manufacturing, quality records of manufacturing facilities, economic/market factors, and drug characteristics such as dosage form and complexity of manufacturing. In collaboration with Vizient, USP also considered demand-side hypotheses, including U.S. market size for the product, price, and line-item fulfillment rates. Currently, the model includes 89% of U.S.-approved generic human prescription National Drug Codes.

Experts on drug shortages, including USP's Expert Volunteers, were surveyed to develop hypotheses on drivers of supply chain vulnerability. In total, USP analyzed over 200 hypotheses and reviewed their impact on drug shortages. Appendix I lists the selected hypotheses tested. These hypotheses were quantified and tested against data on historic and current U.S. drug shortages. The model characterizes patterns in shortages of generic U.S. prescription drugs based on underlying features for drug products. The model accounts for structural risk rather than stochastic events that may be caused by weather, trade, political issues, epidemics, etc. See Appendix II for additional information on model characteristics and performance.

While this paper focuses on essential pediatric oncology medications, the model includes over 2,000 drug products available in the U.S. market. The goal of sharing the insights from this analysis is to garner feedback and refine the approach to better fit specific use cases for government agencies, manufacturers, group purchasing organizations (GPOs), distributors, payors, and providers so they have information that may help them take proactive actions to improve patient access to quality medicines.

> ***The goal of sharing the insights from this analysis is to garner feedback and refine the approach.***

Figure 3 – *Shortages[9] by calendar year, USP's Medicine Supply Map*

Insights

As evidenced in Figure 3, problems with drug shortages have persisted for many years. Novel machine learning algorithms enable new solutions for old problems. Armed with a graph-based analytics platform, USP's team of experts identified, characterized, and quantified factors that contribute to vulnerability of this supply chain. Four attributes were found to have statistically significant associations with supply chain disruptions. Each findings section below reviews the correlations between the attribute and shortage records for all drug products, then analyzes the attributes for the essential pediatric oncology drugs. The attributes are presented in order of their relative importance[10] for identifying vulnerabilities within the drug supply chain.

Finding #1

Injectables with lower prices have more vulnerable supply chains

Lower-priced[11] drugs have a higher likelihood of being in shortage[12] (statistically significant P<.025). The impact of lower prices on supply chain resilience is amplified for the injectable drug subset (statistically significant P<.001). Figure 4 shows relative supply chain vulnerability for different categories of unit prices. For injectable drug products below $10/unit, nearly 60% have a recent shortage record.

Out of the 19 essential pediatric oncology drugs studied, 15 are injectable drugs, and 13 are injectables with a price point below the current[13] average unit price for injectable drugs. These low injectable prices are correlated with decreased supply chain resiliency.

The association of pricing and lack of availability is well documented.[14] Root Cause 1 in the 2019 FDA Drug Shortages: Root Causes and Potential Solutions report[15] was the "lack of incentives for manufacturers to produce less profitable drugs." Lower-priced injectable drugs over the last 20 years have contributed to supply chain fragility. Moreover, the finding that lower-priced drugs have more availability issues should be evaluated within the context of quality and supply chain vulnerability. Price, quality, and availability form a tradeoff triangle where all three components should be considered. From the same FDA Shortage Report[16], Root Cause 2 aligns with our findings that the market does not recognize and reward manufacturers for mature quality management systems.

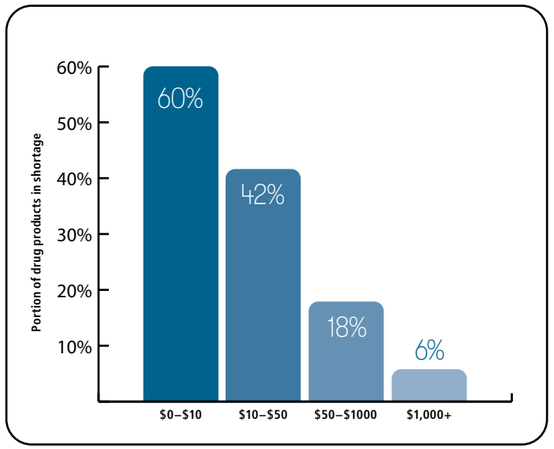

Figure 4 – *Impact of unit price on supply chain vulnerability, USP's Medicine Supply Map*

Finding #2

Greater geographic concentration decreases supply chain resilience

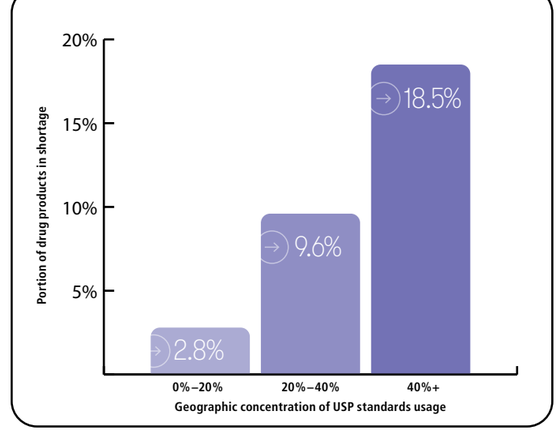

Figure 5 – *Impact of geographic concentration on supply chain vulnerability, USP's Medicine Supply Map*

Drugs with greater geographic concentration in their manufacturing base are more susceptible to shortages (see Figure 5). In this analysis, USP standards usage served as a surrogate for drug manufacturing. For example, if 75% of USP standards usage for a given drug product occurs in India, that drug has a geographic concentration of 75%.

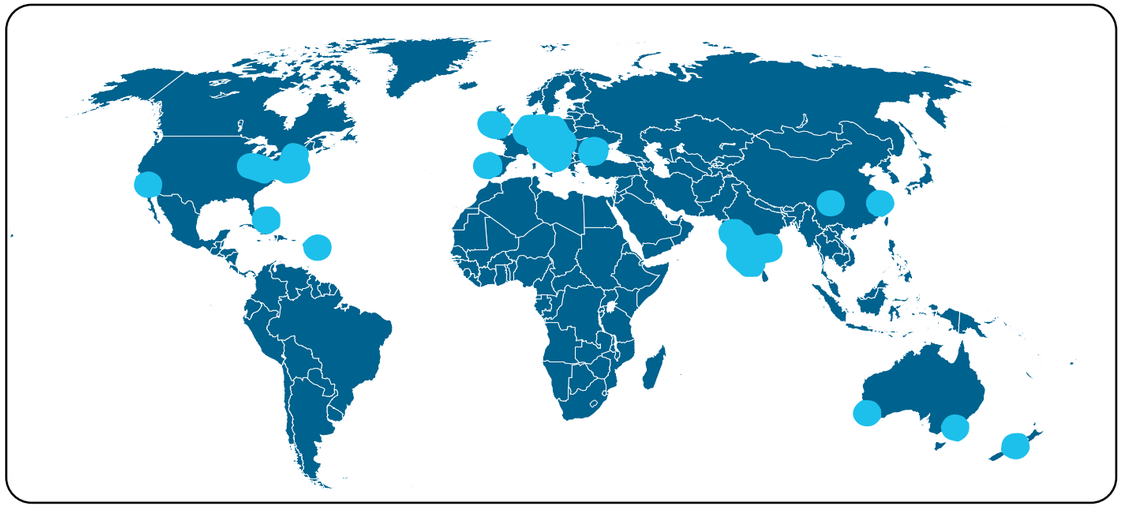

Figure 6 – *Manufacturing locations for essential pediatric oncology drugs, USP's Medicine Supply Map*

Figure 6 shows the manufacturing locations for essential pediatric oncology medications. This level of geographic diversity is lower than the average drug product. This relative lack of geographic diversity decreases supply chain resilience for essential pediatric oncology medications.

Finding #3

Drugs with higher manufacturing complexity are more vulnerable to supply disruptions

Another significant finding associated with supply chain vulnerability is manufacturing complexity. There are numerous ways to assess the complexity of pharmaceutical formulations, such as dosage forms, the number of underlying components, the expertise needed to synthesize the molecule, storage requirements, and the size and molecular structure of the active pharmaceutical ingredient. USP analyzed numerous manufacturing complexity factors to identify associations with supply chain vulnerability. In this study, two attributes, namely dosage form and a specific manufacturing process, demonstrated statistically significant relationships to shortages.

Dosage form: Despite recent improvements, injectables remain vulnerable from a supply chain perspective. Out of 464 injectable drug products tracked in the Medicine Supply Map, 27.4% have an associated shortage record in the past 12 months (see Figure 7). For comparison, only 5.6% of the 1,063 oral solid drug products tracked in the Medicine Supply Map have a recent shortage record. Because 15 out of the 19 essential pediatric oncology drugs are injectables, this manufacturing complexity factor decreases supply chain resilience for this class.

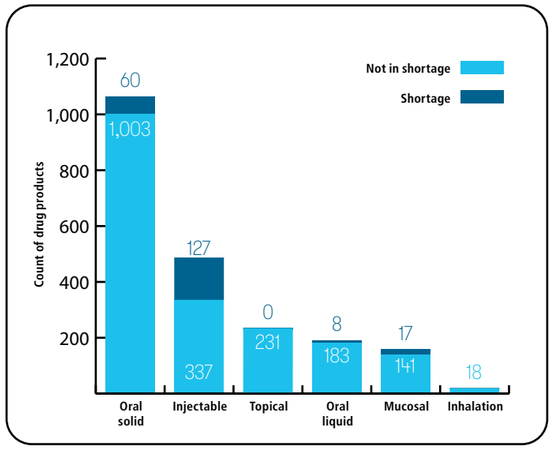

Figure 7 – *Prevalence of shortage records by dosage form, USP's Medicine Supply Map*

Specific manufacturing process: Medicines used in injection drug products often undergo an expensive dehydration process called lyophilization. Lyophilized drugs have lower supply resilience. Of the 19 drug products examined in this study, 15 were sterile injectables and 10 of those were lyophilized.

Finding #4

Quality failures increase supply chain vulnerability

Quality issues are a significant cause for the majority of shortages, according to FDA analysis.[17] The FDA assigns Official Action Indicated (OAI)[18] inspection records for manufacturing violations such as gaps in device compliance, drug quality assurance, or misbranding. In this study, Official Action Indicated inspection records were used as a proxy for manufacturing quality deficiencies and found that quality concerns are associated with supply chain vulnerability (Figure 8). Drug products, particularly injectables, manufactured at sites with a greater number of OAI inspection records have a statistically significant higher likelihood of a shortage event.

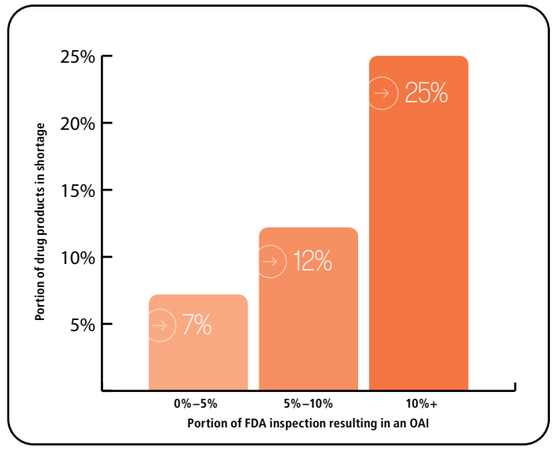

Figure 8 – *Impact of quality records on supply chain vulnerability, USP's Medicine Supply Map*

There were relatively few quality events associated with essential pediatric oncology drugs (Figure 9), and this factor did not have a significant impact on supply chain resilience. While essential pediatric oncology drugs don't have a general history of quality issues, individual quality events have impacted availability for specific drugs.

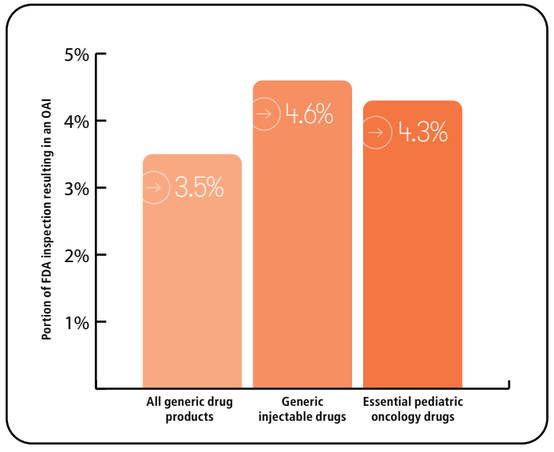

Figure 9 – *Quality records for essential pediatric oncology drugs are similar to quality record patterns for other classes, USP's Medicine Supply Map*

Collective impact of findings on supply chain resilience for essential pediatric oncology drugs

The USP team combined the factors referenced in this paper with additional supply-side data to evaluate supply chain resiliency. Based on 10,000 Monte Carlo simulations of a hyperparameter-tuned random forest model, the Supply Resilience Scores were developed for individual drug products as a proxy for shortage likelihood. The average Supply Resilience Score for an essential pediatric oncology drug was 1.3 standard deviations lower than the average generic drug product. In other words, structural factors inherent to essential pediatric oncology cause these drugs to have a 90% higher likelihood of shortage events than the average drug product, largely driven by the class's association with lower-priced sterile injectables (Finding #1).

Actionable next steps

The findings presented in this paper provide a scientifically substantiated methodology to identify the attributes most likely to indicate a supply resiliency issue. The findings also underscore the criticality of access to data and transparency to support evaluation of supply chain risk. Now that vulnerabilities have been identified, collective and decisive action should be taken to improve supply chain resilience.

1

Continued focus on medications for highly vulnerable populations

The starting point for this paper was a list of 19 essential medications for pediatric oncology patients. Lists such as the FDA Essential Medicines, Medical Countermeasures and Critical Inputs List, the WHO Essential Medicines List and Vizient's list of Essential Medicines for High Quality Patient Care can help identify drugs that might experience demand surges because they may not have therapeutic alternatives and/or may be essential in critical care.

2

Redundancy of supply

Given the inherent fragility of the existing pharmaceutical supply chain, building additional inventory and more manufacturing capacity can help reduce the risk of product shortages. Several organizations have begun investments and/or additional collaborations to bring additional supply to the market. One example is the Vizient Novaplus Enhanced Supply offering that was responsible for providing an additional 676,000 units of propofol during the height of the pandemic and has presently grown to an inventory of over 95 million vials of essential medications housed in the U.S.

3

Transparency of manufacturing data

The availability of data regarding manufacturing functioning and quality is of the utmost importance as evidenced by this analysis. Going forward, such data should be more readily available for stakeholders (governments, GPOs, distributors, and manufacturers) to guide drug manufacturing priority and improve resiliency.

Whether it has been the last 20 months of the pandemic or the enduring hardship for pediatric oncology patients without essential drugs, stakeholders should move beyond discussion and investigation and proceed to meaningful action that can be identified and measured through collaborative efforts such as the Medicine Supply Map. To contribute to these efforts, contact the collaborators of this paper.

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About the collaborators

About USP

For over 200 years, USP has worked to build trust where it matters most: in the world's medicines, dietary supplements, and foods. Through our rigorous science and the public quality standards we set, USP helps protect patient safety and improve the health of people around the world.

USP is an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines. We are working to strengthen the global supply chain so that the medicines people rely on for health are available when needed and work as expected.

usp.org

About Vizient

We are the largest member-driven, healthcare performance improvement company in the country.

Backed by network-powered insights in the critical areas of clinical, operational, and supply chain performance, Vizient® empowers members to deliver exceptional, cost-effective care at every turn.

Together with our members, we are fueling new business models and new approaches to care—all through the power of brilliant connectivity.

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About Angels for Change

Angels for Change is a volunteer-run organization on a mission to end drug shortages through advocacy, awareness, and a more resilient supply chain. Founder Laura Bray, a business professor and consultant, established Angels for Change after her own daughter's Leukemia treatment was disrupted by a drug shortage.

Laura believes lifesaving medicines must be in supply and available at the right place and right time, ensuring access to patients. Angels for Change works with healthcare leaders to help end health crises created by drug shortages.

angelsforchange.org

Appendix I: Select hypotheses tested

Variable	Included in shortage model	Statistical significance
Dosage form	Yes	Yes
Average dosage price	Yes	Yes
Inspections	Yes	Yes
Molecular weight	Yes	No
Count of FDF manufacturing sites	No	Yes
Count of API manufacturing sites	No	Yes
Count of USP standards users	No	Yes
Network demand for drug product	No	Yes
Line-item fill rate	No	Yes
Age of the drug	No	Yes
Geographic concentration of API manufacturers	No	Yes
Geographic concentration of FDF manufacturers	No	Yes
Geographic Concentration of USP Standards Users	Yes	Yes
Therapeutic class	No	Sometimes
Special handling	No	No
Lyophilization	No	Yes
FDA recalls	No	Yes
FDA warning letter	No	Yes
History of drug shortages	No	Yes

Appendix II: Model characteristics and performance

The full dosage form model has an accuracy of 89.0% (see Figure 10), representing the percentage of total cases that are either true positives or true negatives. Additionally, the full dosage form model can accurately predict shortages 23.4% of the time, but is designed to be flexible so that the accuracy at predicting shortages can be increased by sacrificing the accuracy of predicting non-shortages (63.9%). An injectable drug model was also created to predict drug shortages for only injectable drugs, and this model produces an overall accuracy of 71.7% with the ability to accurately predict drug shortages 42.0% of the time and non-drug shortages 60.0% of the time.

Metric	All drugs model	Injectable only model
Accuracy	89.0%	71.7%
AUC[19]	60.8%	64.1%
Precision	63.9%	60.0%
Recall	23.4%	42.0%

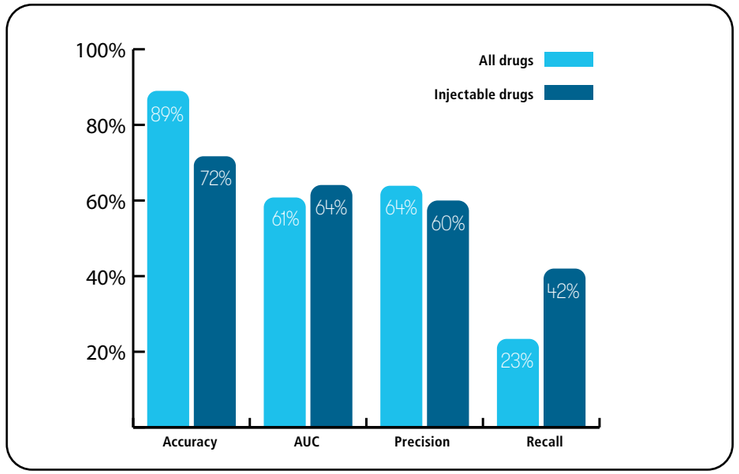

Figure 10 – *Drug Supply Chain Resiliency Model Performance, USP's Medicine Supply Map*

References

1. Based on USP's Drug Supply Chain Resiliency Model and analysis contained in this paper.
2. Unguru, Yoram et al. "Chemotherapy and Supportive Care Agents as Essential Medicines for Children With Cancer." JAMA pediatrics vol. 173,5 (2019): 477-484. doi:10.1001/jamapediatrics.2019.0070.
3. USP is an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines.
4. Vizient is the nation's largest member-driven healthcare performance improvement company.
5. Angels for Change is a nonprofit 501(c)(3) organization committed to resolving drug shortages.
6. USP's Medicine Supply Map is a graph-based analytics solution that combines 40+ discrete public and proprietary datasets to identify, characterize, and quantify risk in the upstream supply chain.
7. Analysis from USP's Medicine Supply Map.
8. Drug Shortage Bulletins are copyrighted by the Drug Information Service of the University of Utah, provided by ASHP as its exclusive authorized distributor, and used with permission. Please refer to the full Copyright and Disclaimer notice at https://www.ashp.org/drug-shortages/current-shortages.
9. Ibid.
10. Relative importance rank determined by a backward selection algorithm applied to random forest simulations, combined with input from subject matter experts.
11. Pricing data based on publicly available WAC pricing.
12. Throughout this paper, shortage correlations are based on drug products containing shortage records during the past 12 months (8/19/2020 to 8/18/2021).
13. Volume weighted WAC pricing from January 2019 through July 2019.
14. 2019 Drug Shortages Report, Updated February 21, 2020, https://www.fda.gov/media/131130/download.
15. Ibid.
16. Ibid.
17. https://www.fda.gov/news-events/fda-voices/help-reduce-drug-shortages-we-need-manufacturers-sell-quality-not-just-medicine.
18. https://www.fda.gov/media/87643/download.
19. Area under curve (AUC) for the receiver operating characteristic curve is the normalized probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one.

To contribute to these efforts, contact the collaborators of this paper: