DATA BRIEF
Prepared for HHS/ASPE Office of Science and Data Policy
January 8, 2025

Analysis of Drug Shortages, 2018-2023

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KEY POINTS

- Between 2018 and 2023, a total of 258 unique active ingredients (i.e., molecules) went into national shortage per the FDA's report to Congress. Using historical archives of the FDA Drug Shortages resources[1,2] and the FDA NDC Directory[3], we found that these 258 molecules are represented by 1,961 unique CDER-regulated prescription drug products (identifiable by their 9-digit NDC numbers).*
- According to our analysis of publicly available FDA data sources, over twice as many generic drug shortages began (n = 1,391) as brand drug shortages (n = 600), which is partly due to generic drug products being more common in the market. An additional 47 drug product shortages involved unapproved drugs with market authorization.†
- Injectable drug products made up half (n = 1,018) of all drug shortages, compared to 42.3 percent (n = 863) for oral drug products and 7.7 percent (n = 157) for topical drug products. This is highly disproportionate, as oral medications are by far the most common type of drug marketed in the United States.
- Using the data from 2018 to 2023, we find that drug shortages last roughly twice as long for injectable products (median = 4.6 years) as for oral products (median = 1.6 years) or topical products (median = 2.2 years).
- Shortages of essential products last much longer (median = 4.0 years) than those medicines that are not on the essential medicines lists used in this analysis (median = 2.3 years).‡ Essential medicines also accounted for roughly one-third (n = 599 or 29.4 percent) of the drug products that went into shortage.
- The number of generic drug products with an ongoing shortage decreased from 2020 to 2023, while the number of brand drug products increased slightly. There was a spike in drug shortages in the middle of 2020, possibly due to the COVID-19 pandemic, but this decreased over the next two years before starting to rise again in 2023. Since the creation of the Executive Order Essential Medicines List in October 2020 (which also coincided with the COVID-19 pandemic), there has been a substantial decrease in the number of generic essential medicines with an ongoing shortage.

* Whereas FDA's report to Congress was based on internal data sources and classified drug shortages based on unique molecules, we performed an analysis at the level of 9-digit NDCs using publicly available data.
† For more information, see https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs.
‡ We identified essential medicines as those included in either the FDA-published Executive Order Essential Medicines List or the Essential Medicines List published by Advanced Regenerative Manufacturing Institute, which is largely a subset of the FDA EML.

INTRODUCTION

Drug shortages are a persistent problem in the United States and this issue has become increasingly important, as the number of ongoing drug shortages has risen since 2017.[4] A 2019 report by the interagency, FDA-led Drug Shortages Taskforce identified several economic forces as the root causes of drug shortages.[5] The first is related to profitability. Many shortages occur in markets with generic drug competition. Once a brand drug loses its patent rights and all FDA-granted exclusivities, generic drug manufacturers enter the market and drive prices down. This gradually erodes profits for all market participants (brand and generic combined) and, in the long run, can lead to insufficient economic incentives for manufacturers to enter or remain in those markets. Some drug suppliers eventually exit the market, leaving the supply chain less diversified and more prone to drug shortages. When there are fewer suppliers in a market, any disruption or delay experienced by one supplier can have a large impact on total market supply. Natural disasters, for example, can lead to unexpected facility closures, which can heavily affect drug markets with few suppliers.

The 2019 Drug Shortages Taskforce report also documented that purchasers, group purchasing organizations, and consumers need more information on the clinical and financial impacts of shortages on patients and healthcare delivery to make informed buying decisions to ensure a reliable supply. Specifically, purchasers have limited information that can be used to assess the manufacturers' quality systems, back-up manufacturing capabilities, or risk-management plans when selecting a drug and often choose drugs solely based on price.[5] This creates a tendency for the market to reward drug companies that achieve lower costs by sacrificing investment in resilient manufacturing practices (e.g., mature quality management systems, backup manufacturing capability, risk-management plans, modernized manufacturing equipment). Consequently, drug manufacturers often rely on outdated or suboptimal systems of quality control, which increases the likelihood of shortages or supply disruptions due to regulatory inspection failures, product recalls, production pauses to address quality issues, etc. In addition, drug manufacturers have unique logistical and regulatory challenges that make recovery from a supply disruption slow and difficult.[5] For example, when manufacturers wish to increase production, either by modifying an existing facility or building a new one, they may have to obtain approvals from many different national regulatory bodies, which can take time. Further, since drug manufacturing facilities typically operate above 80 percent capacity, firms often cannot increase production substantially without incurring additional costs associated with purchasing new equipment or new property, which makes it difficult to increase production when a shortage occurs.[5]

The pharmaceutical supply chain has become more complex and global in the past two decades, and as of August 2024, only 24 percent of active pharmaceutical ingredient (API) manufacturing facilities for U.S.-marketed drugs were in the United States.[6] When a supply shortfall occurs, efforts to increase production can involve multiple companies located in different countries, which can slow the response as it may involve obtaining regulatory approval from multiple national regulatory bodies.

Drug shortages impact public health and lead to delays in medical care, higher rates of medication errors, and increased side effects as patients switch to unfamiliar and potentially less ideal treatments.[7] A scoping literature review found that drug shortages were associated with elevated mortality in 10 of 16 studies, increased incidence of adverse reactions in 14 of 24 studies, and higher out-of-pocket costs in 5 of 5 studies.[8] For example, a study on norepinephrine shortages from 2011 to 2012 found that in-hospital mortality increased by 3.7 percentage points during the shortage, which coincided with increased use of alternative treatments for patients with septic shock.[9] The full impact of shortages on public health, however, is difficult to quantify in its entirety given the complex range of short and long-term effects that patients may experience because of a drug shortage.[5]

STUDY OBJECTIVES

Given the impact of drug shortages on patients and the persisting economic pressures that lead to supply chain vulnerabilities, there is a need to understand recent trends in drug shortages and patterns in the types of drugs that experience shortages. The goals of this study are as follows:

(1) Identify and characterize all drug shortages that began between January 2018 and December 2023 and involved drugs marketed in the United States regulated by the Center for Drug Evaluation and Research (CDER).[§,**]

(2) Identify those drugs that had an ongoing shortage from 2020 to 2023, even if the shortage began before 2018.

(3) Assess trends in the frequency of new and ongoing shortages, and consider how these trends vary by dosage form, brand versus generic status, and essential medicine status.

(4) Estimate shortage durations and compare the rate at which shortages are resolved for different types of drugs, i.e., based on dosage form, brand versus generic status, and essential medicine status.

(5) Evaluate the prevalence of essential medicines in new and ongoing drug shortages and compare their trends to drugs that are not designated as essential by either the Executive Order (EO) Essential Medicines List (EML) published by FDA or the EML published by the Advanced Regenerative Manufacturing Institute (ARMI).

This study makes several contributions to ongoing research on drug shortages in the United States. When a shortage is resolved, it typically remains on the FDA website for six months and then is removed. While this process keeps the public informed on relevant and current shortages, it makes assembling complete historical records, and calculating shortage duration, difficult. Additionally, analyses of drug shortages are typically performed at the level of the molecule, but a single shortage could affect numerous drug products—one possible indicator of the magnitude of the shortfall. Another challenge in drug shortage analyses is the identification of drug subgroups, including essential medicines, which are known to have a history of shortage but are not identified by NDC number in the EO EML published by FDA or the EML published by ARMI. Using FDA web archives, we identified all drugs (including their 11-digit NDCs) that went into shortage between 2018 and 2023 and constructed a history of each drug's shortage status over time. We used these records to estimate the date when the shortage was first marked resolved and the corresponding shortage duration. Because we extracted each drug's NDC number, we were also able to characterize the types of drugs that went into shortage by matching to archives of the FDA NDC Directory, which also delists drugs removed from the market. Finally, by comparing drug descriptions in the EMLs to descriptions in the NDC Directory, we were able to identify essential medicines and assess trends in their shortages during the study period.

[§] In this analysis, we use the terms "drug" and "product" to refer to a distinct 9-digit National Drug Code (NDC). The 9-digit NDC identifies the labeler and product of a given molecule, strength, and dosage form.

[**] We did not include shortages of drugs under the jurisdiction of the Center for Biologics Evaluation and Research (CBER) because we could not estimate the shortage resolution date.

METHODS AND DATA SOURCES

Drug Shortages Data

In certain circumstances, drug manufacturers are required to notify FDA when a drug shortage begins or is expected to begin.[10] To inform the public of the shortage, FDA provides (a) a downloadable drug shortage Excel file that it first published in December 2019,[1] and (b) a webpage that lists all ongoing and recently resolved shortages, with links to separate pages containing 11-digit NDCs involved in each shortage.[2] FDA removes drugs from its shortage list six months after the shortage resolves.[11] FDA posts notifications of discontinuations of production that do not lead to shortages when they are received from the companies and removes them one year after posting. To capture all new drug shortages between January 2018 and December 2023—including those that FDA removed from its shortage list before our study began in January 2024—we used archived versions of the downloadable drug shortage Excel file, which we accessed using the Internet Archives.[12,††] We supplemented these files with archives of the drug shortage webpage.[‡‡] If a 10-digit NDC was listed in either source, we converted it to 11 digits by adding a leading zero in the appropriate location.[13] The NDC was missing or incomplete for 137 out of 3,799 total (4 percent) extracted 11-digit NDCs; therefore, we searched the NDC Directory and the web (including DailyMed, CMS publications, manufacturer websites, wholesaler websites, and healthcare provider websites) to identify the correct 11-digit NDC.

We processed the drug shortages data in several steps. After extracting all 11-digit NDCs, we collapsed them into 9-digit NDCs and de-duplicated records by only retaining unique combinations of 9-digit NDCs and shortage start date (month and year). We performed our analysis at the 9-digit NDC level, which uniquely identifies the molecule, strength, formulation, and labeler, rather than the 11-digit NDC level, which additionally identifies the package quantity and package size. In this brief, we use the terms "drug" and "product" synonymously with the 9-digit NDC and "package" synonymously with the 11-digit NDC. Roughly three percent of drugs had multiple packages with different shortage durations. For each of these drugs, we assumed the shortage duration was equal to that of the package with the longest shortage duration. Under this approach, we considered a product's shortage to be fully resolved only once all of its packages were no longer in shortage. We defined a shortage event as a unique combination of molecule, strength, dosage form, and shortage start date. Some shortage listings included a reason for the shortage, if specified or reported to FDA by the manufacturer. We classified each description into one of seven aggregate reasons, which were based on the information provided by the manufacturers to FDA.[§§] For shortages that were resolved between 2018 and 2023, we estimated the resolution date as the earliest "Date of Update" in any of the historical shortage listings with a status of "Resolved."

In 15.1 percent of cases, a package was delisted without being marked resolved. We treated these observations as right-censored and calculated the shortage duration as the difference between the initial posting date and the last date when the shortage listing was updated in our records. We treated drugs that had not gone into shortage by the date of our final data extraction (December 21, 2023) in this same way. We included delisted drugs with unresolved shortage status in our estimates of drug shortage

[††] We extracted all 39 available archives of the file, spanning December 29, 2019, to December 21, 2023.
[‡‡] We used 84 historical versions of the drug shortage webpage (spanning January 9, 2018, to December 1, 2022) to extract 13,040 individual webpages that listed specific drugs in shortage and their 11-digit NDCs.
[§§] The seven categories included: increase in demand for the drug, shortage of the active pharmaceutical ingredient (API), manufacturing delay, quality control issues or regulatory issues, discontinuation of a drug, shipping delay, or other.

duration. We also included them in our count of ongoing shortages in a given month if the drug had not yet been delisted as of that month.

In 6.4 percent of cases (n = 140 products), a second shortage appeared in the dataset despite the product already being in an ongoing shortage. This may be due to slight discrepancies in the listed initial posting date as shortage postings were updated, or it may be the result of a new 11-digit NDC associated with the product being added to the posting later. We removed these later instances to avoid overestimating the number of drug shortages.

FDA NDC Directory

We merged the resulting drug shortage dataset with data from the FDA NDC Directory.[3] We used the Internet Archives to extract all historical versions of the NDC Directory that were available from 2018 to 2023, since FDA updates the NDC Directory daily based on biannual submissions from registered manufacturers.[3] The NDC Directory provided information about the drugs in shortage, including application number, application type, active ingredients, strength, dosage form, and route of administration. We classified Abbreviated New Drug Applications (ANDAs) as generic drugs and we classified New Drug Applications (NDAs) and Biologics License Applications (BLAs) as brand drugs. In some cases, a shortage involved an unapproved drug that was being temporarily imported into the United States to help resolve a drug shortage.[***] We classified all drugs in shortage as injectables, orals, or topicals based on the route of administration and dosage form listed in the NDC Directory.

Essential Medicines Lists

We combined the EO EML published by FDA[14] with the EML sponsored by the Office of the Assistant Secretary for Administration for Strategic Preparedness & Response (ASPR) and published by ARMI[15,†††]. The EO EML includes drugs that are "most needed for patients in U.S. acute care medical facilities, which specialize in short-term treatment for severe injuries or illnesses, and urgent medical conditions."[14] Drugs in the ARMI EML "were identified as either critical for minimum patient care in acute settings or important for acute care, with no comparable alternative available."[15] The ARMI EML overlaps heavily with the acute care drugs in the EO EML and lists three additional molecules that are not in the EO EML. The drugs included in the EO EML and ARMI EML have not changed since their initial publication in 2020 and 2022, respectively. Therefore, we designated drugs on either list as essential for the full study period.

Overview of Analytic Methods

We calculated descriptive statistics of new and ongoing drug shortages from 2018 to 2023. We considered counts of drugs/products (i.e., 9-digit NDCs) and counts of unique shortage events (i.e., unique combination of molecule, strength, form, and shortage start date), since a single shortage could involve multiple drugs. For each drug product, we estimated the shortage duration as the difference between the initial posting date and the estimated resolution date. We fit Kaplan-Meier survival functions to assess differences in shortage duration by dosage form, brand status, and essential medicine status. Kaplan-Meier survival curves are non-parametric estimators of the survival function that account

[***] Unapproved drugs are those that have not been formally reviewed by FDA for safety, efficacy, and quality. FDA authorizes certain unapproved drugs for marketing in the United States, including drugs that treat serious conditions with no FDA-approved medication (or limited supply of FDA-approved drugs). In our analysis, we counted these unapproved drugs only if their NDCs were included in the FDA drug shortage posting.

[†††] The Advanced Regenerative Manufacturing Institute is a member-based nonprofit organization that leverages stakeholder engagement to identify and solve problems impacting the healthcare industry.

for right-censoring in the data. For example, if a drug went into shortage in January 2020 and was still in shortage at the end of December 2023, then the shortage duration is known to be at least four years, but an exact duration is not known.

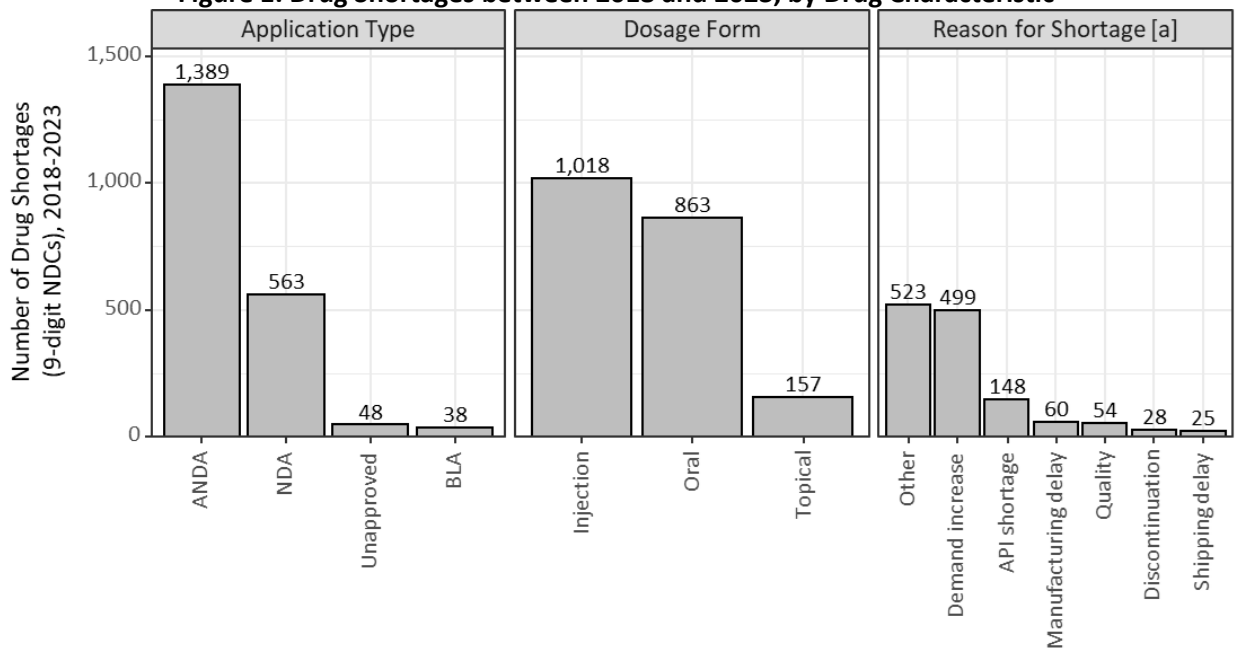
RESULTS

Types of Drugs Involved in Shortages

From 2018 through 2023, 1,986 drugs (i.e., 9-digit NDCs) went into shortage a total of 2,063 times. Of the 2,063 instances when a drug went into shortage, 98.8 percent (n = 2,038) had a matching record in the NDC Directory. In this section, we analyze these 2,038 drug shortages, which correspond to 1,961 unique drugs.[‡‡‡]

As Figure 1 shows, of the drug shortages that started between 2018 and 2023, about two-thirds were of small-molecule generics (n = 1,389 ANDAs), and about one-quarter were of small-molecule brand drugs (n = 563 NDAs). Only 1.9 percent of drug shortages were of biologics (n = 38 BLAs).[§§§] Half the drug shortages were of injectables (n = 1,018; 50.0 percent), followed by oral drugs (n = 863; 42.3 percent) and topical drugs (n = 157; 7.7 percent). A reason for the shortage was given for about two-thirds of products (n = 1,337), but many of these listed "other" as the reason (n = 523; 39.1 percent). Of the cases where a reason was given by the manufacturer, the most common was an increase in demand for the drug (n = 499; 37.3 percent), followed by an API shortage (n = 148; 11.1 percent).[****]

Figure 1. Drug Shortages between 2018 and 2023, by Drug Characteristic



[a] The shortage reason was only reported for 1,337 of the 2,038 drug shortages from 2018 to 2023.

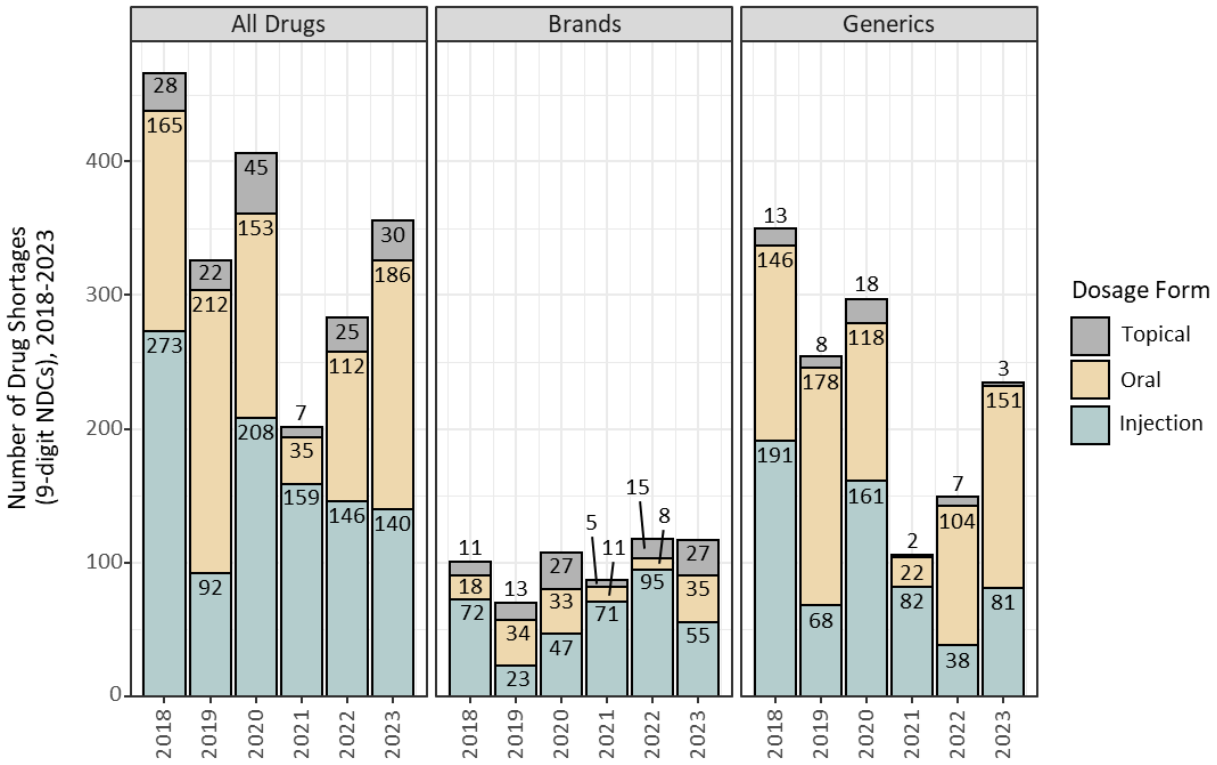
[‡‡‡] Of the drugs with a matching record in the NDC Directory, n = 1,887 drugs went into shortage once, n = 71 drugs went into shortage twice, and n = 3 drugs went into shortage three times (all fluorescein injection).

[§§§] As stated above, we did not analyze CBER-regulated drugs that went into shortage and only included CDER-regulated drugs.

[****] FDA has provided statistics based on their internal data, which classify many shortages reported here as having "other" for the reason. FDA found that, from 2013 to 2017, most shortages were due to manufacturing or product quality problems (62 percent) or an increase in demand (12 percent).[5] This was also true in 2023, when 55 percent were due to an increase in demand and 30 percent were due to manufacturing or product quality issues.[16]

More drugs went into shortage in 2018 (n = 466) than any other year in the study period (see Figure 2). The year 2021 had the fewest new drugs in shortage (n = 201), but this increased to 356 drugs in 2023. More oral drugs than injectables went into shortage in 2019 and 2023, but the reverse was true for all other years in the study period. Topical drugs consistently made up a very small proportion of the drugs that went into shortage. In general, the number of injectable drugs that went into shortage showed a steady decline over the study period, decreasing by 48.7 percent from 2018 (n = 273) to 2023 (n = 140).

Figure 2. Drugs Shortages that Began between 2018 and 2023, by Year, Brand Status, and Dosage Form

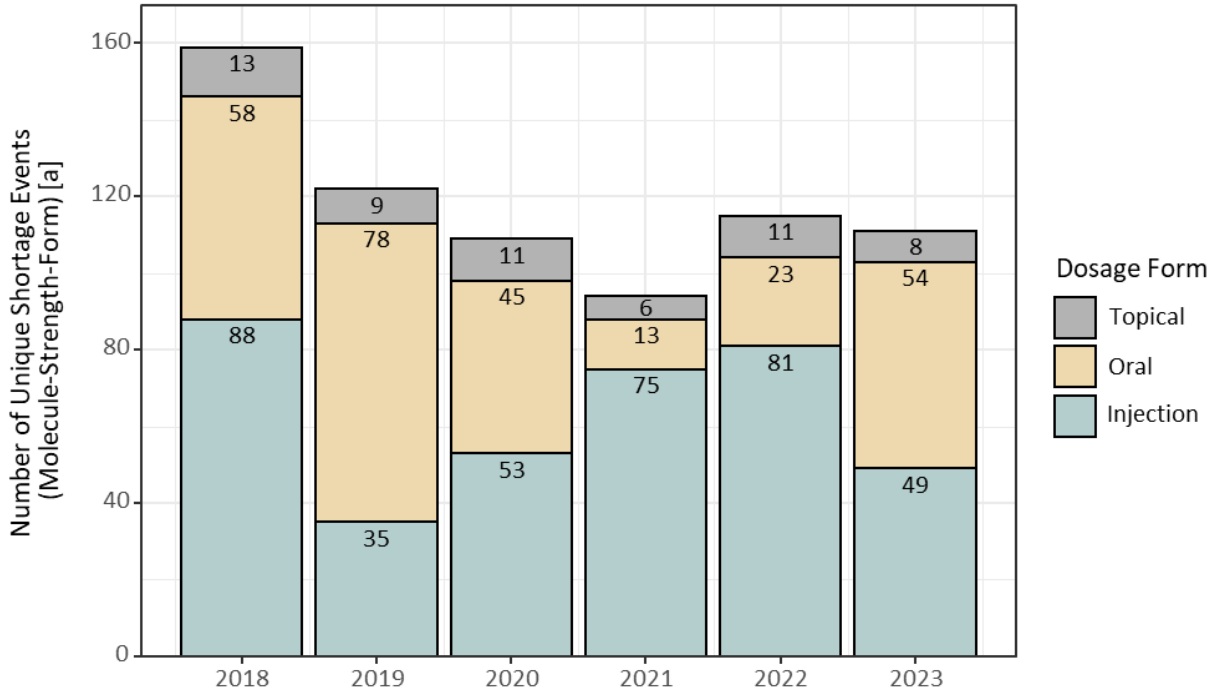


Note: brands include drugs approved through NDAs and BLAs. Generics include drugs approved through ANDAs. Unapproved drugs are included in "All Drugs" but are not shown as a separate panel due to very small sample size.

There were 710 unique shortage events that began between 2018 and 2023,[††††] and on average, each shortage event involved 2.9 different drugs.[‡‡‡‡] As Figure 3 shows, there were more new shortage events in 2018 (n = 159) than any other year, which is consistent with the drug-level analysis of Figure 2. After this initial peak, the number of new shortage events showed no linear trend over the remaining years (2019 to 2023) and fluctuated between 94 and 122. Over the full study period, shortages of injectables made up 53.7 percent (n = 381) of all new shortage events, compared to 38.2 percent (n = 271) for oral drugs and 8.2 percent (n = 58) for topical drugs. New shortage events were therefore 40.6 percent more likely to involve injectable drugs than oral drugs. Whereas Figure 2 showed a decreasing number of injectable drugs going into shortage, there was not a similar decline in the number of unique shortage events of injectables.

[††††] We define a shortage event as a unique combination of molecule, strength, dosage form, and shortage start date.
[‡‡‡‡] Specifically, the 710 shortage events corresponded to 2,038 instances of a drug (i.e., 9-digit NDC) going into shortage, giving 2,038/710 = 2.9 drugs per shortage event.

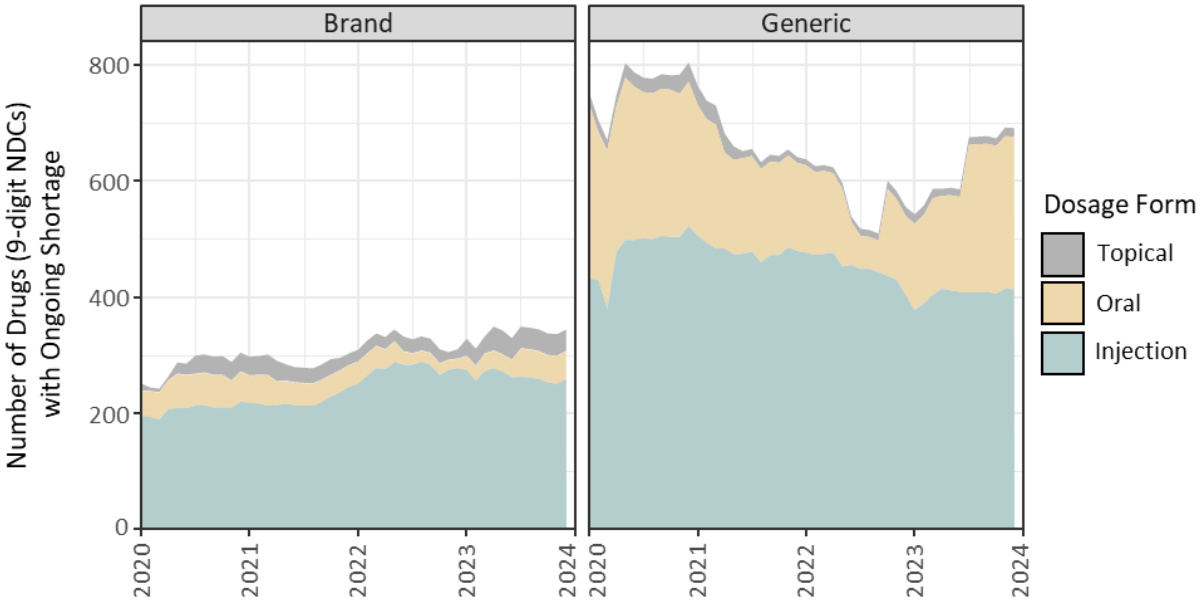
Figure 3. Number of New Drug Shortage Events between 2018 and 2023, by Year and Dosage Form



[a] To quantify shortage events, we counted the number of unique combinations of molecule, strength, and dosage form.

Overall, the total number of drugs with an ongoing shortage increased by 1.7 percent from the beginning of 2020 (n = 1,043) to the end of 2023 (n = 1,061) (see Figure 4), indicating that drugs were added to the shortage list slightly more quickly than they were removed. The number of brand drugs with an ongoing shortage increased by 37.1 percent from January 2020 (n = 251) to December 2023 (n = 344). The number of generic drugs with an ongoing shortage decreased by 8.1 percent from January 2020 (n = 753) to December 2023 (n = 692). During the four-year period, the number of injectable drugs in shortage rose by 33.5 percent for brands (from n = 194 to n = 259) but decreased by 4.2 percent for generics (from n = 432 to n = 414). The number of oral drugs in shortage rose by 6.7 percent for brands (from n = 45 to n = 48) but decreased by 12.6 percent for generics (from n = 301 to n = 263). The number of topical drugs with an ongoing shortage roughly tripled for brands, from 12 to 37, and declined by a quarter for generics, from 20 to 15.

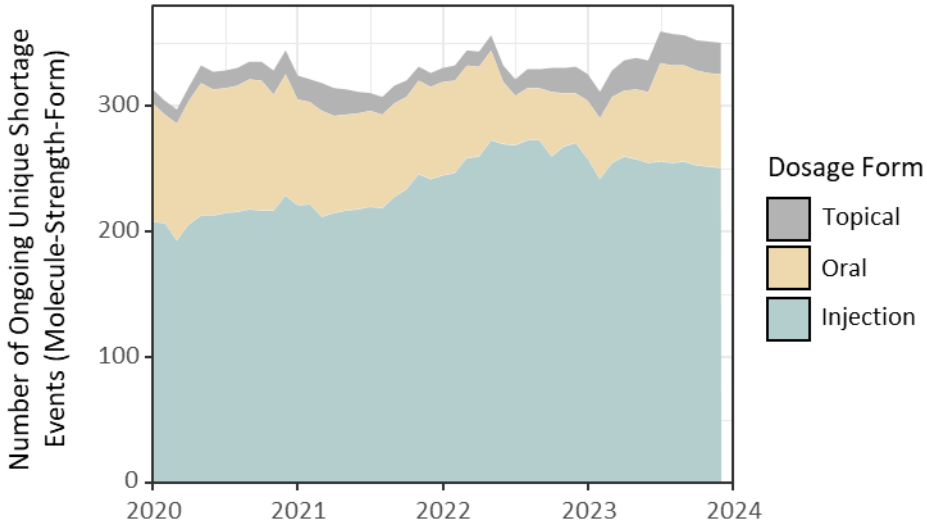
Figure 4. Drugs with Ongoing Shortage from 2020 to 2023, by Year, Brand Status, and Dosage Form



Note: brands include drugs approved through NDAs and BLAs. Generics include drugs approved through ANDAs. Unapproved drugs were analyzed but are not shown here as a separate panel due to very small sample size.

The total number of ongoing shortage events increased by 11.8 percent from January 2020 (n = 313) to December 2023 (n = 350) (see Figure 5). Ongoing shortage events of injectables increased by roughly one-fifth, from 208 to 251. Ongoing shortage events of orals decreased by slightly more than one-fifth, from 94 to 74. Ongoing shortage events of topicals more than doubled from 11 to 25.

Figure 5. Unique Ongoing Shortage Events between 2020 and 2023, by Year and Dosage Form

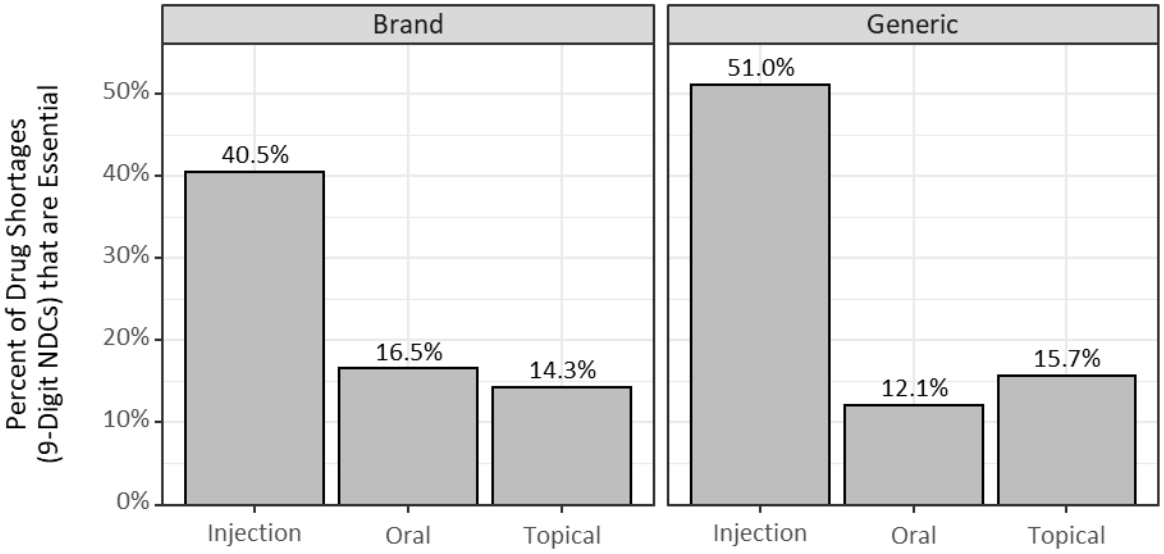


Shortages Involving Essential Medicines

Many essential medicines have a history of going into shortage and were designated as essential based on clinical necessity. It is therefore unsurprising that a large proportion of drugs that went in shortage from 2018 to 2023 (n = 599; 29.4 percent) were essential medicines. Among injectable brand drugs that went into shortage, 40.5 percent (n = 147) were essential medicines (see Figure 6). Among injectable

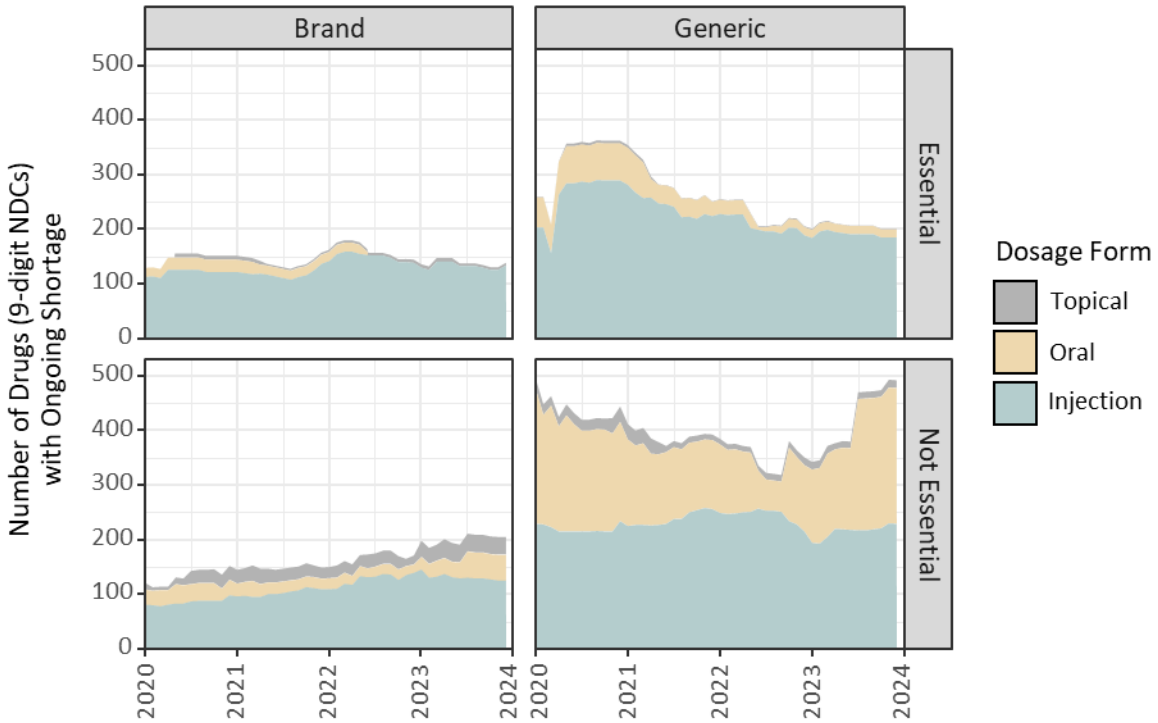
generic drugs, half (n = 317; 51.0 percent) were essential. Essential medicines were generally two to four times more common among injectable drugs in shortage than oral or topical drugs in shortage.

Figure 6. Essential Medicine Shortages, by Brand Status and Dosage Form, 2018 to 2023



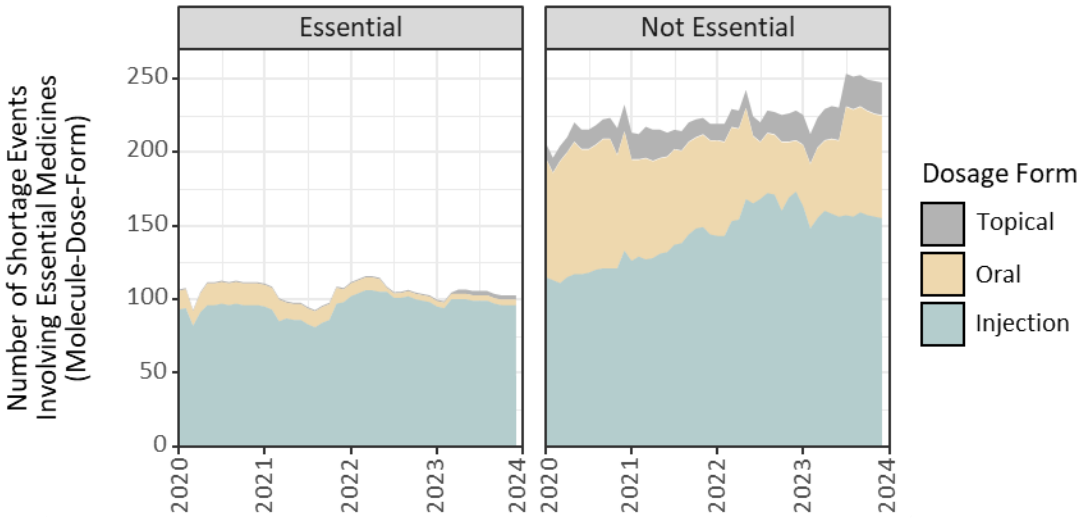
The number of drug products not designated as essential with an ongoing shortage grew by 12.7 percent from January 2020 to December 2023, whereas the number of essential medicine products with an ongoing shortage decreased by 15.0 percent, as can be seen by comparing the bottom panels of Figure 7 to the top panels. During this four-year period, the number of essential medicines with an ongoing shortage dropped by 22.4 percent for generic drugs (from n = 259 to n = 201) but increased by 6.9 percent for brand drugs (from n = 130 to n = 139). The number of drug products not designated as essential with an ongoing shortage dropped by 0.6 percent for generics (from n = 494 to n = 491) but rose by 69.4 percent for brands (from n = 121 to n = 205).

Figure 7. Essential Drugs in Shortage, by Year, Brand Status, and Dosage Form



The number of ongoing shortage events that involved essential medicines decreased slightly from 107 in January 2020 to 103 in December 2023 (see Figure 8). Consistent with Figure 7, though, the number of shortage events of drug products not designated as essential grew, from 206 to 247.

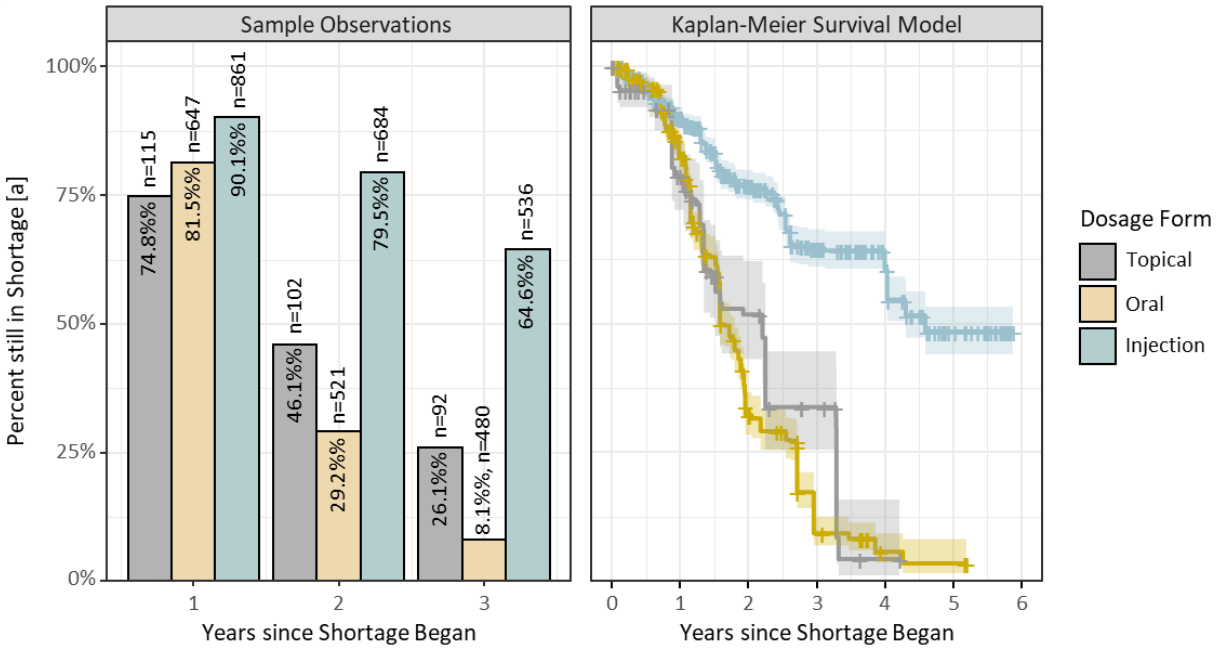
Figure 8. Ongoing Drug Shortage Events involving Essential Medicine(s), by Year and Dosage Form



Shortage Duration by Dosage Form, Brand Status, and Essential Medicine Status

There were very large differences in shortage resolution rates based on dosage form (see Figure 9). One year after the shortage began, 90.1 percent of injectable drugs were still in shortage, compared to 81.5 percent of oral drugs and 74.8 percent of topical drugs. Three years after the shortage start date, however, 64.6 percent of injectable drugs were still in shortage, compared to only 8.1 and 26.1 percent of orals and topicals, respectively. The Kaplan-Meier survival plot (right panel of Figure 9) shows that, among dosage forms, there are large, statistically significant differences in the distribution of shortage duration. The median shortage duration was 1.59 years for oral drugs (95 percent confidence interval: 1.59 – 1.80 years) and 2.21 years for topical drugs (1.52 – 2.25 years). Injectables, however, stayed in shortage for more than twice as long, with a median shortage duration of 4.60 years.[§§§§]

Figure 9. Drug Shortage Resolution Rates, by Dosage Form

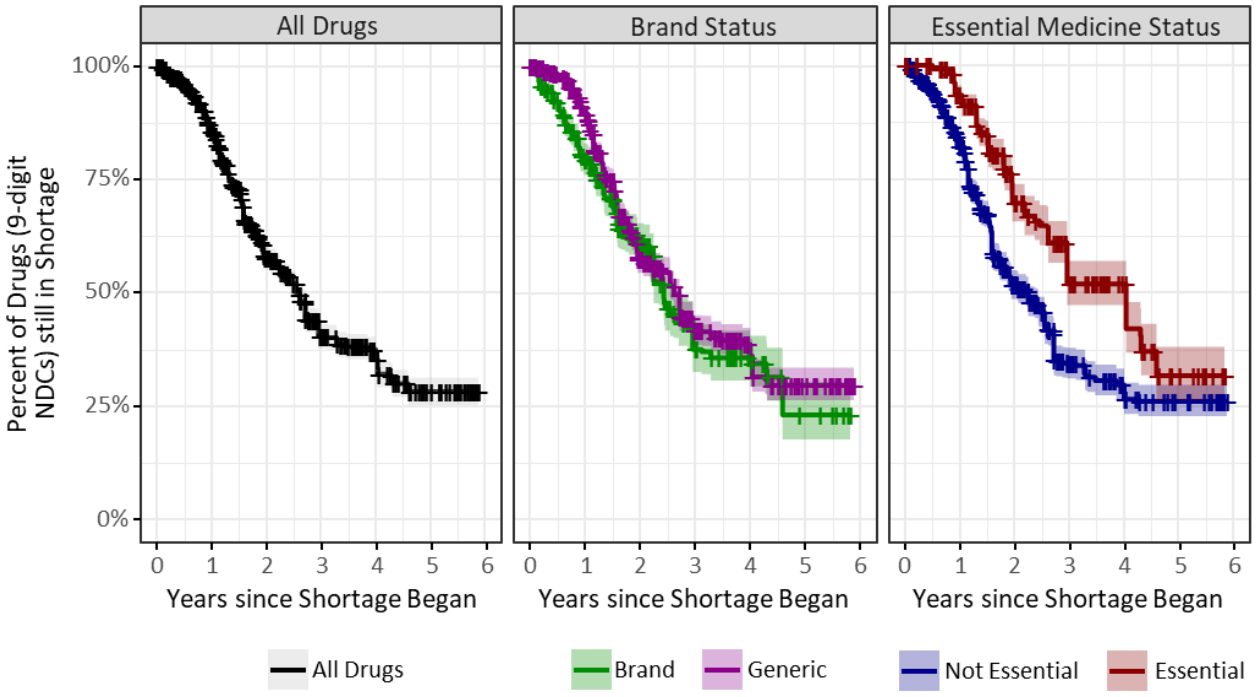


[a] Analysis is limited to drug shortages that began in 2018 through 2023. In the left panel, each proportion was calculated among the group of drugs for which shortage had been observed for at least the listed duration.

As illustrated in Figure 10, across all drugs, the median shortage duration was 2.55 years (95 percent confidence interval: 2.44 – 2.72 years). Shortages of drug products not designated as essential resolved more quickly, with a median shortage duration of 2.25 years (1.93 – 2.43 years). Essential medicines resolved at a significantly slower rate, with a median duration of 4.04 years (2.96 – 4.04 years). Brand drugs and generic drugs had overlapping survival curves, indicating similarities in their distributions of shortage duration. However, shortages resolved slightly more quickly for brands, which had a median duration of 2.43 years (2.25 – 2.71 years), than generics, which had a median duration of 2.61 years (2.55 – 2.72 years).

[§§§§] The 95 percent lower confidence bound is 4.30 years for the median shortage duration of injectables. The upper confidence bound cannot be estimated because the 95 percent upper estimate of the survival curve does not cross the median threshold of 50 percent, as seen in the right half of Figure 9.

Figure 10. Kaplan-Meier Survival Analyses for All Drugs and Drug Subgroups



DISCUSSION AND CONCLUSIONS

Drug shortages can be caused by several factors. Consolidation in the supply chain, product discontinuations, limited domestic manufacturing capacities, quality control issues, and natural disasters are all correlated with higher rates of drug shortages.[17–19] In 2020, the FDA reported that 62 percent of all drug shortages were caused by manufacturing and product quality problems resulting in supply disruptions.[5] Some researchers suggest that the practice of maintaining low to no excess manufacturing capacity—which is particularly common with generic drugs—may increase the number of drug shortages by making the supply chain more vulnerable when disruptions do occur.[20] Furthermore, as of March 2021, about half of FDA-registered finished dosage form manufacturing facilities and most API manufacturing facilities were located outside the United States,[21] which increases supply chain complexity and limits the United States' ability to respond to supply chain disruptions.[22] These factors impact the number of drugs in shortage, which we have quantified in this study.

We found that more drugs went into shortage in 2018 than in any other year of the study period, and that 2020 had the second highest number of drugs entering shortage. The relatively high number of drugs entering shortage in 2020 is not unexpected given that supply chain disruptions were common during the COVID-19 pandemic and affected pharmaceutical markets.[23] The overall pattern in the number of new drug shortages that we identified from 2018 to 2023 is mirrored in the American Society of Health-System Pharmacists (ASHP) report, though ASHP counts unique molecules and includes regional shortages, which is different from how we define a drug.[24] The high number of drugs that went into shortage and high number of unique drug shortages in 2018 can at least partially be explained by Pfizer's closing of a Kansas manufacturing facility for remediation in 2017, which resulted in reduced manufacturing capacity for many drugs that continued into 2018.[25–27] Additionally, in 2017 Hurricane

Maria devastated multiple pharmaceutical manufacturing facilities in Puerto Rico, and these manufacturing disruptions continued causing drug shortages in 2018.[28]

The number of new drug shortages per year had been experiencing a decline since Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, which gave FDA more authority to address drug supply chain challenges.[24,25] Moreover, since the creation of the EO EML in October 2020,[14] there has been a steady decline in the number of generic essential medicines in shortage and a relatively constant number of branded essential medicines in shortage. This decline, however, was likely also related to the COVID-19 pandemic, which was associated with more generic drug shortages. In particular, the number of ongoing shortages of generic essential medicines increased from 209 in March 2020 to 324 in April 2020 and remained above 300 until April 2021.

FDA has reported that sterile injectables account for most drug shortages.[5,29,30] Our analysis corroborated this, as we found that injectables accounted for 60 percent of brand drug shortages and 45 percent of generic drug shortages from 2018 to 2023. In most of our analyses, we found that generic drugs are more vulnerable to shortage than brand drugs. Low profitability of generic drugs coupled with relatively high development costs disincentivize market entry, leading to a less diversified supply chain that relies on cost-cutting measures like moving manufacturing abroad and operating without excess capacity.[31] In 2020, FDA reported that forty percent of generic drug markets have a single manufacturer supplying the market; this market concentration contributes to generic drug shortages.[5]

We found that injectables not only went into shortage at higher rates than orals or topicals, but they also stayed in shortage substantially longer.[*****] The percentage of drug shortages that were still unresolved after three years was roughly two to eight times higher for injectable drugs (65 percent) than oral or topical drugs (8 and 26 percent, respectively). Brand injectable drugs experienced an increase in ongoing shortages from 2020 to 2023, but for generic injectables, this decreased slightly, dropping below pre-pandemic drug shortage levels by the end of 2023. Nearly half of the injectable drugs added to the shortage list from 2018 to 2023 were essential medicines. Fewer companies are making older sterile injectable drugs.[32] The small number of manufacturers and limited production capacity for older injectables in addition to complex manufacturing processes and long lead times make injectables especially vulnerable to shortage.[32] Failure to comply with FDA's current good manufacturing practices violations are also more common among injectables, which result in production delays and/or stoppages.[33]

Similar to injectables, we found that shortages of essential medicines took substantially longer to resolve than products not designated as essential—though the number of ongoing drug shortages involving essential medicines decreased from 2020 to 2023. To an extent, it is not surprising that essential drugs make up a large portion of shortages, as essential medicines such as antibiotics, cancer treatments, and insulin are critical for treating life-threatening illnesses, putting them in high demand that persisted during the COVID-19 pandemic despite some patients delaying or canceling certain medical care to avoid COVID-19 exposure. Given that the demand for these drugs may not have declined during the pandemic, the observed spike in the number of generic essential drugs in shortage in 2020 could be attributable to the COVID-19 pandemic, which caused delays and disruptions in drug manufacturing,

[*****] As a check of robustness, we re-calculated the median shortage durations while excluding drugs that went into shortage in 2020 or 2021, during the COVID-19 pandemic. The exclusion of drugs that went into shortage during the COVID-19 pandemic has a small effect on the overall estimates and mostly increased the width of the confidence intervals. For example, with the exclusion of these two years, we found the median shortage duration to be 2.55 (95 percent confidence interval: 2.37 – 2.72) years for all drugs, 1.80 (1.59 – 1.93) years for orals, 2.21 (1.52 – 3.29) years for topicals, and not estimable for injectables (but with a 95 percent lower confidence bound of 4.31 years).

procurement, importation, delivery, and other processes affecting supply chains.[34] The impact of these supply disruptions during the COVID-19 pandemic appears to have been particularly high for generic essential drugs, many of which have a history of going into shortage and higher shortage risk in general.

Drug shortages affect public health in the United States and will continue to pose challenges in the future, especially as the pharmaceutical industry continues to globalize and consolidate. Based on our findings, injectables, essential medicines, and generic drugs are more vulnerable to shortages compared to orals and topicals, products not designated as essential, and brand drugs, respectively. Our results also reflect the negative effects of natural disasters and pandemics on drug shortages. Given the grave impact of drug shortages on public health, improving the resiliency of the U.S. drug supply is essential.

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Suggested Citation

McGeeney, J.D., McAden, E., & Sertkaya, A. *Analysis of Drug Shortages, 2018-2023*. Prepared by Eastern Research Group, Inc. for the Office of the Assistant Secretary for Planning and Evaluation (ASPE), U.S. Department of Health and Human Services (HHS). January 2025.

Acknowledgments

We gratefully acknowledge Trinidad Beleche (HHS/ASPE), Oluwarantimi Adetunji (HHS/ASPE), Andrea Monge (HHS/ASPE), and Kathleen Miller (HHS/ASPE) for their leadership, guidance, and input throughout this study.

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Funding

This report was prepared for the U.S. Department of Health and Human Services (HHS) Office of the Assistant Secretary for Planning and Evaluation (ASPE) under contract no. HHSP233201500055I and task no. 75P00123F37008.