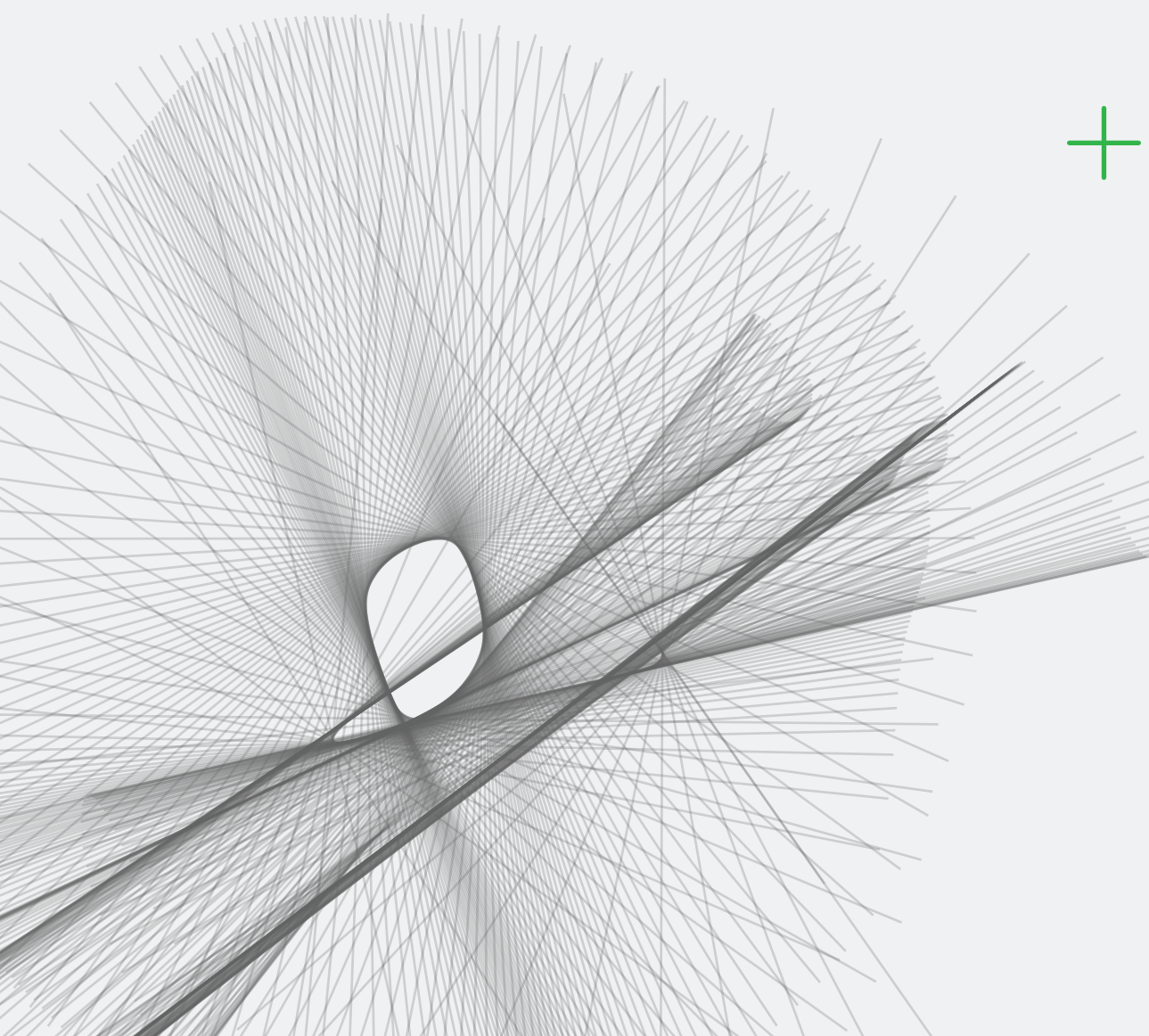


Drug Shortages in the U.S. 2023

A CLOSER LOOK AT VOLUME AND PRICE DYNAMICS



NOVEMBER
2023

Introduction

Drug shortages have recently received widespread news coverage for their impact on patient care and public health. The number of drug shortages in the U.S. is increasing as more shortages continue to be reported than resolved. Stakeholders have recommended various approaches to mitigate shortages, such as prioritizing essential medicines, stockpiling, and making changes to reimbursement or statutory rebates. Shortages appear to be driven by a variety of causes that need to be better understood, as they may impact which solutions will best address them.

In this report, shortages reported by the Food and Drug Administration are assessed in conjunction with sales and volume data of these medicines in the U.S. market. Characteristics of shortages, including product type, form, and the number of manufacturers are evaluated. Market concentration is assessed for molecules with shortages based on current sales data. The causes and impacts of shortages across a range of therapy areas are analyzed and presented here.

We intend for this report to provide a foundation for meaningful discussion about the mechanisms that can be put in place to mitigate shortages in the future and steps stakeholders can take to ensure patient access to medicines.

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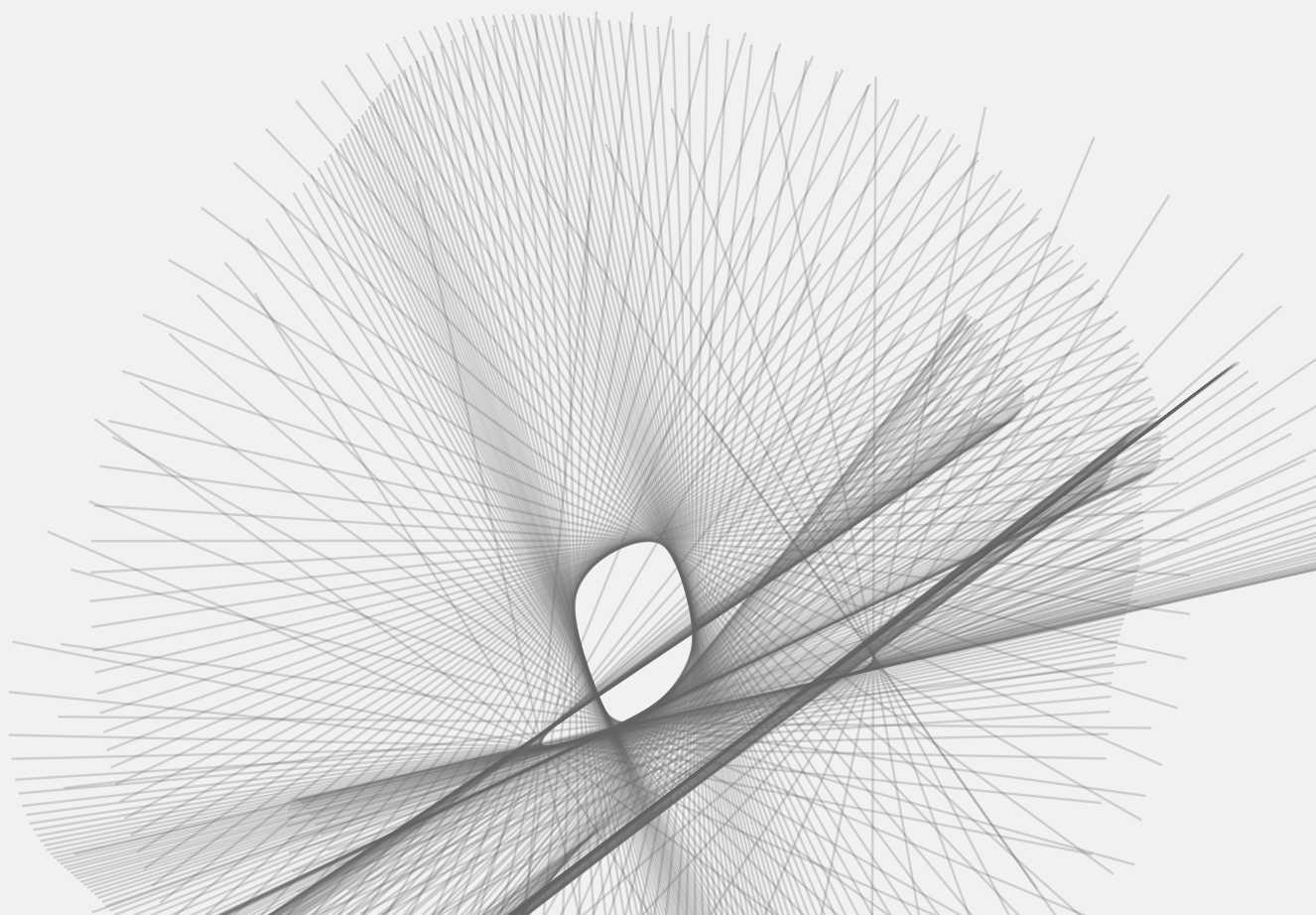
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Table of Contents

Overview	2
Overview of shortages in the U.S.	4
Oncology shortages	12
Shortages across other therapy areas	17
Notes on sources	24
Definitions	25
Methodologies	26
References	27
About the authors	28
About the Institute	29



Overview

Drug shortages occur when the demand of a drug exceeds the supply and are an ongoing issue in the U.S. healthcare system, although the number and severity of shortages has changed over time. While the overall number of shortages may be lower than it was more than a decade ago, the causes and impacts have shifted, requiring different strategies to resolve and prevent shortages. All stakeholders involved in the supply and distribution of medicines, from active ingredient manufacturers to pharmacists, play a role in preventing shortages and ensuring patient access to medicines.

OVERVIEW OF SHORTAGES IN THE U.S.

As of June 2023, there are 132 molecules in the U.S. market with active shortages, impacting a range of therapy areas including pain/anesthesia, oncology, central nervous system, and infectious disease. Over the past five-and-a-half years, three times as many new molecule shortages have occurred as have been resolved, with shortages typically lasting more than a year.

Shortages tend to be in generic (84%) and injectable drugs (67%) and are more frequently multi-source, while shortages were more often single-source generics in 2011, reflecting efforts by regulators and industry to increase generic approvals. Despite shortage molecules predominantly being multi-source, markets remain highly concentrated in a few suppliers, impacting the ability to readily resolve shortages when a leading supplier is affected, and new or existing manufacturers must build or expand manufacturing capacity to account for the gap in supply.

Shortages are more common at lower prices, with 56% of molecules in shortage priced less than \$1.00 per unit. An extended unit measured in these analyses is a volume metric, which varies by the type of form a drug takes (oral, injectable, etc.). As injectables are typically measured in milliliters and doses often comprise multiple units, the cost for a dose may be more for an injection than for an oral drug where extended units measure a pill or capsule, which is effectively reflecting a dosage unit. These costs, while not directly comparable, reflect that competition may be driving some of these drugs below their cost of production and distribution. The resulting underinvestment by manufacturers in maintenance and quality or forced exits from the market further constrain competition and challenge market resilience, as well as disincentivizing new entrants.

The planned discontinuations of drug packs rarely lead to shortages and may be a result of strategic business decisions or medicines being withdrawn from the market; however, market exits can disrupt other participants, although regulatory requirements to notify the FDA of planned discontinuations play a key role in enabling other companies to react appropriately.

ONCOLOGY SHORTAGES

Although oncology shortages have only impacted a small share of overall volume, inspection-driven disruptions and market exits have led to significant shortages in older genericized chemotherapeutics and particularly platinum-based chemotherapeutics. Treatment for cancer patients is strongly impacted and may be delayed by chemotherapy shortages, given their use as backbone therapies across multiple indications and limited options for therapeutic interchangeability.

Oncology drugs with significant shortages have highly concentrated markets despite multiple suppliers. Additionally, prices are low, making it more difficult for new or existing suppliers to achieve a return on investment for building or increasing manufacturing capacity to address shortages when major players have

Shortages more frequently occur in multi-source generics where markets are highly concentrated in a few suppliers, impacting resilience and prolonging shortages.



had disruptions. Despite reported shortages, overall oncology volume has continued to increase signaling shortages as a potential issue of disparate drug availability among regional health centers and individual providers, causing patients to delay receiving timely treatments.

SHORTAGES ACROSS OTHER THERAPY AREAS

Drug shortages have occurred across several therapy areas with causes ranging from increased demand to manufacturing disruptions, meaning a single solution may not prevent or resolve future shortages.

Public health measures during the COVID-19 pandemic disrupted the seasonal pattern of bacterial infections, particularly in children, and a return to historic infection levels in late 2022 led to a shortage in pediatric oral liquid antibacterials as the pandemic resulted in unpredictable demand. Conversely, injectable antibacterial shortages began in late 2021 when market share leaders experienced manufacturing delays while overall injectable antibacterial volume has been declining. Continued antibacterial shortages could inadvertently contribute to antimicrobial resistance, as changes in prescription behavior may lead to an increased use of broad-spectrum antibacterials, potentially exacerbating this global concern.

Anesthetic shortages have been persistent since 2017, particularly in local anesthetics, driven by a lidocaine shortage. General anesthetics and muscle relaxants have seen pandemic related shortages as these medicines have been utilized in hospitalized COVID-19 patients, resulting in supply-chain shocks that drove volumes up substantially. Though shortages remain in general anesthetics and muscle relaxants, the impact has lessened as these pandemic waves have subsided.

Psychiatric medicines have seen significant volume increases in recent years following greater awareness among the general public and increased modes of accessibility to providers (e.g., telehealth). Overall ADHD volume has increased 12% since 2017, leading

to shortages due to increased demand, particularly in amphetamine salts, despite regulators noting available manufacturing capacity. Shortages in mental health have been confined to a limited number of molecules and generally resolved quickly, despite significant growth in mental health prescriptions in recent years.

GLP-1 agonists are a novel mechanism and illustrate that shortages can also affect new drugs prior to patent expiry, despite innovators strong incentives to always have excess stock available. These drugs have shown such significant promise for people living with diabetes and obesity that use has more than doubled since the end of 2020, driven by new patients across diabetes and obesity. This unprecedented surge in new patients and demand has caused shortages across many of these innovative medicines, limiting access for existing patients and new patients wishing to start therapy.



Shortages can have different causes depending on the market dynamics at play and require a variety of solutions and participation from all stakeholders to resolve and prevent future shortages from occurring.

Overview of shortages in the U.S.

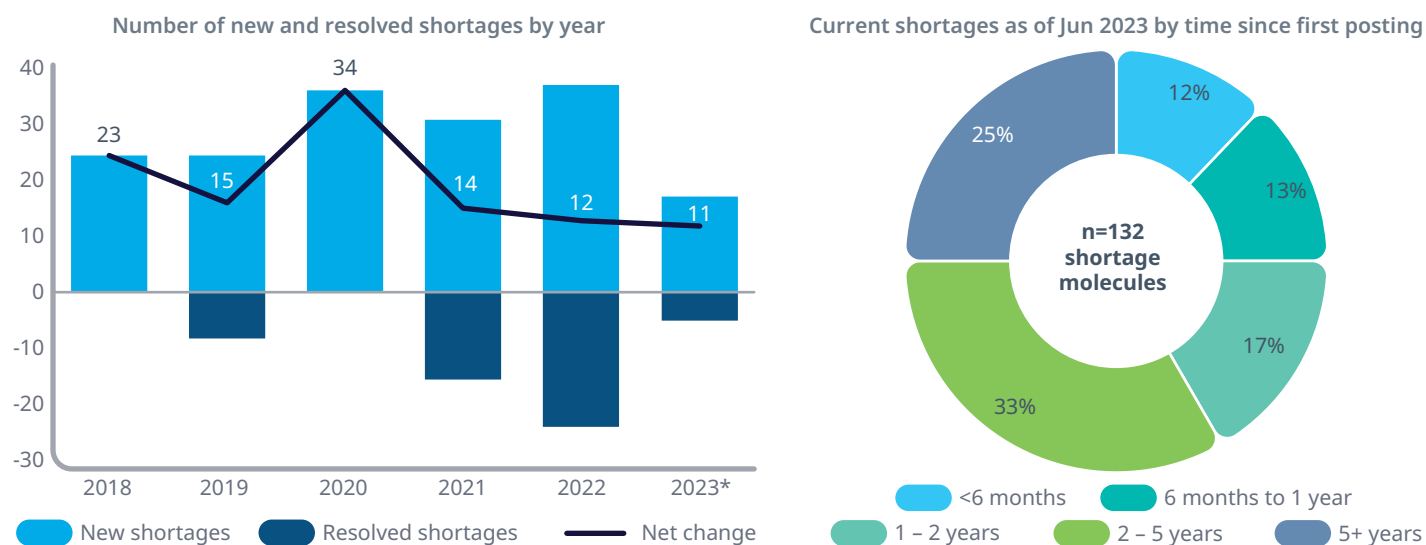
- Drug shortages are an ongoing issue in the U.S. healthcare system, although the number and severity of shortages have changed over time, with 132 active shortages as of June 2023.
- Over the past five-and-a-half years, 160 new molecule shortages have occurred through June 2023 while only 51 have resolved, and more than half of current shortages have been ongoing for more than two years.
- Shortages tend to be in generic and injectable drugs, with 84% and 67% of shortages, respectively, while shortages in oral drugs are less common. Of the 132 drugs in shortage, 12 are branded and the remaining 120 are generic, and generic shortages most often affect injectable medicines.
- Multi-source generic molecules are more likely to be in shortage than single-source molecules, while shortages were more often single-source generics in 2011, reflecting efforts by regulators and industry to increase generic approvals over the last decade.
- Despite shortage molecules predominantly being multi-source, markets remain highly concentrated in a few suppliers, impacting the ability to readily resolve shortages when a leading supplier is affected, and new or existing manufacturers must build or expand manufacturing capacity to account for the gap in supply.
- Shortages are more common at lower prices, with 56% of molecules in shortage priced less than \$1.00 per unit, where competition may be driving some of these drugs below their cost of production and distribution, causing manufacturers to exit the market and disincentivizing new entrants.
- Planned pack discontinuations rarely lead to shortages, but market exits can disrupt other participants, although regulatory requirements to notify the FDA of planned discontinuations play a key role in enabling other companies to react appropriately.



Drug shortages have been an ongoing issue in the U.S. healthcare system for more than a decade, with 132 active shortages as of June 2023.

More shortages continue to be reported than resolved with 58% of current shortages ongoing for more than two years

Exhibit 1: Net shortage increase by year and time since first posting of current shortages



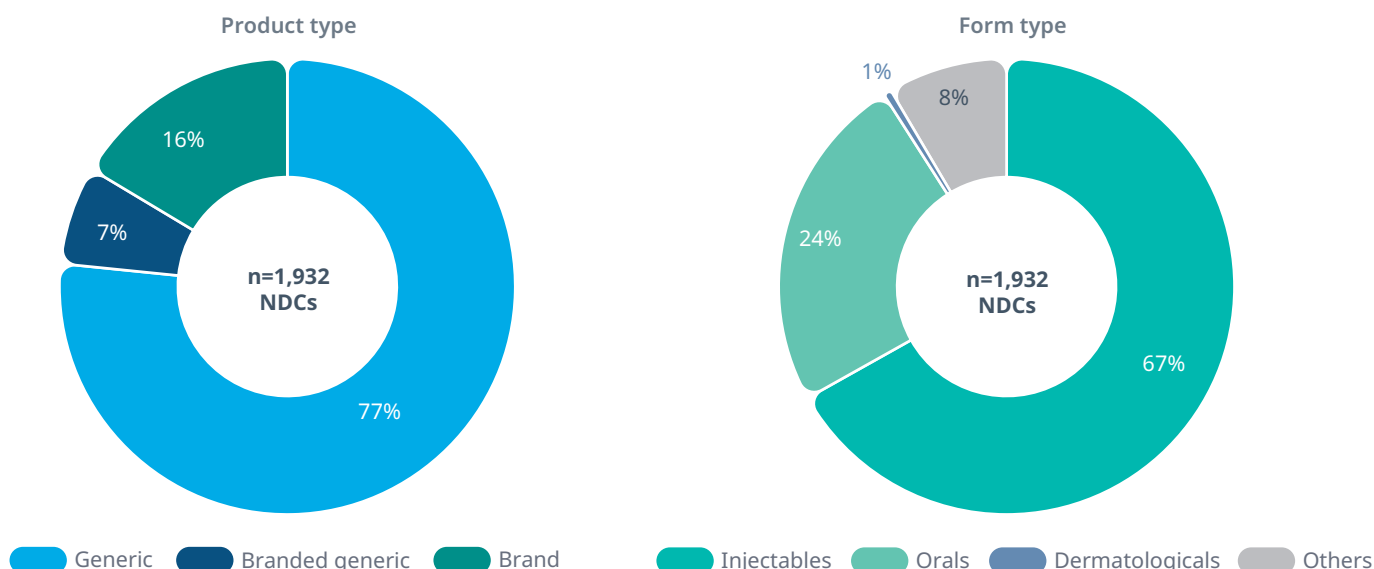
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Over the past five-and-a-half years, an average of more than 25 new molecule shortages have occurred annually, with 160 in total added through June of 2023 and only 51 resolved.
- Resolved shortages have been more clustered in time without a steady pattern, with the largest number being resolved in the second and third year of the COVID-19 pandemic.
- For the currently active shortages affecting 132 molecules, 75% have been active for more than a year and 58% have been ongoing for more than two years.
- Many shortages are affecting medicines with complex manufacturing processes, and the limited ability of new or existing manufacturers to increase or add new capacity is an underlying reason for extended durations of shortages.
- While some shortages are short-term and may be related to unexpected seasonal demand, others are more systemic and suggest more complex drivers of the shortages.

Notes: Molecules are included as new in the year the shortage was initially posted to the FDA Drug Shortages Database. Molecules are included as resolved when the shortage has resolved and included in the year of the date of update for the shortage. Molecules where a shortage occurred and was resolved and a subsequent shortage occurred in the following years would be represented more than once.

84% of the drugs in shortage in the last six years are generics, 67% injectables, and 24% orals

Exhibit 2: FDA shortages by product type and form, 2017–Jun 2023



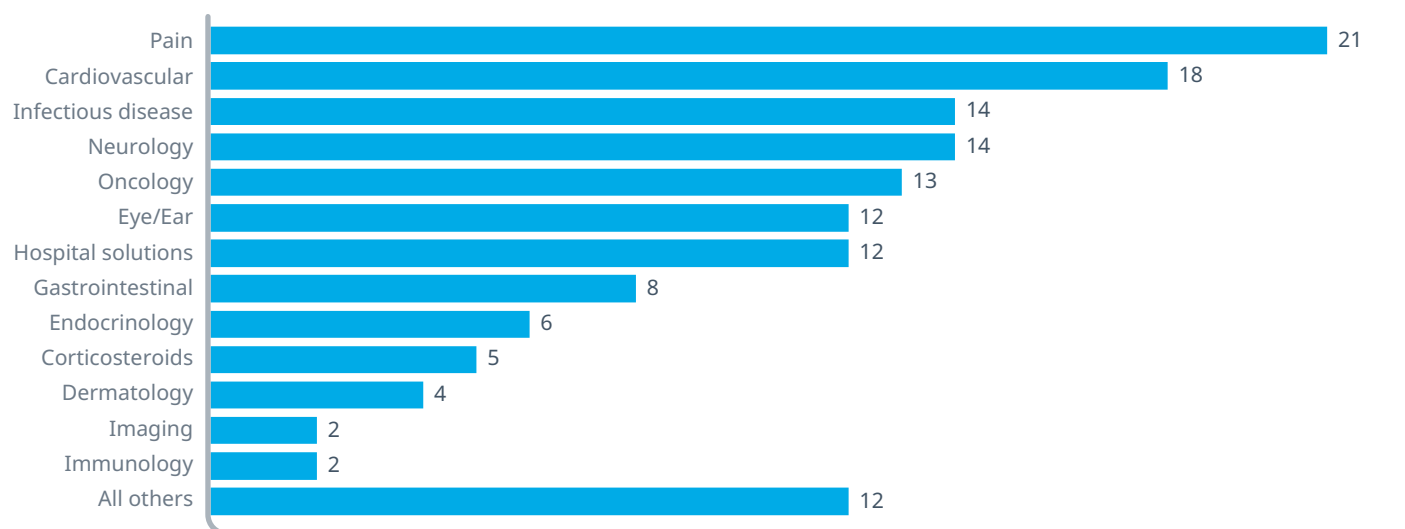
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- The vast majority of shortages — 84% of national drug codes (NDCs), which are unique identifiers for individual pharmaceutical packs for each company — are generic or branded generic drugs. Injectables represent 67% of shortage NDCs.
- Generic injectables represent 65% of generic NDCs in shortage, similar to injectables, and 67% of shortages overall.
- Generally generic medicines are much lower cost than brands and some observers have begun to suggest that some generic prices may be too low to support sustainable markets.
- The FDA commissioner in August 2023 said “...the fundamental problem is that we have two drug industries in the U.S. — the innovator industry...[and] the generic side, and a lot of the prices are too low... the price has been driven down below the cost of manufacturing and distributing the drug.”¹
- Prices driven below the cost of manufacturing and distributing can result in some competitors discontinuing production of molecules, reducing necessary maintenance activities and generally contributing to less resilience in manufacturing supply of those medicines.

Notes: See Definitions for more information about national drug codes (NDCs).

Shortages are concentrated in pain, including anesthesia, cardiovascular, infectious diseases, neurology and oncology

Exhibit 3: Molecules with current shortages as of June 2023 by therapy area



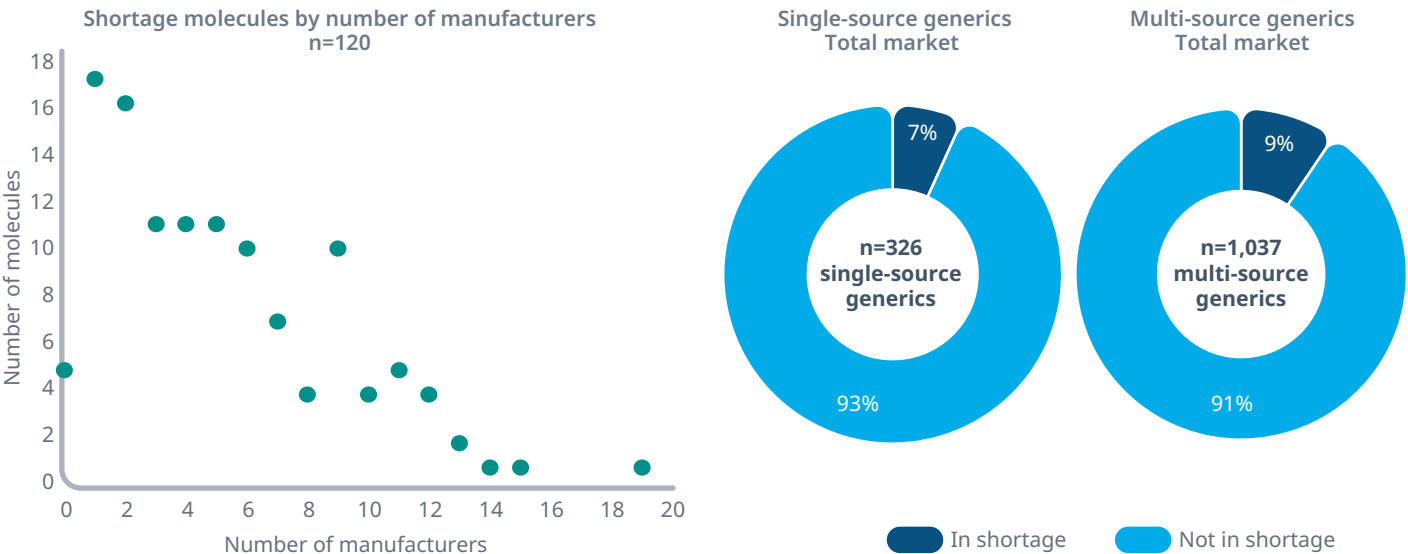
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Many shortages are focused in just a few therapy areas, including pain/anesthesia, cardiovascular, infectious diseases, central nervous system, and oncology, and these areas have been leading causes of shortages over the past decade.²
- A dozen years ago, a peak of shortages drove significant levels of attention and several policy responses, including increased generic approvals and the creation of the current FDA shortage reporting system.
- Current oncology shortages, including those in supportive care, are concentrated in platinum-based chemotherapies, and while there are 13 active shortages now compared to 28 in 2011, there are important similarities in the two periods a dozen years apart.
- Shortages have continued to be concentrated in sterile injectables and in generic drugs, and the same classes leading shortages today were also impacted the most in that earlier period.
- Antibacterial shortages, whether pharmacy or hospital-dispensed, are a significant concern affecting multiple aspects of healthcare delivery and have occurred throughout the past decade. These shortages impact treatment choices, requiring shifts to more potent treatments earlier for a patient, reducing future escalation opportunities and worsening issues related to antimicrobial resistance.

Notes: Molecules used to treat diseases across different therapy areas may be represented in multiple therapy areas. Oncology includes supportive care.

Multi-source generic molecules are more likely to be in shortage than single-source molecules

Exhibit 4: Generic molecules by shortage status and number of manufacturers, Jan-Jun 2023



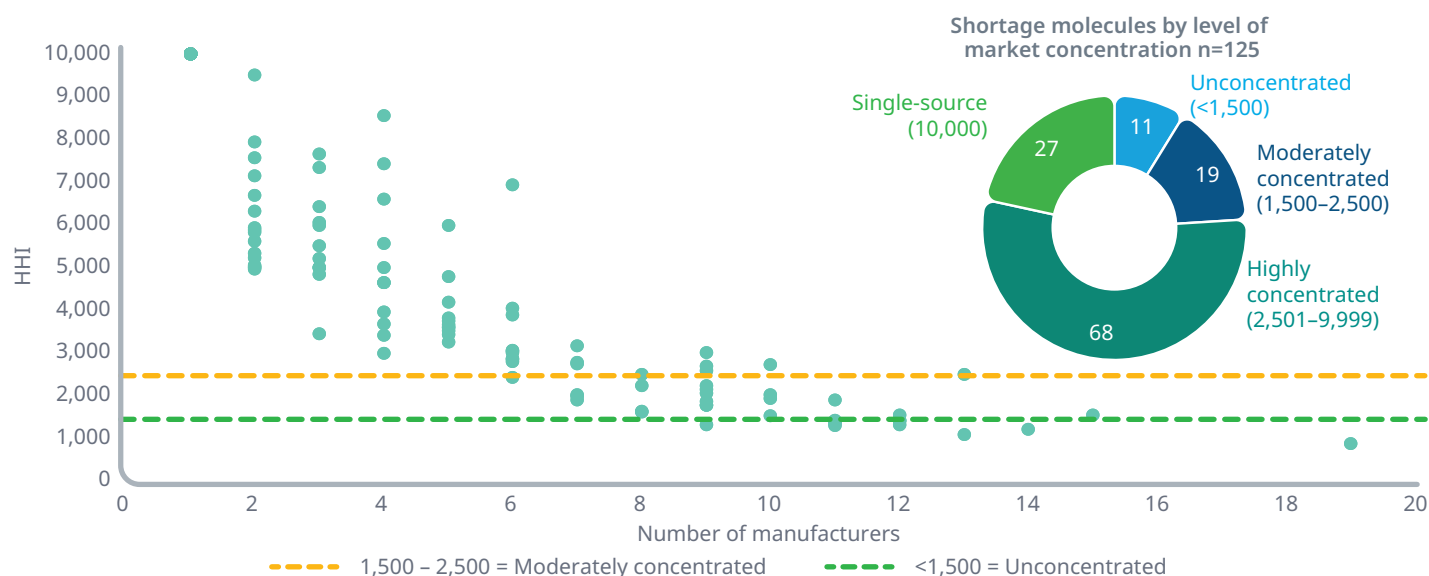
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Current shortages are more often affecting molecules with multi-source manufacturing, reflecting that market resilience is driven by diversified supply, not only the number of companies involved. Of the medicines with generics available and affected by shortages, only 17 of them were single-source, while the vast majority were multi-source, one with 19 companies involved.
- Single-source generic medicines are much less common today than they were in 2011,² largely as a result of sustained efforts by the FDA and industry to increase generic approvals for previously single-source drugs.
- Those efforts further contributed to the lower frequency of single-source generics in shortage, which represents 7% of those medicines in the market compared to 9% of multi-source generics being in shortage.
- Single-source generic makers' market predictability may be allowing them to manage buffer stocks and mitigate the impacts of market volatility with less financial risk than is possible in multi-source markets.
- The multi-source generics in shortage are a further illustration that the presence of a company as a manufacturer does not always translate into the ability to react to a competitors' shortage and fill a gap in supply.

Notes: Generic molecules are those where generics or branded generics are available, and brands may still be available. Brand molecules are those where only brands are available. Manufacturers included if they represent at least 1% of volume in the first six months of 2023.

Most molecules with shortages are multi-source but remain highly concentrated, impacting resilience to shortages

Exhibit 5: Shortage molecule Herfindahl-Hirschman Index (HHI) and number of companies, Jan-Jun 2023



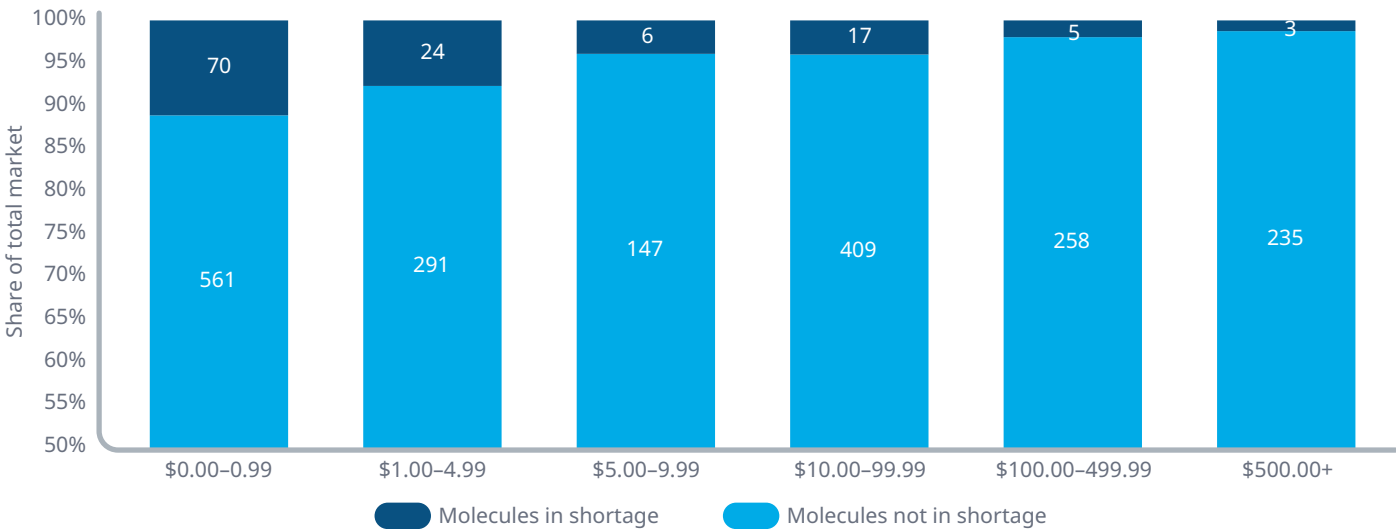
Source: FDA Drug Shortages Database, Jun 2023; IQVIA National Sales Perspective, Jul 2023; IQVIA Institute, Jul 2023.

- The concentration of market share among competitors is a key indicator of the potential resilience of the market to an unexpected driver of shortages and can be measured with the Herfindahl-Hirschman Index (HHI).
- Natural disasters, active or inactive ingredient supply issues, as well as disruptions to packaging materials such as vials can all contribute to manufacturing supply issues, and when those issues affect a significant share of a molecule, shortages may result.
- Another driver of disruptions has been regulatory oversight, where FDA inspections have triggered shutdowns of some sites and where those companies are leading suppliers of a medicine, the shortages are difficult for their peers to resolve.
- Over three-quarters of current shortages are in highly concentrated markets (including single-source), indicating that issues in supply from leading suppliers or the only supplier may result in prolonged shortages as significant lead-time is needed for a new or existing company to build or expand capacity in a complex generic, not accounting for further delays that may be driven by commercial uncertainties delaying investment decisions.

Notes: Seven molecules with current shortages have no sales in the first six months of 2023 and are not included here. Manufacturers included if they represent at least 1% of volume in the first six months of 2023. See Definitions for more information about Herfindahl-Hirschman Index (HHI).

Shortages are more common at lower prices with 56% of molecules in shortage priced less than \$1.00 per unit

Exhibit 6: Average invoice price per extended unit of molecules, Jan–Jun 2023, n=2,026



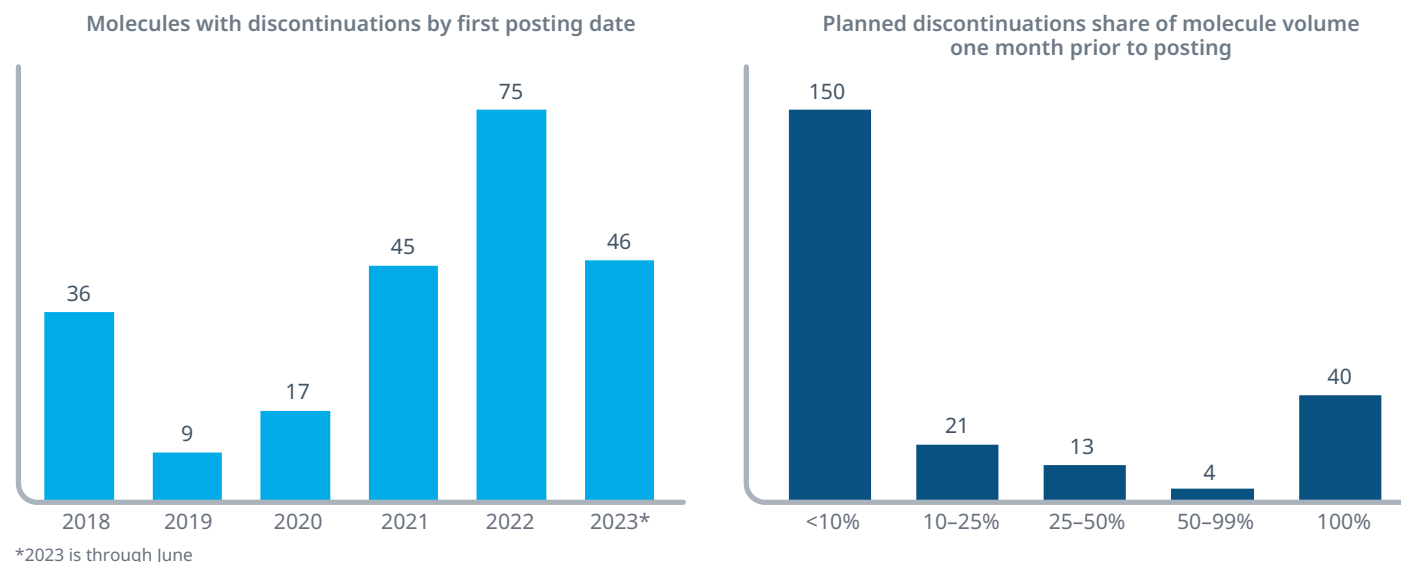
Source: FDA Drug Shortages Database, Jun 2023; IQVIA National Sales Perspective, Jul 2023; IQVIA Institute, Jul 2023.

- Shortages are more common in drugs with very low list prices, with 11% (70 of 631) of drugs priced less than \$1.00 per extended unit in shortage, compared to 1.3% (3 of 238) of those priced more than \$500 per unit.
- Low priced drugs (<\$1) accounted for 56% of the 125 drugs in shortage with reported volume in this analysis.
- An extended unit is defined as a milliliter for some injections, and as a pill for oral solids (see Definitions for more details). These variations notwithstanding, more than half of shortages are affecting drugs with very low list prices.
- These list prices do not take into account discounts and rebates, which apply in the supply chain and further erode a manufacturer’s realized prices.
- With the list prices of these medicines eroded to very low levels, returns on investments in new facilities or increased capacity are among the more challenging decisions being made in the generic sector.
- Competition in generic molecules may be driving some of these drugs below their cost of production and distribution, although these details are opaque and unclear, causing manufacturers to exit the market and disincentivizing new entrants.

Notes: Seven molecules with current shortages have no sales in the first six months of 2023 and are not included here.

Planned pack discontinuations rarely lead to shortages, but market exits can disrupt other participants and affect resilience

Exhibit 7: Planned discontinuations by first posting date and volume share prior to posting



Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- As prices have declined, one suggestion has been that companies will discontinue manufacturing where they are not making a profit and this does appear to be a fairly common occurrence, with companies discontinuing at least one form/strength of 228 molecules since the end of 2017.
- These discontinuations have not resulted in shortages, although other drugs reported as current shortages have a history of company discontinuations in the months or years leading up to the start of their shortages.
- Nearly two-thirds of discontinuations were of NDCs with <10% share of their molecule, reflecting rational business decisions of companies failing to achieve sustainable market shares.
- The remaining one-third of discontinuations have had more significant market shares and there could be multiple reasons why these have not resulted in a shortage, although they are not precluded from it happening in the future.
- The FDA requirements to notify the agency of planned discontinuations plays a key role in enabling other companies to react appropriately.
- Reformulations and transitions to newer or better treatments options, where the planned discontinuation is part of a strategic shift, make a discontinuation less likely to result in a market disruption.
- Finally, there are cases where a medicine is being withdrawn for clinical reasons, and the planned discontinuation does not result in a shortage.

Notes: Molecules with discontinuations and current or resolved shortages have been defined as shortages and are not plotted here. Molecules may have more than one planned discontinuation but are only plotted once based on earliest discontinuation posting on FDA Drug Shortages Database. Nineteen molecules with planned discontinuations had no volume one month prior to posting of the discontinuation and are assumed to have represented 100% of molecule volume prior to discontinuation.

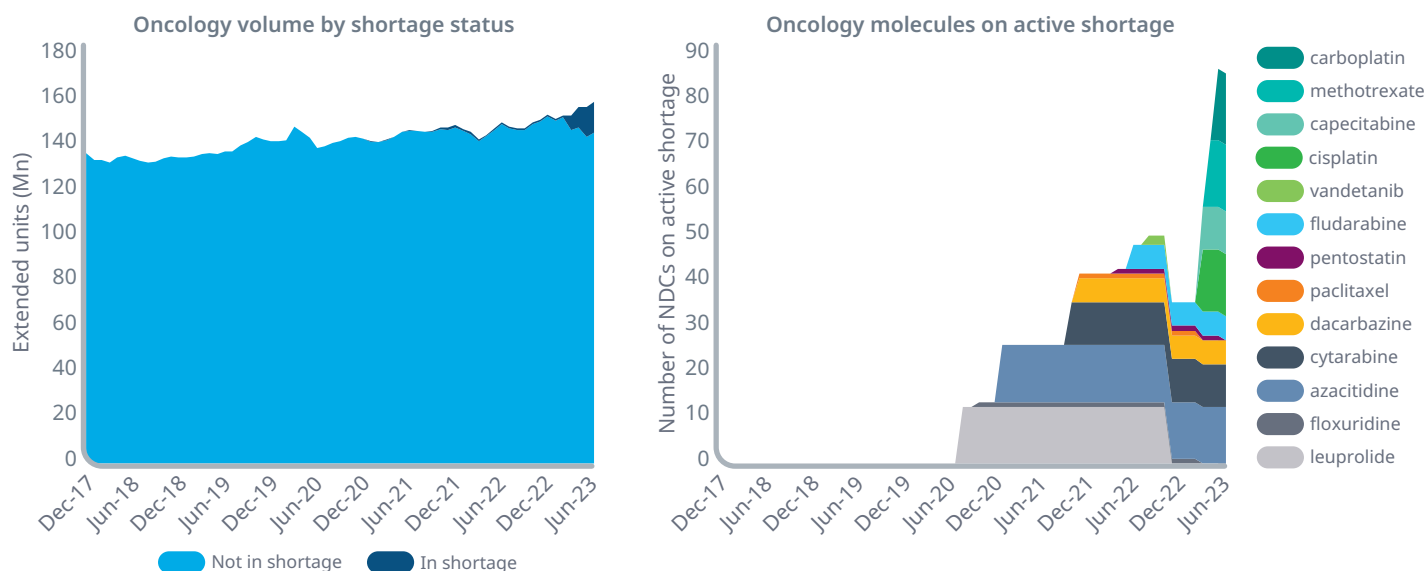
Oncology shortages

- Oncology shortages were exacerbated during the COVID-19 pandemic and although only a small share of overall oncology volume has been impacted, shortages have been concentrated in older genericized chemotherapeutics and particularly platinum-based chemotherapeutics, raising concerns for patients needing these medicines as part of their cancer care.
 - Twelve oncology molecules have had shortages over the last 18 months and impacting 1% to 100% of the volume over that period, with 11 injectable and one oral shortage.
 - Inspection-driven disruptions and market exits have led to shortages of oncology molecules, leaving other manufacturers to increase production to fill the supply gaps.
- Oncology drugs with significant shortages are highly concentrated markets despite multiple suppliers with low prices, making it more difficult for new or existing suppliers to achieve a return on investment for building or increasing manufacturing capacity to address shortages.
 - The manufacturing complexity associated with some oncology medicines and highly commoditized prices have reduced the number of active manufacturers in many molecules over a period of years.
 - Competitive pressures have most often created markets with high concentration, where one or just a few companies have a majority of the market, limiting the resilience of the market to any unexpected disruptions.

Platinum-based chemotherapy shortages have had an outsized impact on patient care because of their central position in a wide range of regimens across tumors and multiple lines of therapy, often where there are few therapeutic alternatives.

Oncology shortages exacerbated during the COVID-19 pandemic but represent a small share of overall oncology volume

Exhibit 8: Oncology volume and molecules by shortage status, Dec 2017–Jun 2023



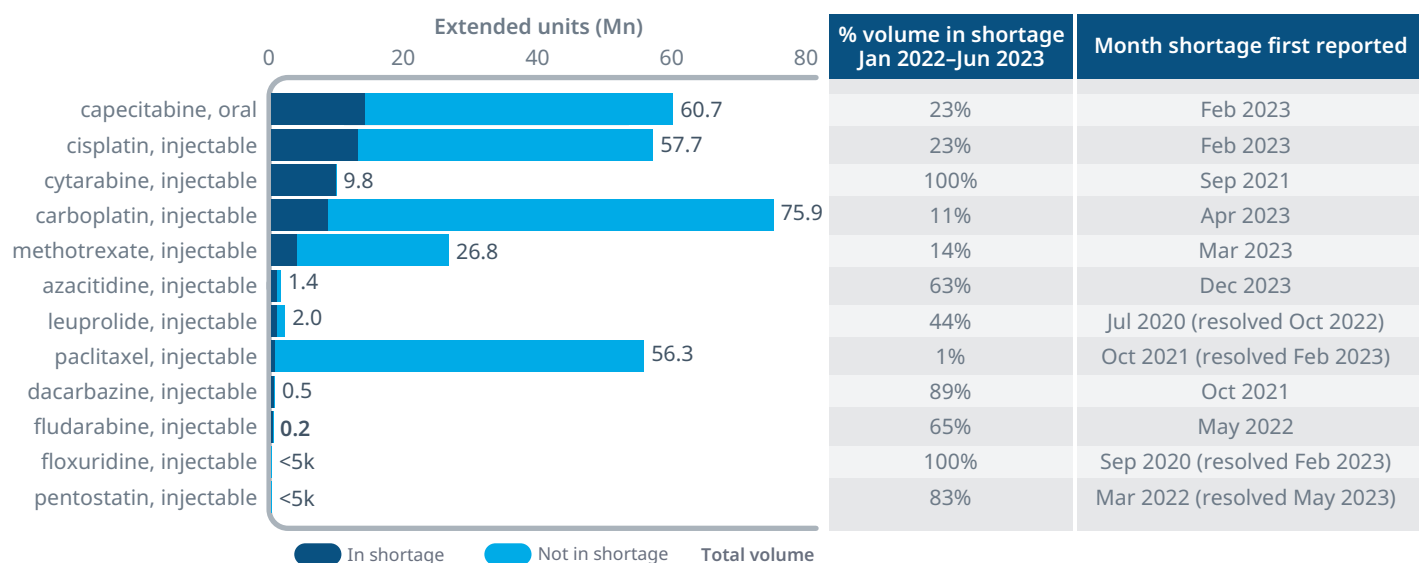
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- As of June 2023, there are eight cancer medicines with active shortages while five other medicines have seen shortages over the last five years that have resolved.
- Oncology has seen a growing number of shortages since 2020, with four new molecule shortages between March and June 2023: cisplatin, methotrexate, capecitabine, and carboplatin.
- Although there are shortages having significant impacts across these molecules, the volume in shortage accounts for only 9% of the total oncology volume in June 2023, and overall oncology volume continues to grow, up 6% from June 2022.
- Oncology shortages have been concentrated in older genericized chemotherapeutics, and platinum-based chemotherapeutics — carboplatin and cisplatin — have been particularly impacted by shortages beginning in February 2023, causing concerns for patients who rely on these life-saving medications.

Notes: Analysis includes medicines with a focus on cancer therapeutics and does not include supportive care. Shortages are determined at the pack level and included only during the period for which the pack was in shortage.

Oncology shortages are primarily impacting injectables with 100% of cytarabine volume in shortage over the last 18 months

Exhibit 9: Oncology molecule volume in shortage, Jan 2022–Jun 2023, extended units (Mn)



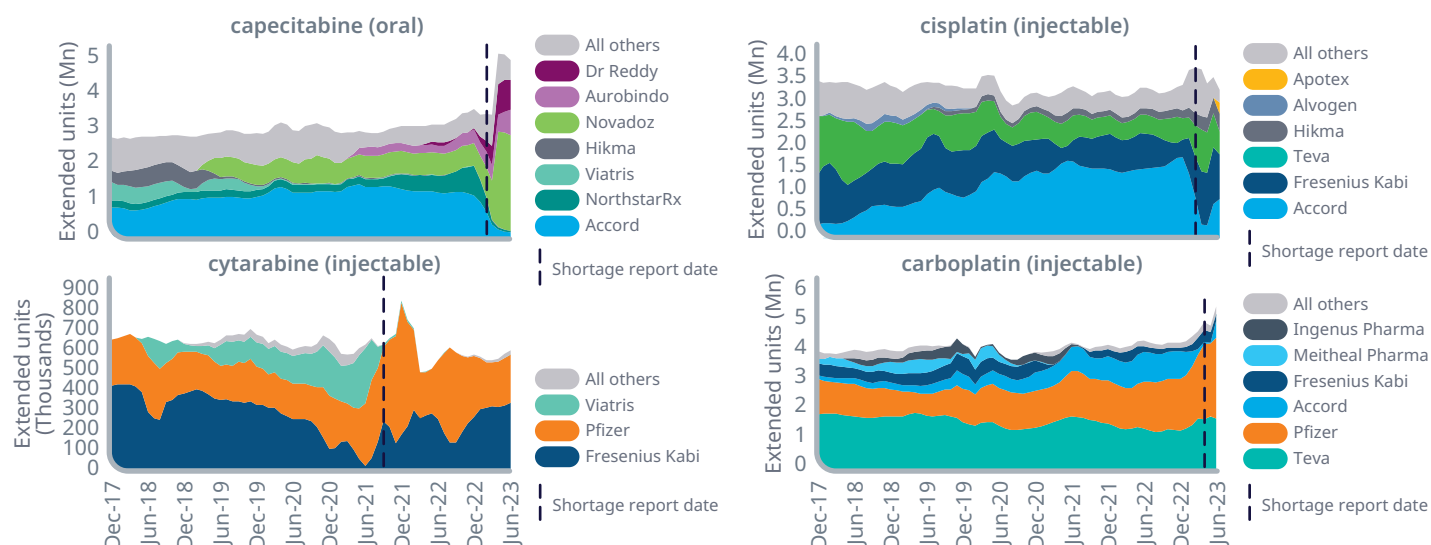
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Twelve molecules have had shortages over the last 18 months, impacting 1% to 100% of the volume over that period, with 11 injectable and one oral shortage.
- Four molecules account for 87% of the shortage volume since January 2022: capecitabine, cisplatin, cytarabine, and carboplatin.
- While capecitabine and cisplatin shortages have impacted 23% of the total volume and carboplatin shortages 11%, cytarabine shortages have impacted 100% of the volume, raising concerns for access to this medicine for patients with hematological cancers.
- While other medicines with shortages in the last 18 months account for less volume, many of these are used to treat rare cancers with smaller patient populations where shortages can have significant impacts for these patients.
- Dacarbazine, used in the treatment of malignant melanoma and Hodgkin lymphoma, has been in shortage since late 2021, with 89% of the volume in the last 18 months impacted by shortages. Dacarbazine is included in the treatment regimen used most commonly for Hodgkin lymphoma,³ raising concerns for consistent treatment of patients with this rare cancer.

Notes: Analysis includes medicines with a focus on cancer therapeutics and does not include supportive care. Vandetanib had no sales during the period it was in shortage and is not included here. Shortages are determined at the pack level and included only during the period for which the pack was in shortage.

Oncology shortages likely due to inspection driven disruptions and market exits of major players

Exhibit 10: Volume by corporation for select oncology shortages, Dec 2017–Jun 2023, 3-month rolling avg extended units (Mn)



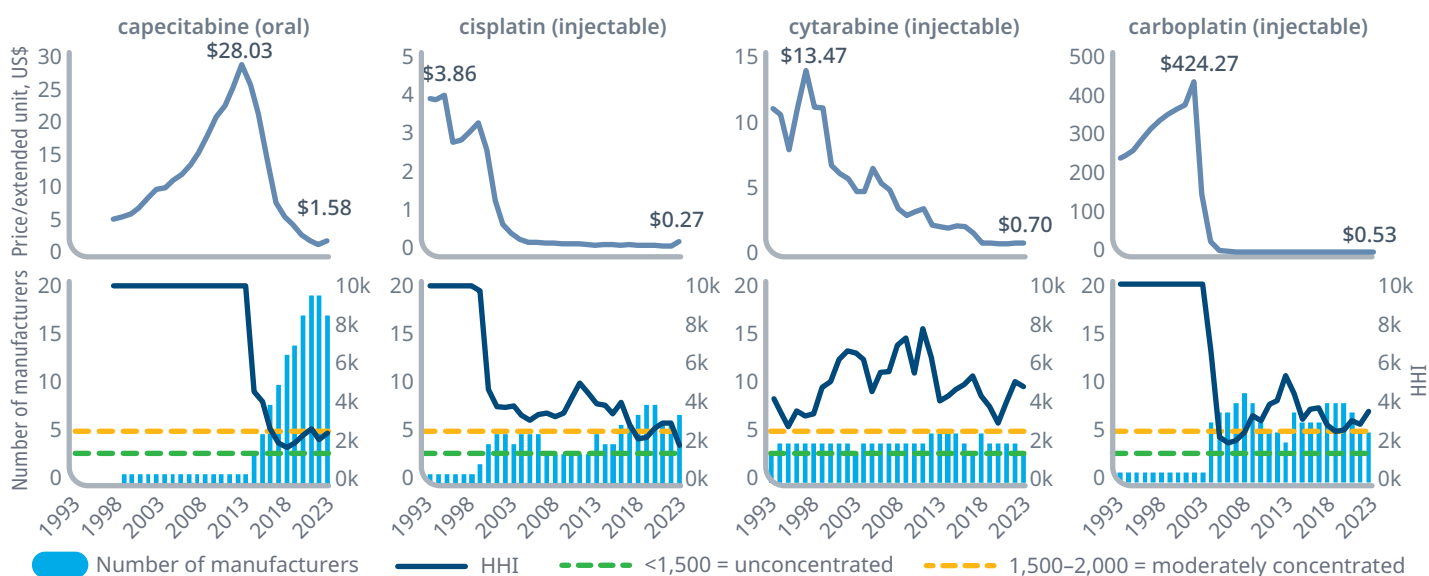
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- The most significant shortages by volume in oncology have been the result of manufacturing disruptions and exits from manufacturers accounting for significant market shares.
- For capecitabine, cisplatin, and carboplatin, these shortages began between February and April 2023, shortly after FDA facility inspections in late 2022 noted deficiencies at Intas Pharmaceuticals — which sells medicines in the U.S. market under Accord Healthcare — leading to import restrictions on these drugs and many others.⁴
- Prior to this, Accord entered these markets during the period 2015–2017, following abbreviated new drug application (ANDA) approvals. Leading up to the shortage events, Accord accounted for 22% of the carboplatin market, 33% of the capecitabine market, and 53% of the cisplatin market.
- As a result of inspections, Intas (Accord) took the manufacturing line out of production, leading to significant disruptions to these medicines and requiring other manufacturers to increase production to account for the lost volume, which they largely were able to do.
- The cytarabine shortage began in 2021 following the exit of Viatris which accounted for 44% of the market prior to discontinuation, leaving the other two manufacturers to increase production.
- Notably, supply typically rises exponentially following the announcement of a shortage, rather than falling. This is likely a result of stockpiling by healthcare organizations due to fear of limited future access. Generally larger, better resourced purchasers have been better able to adapt to disruptions, whereas smaller community oncology providers have reported shortages and, in some cases, have had to suspend or delay treatments or refer patients to be treated elsewhere.

Notes: Manufacturers with less than 3% of total volume and repackagers are included in all others. Shortage report date represents the earliest initial posting date of the shortage in the FDA Drug Shortages Database.

Oncology markets are highly concentrated, inhibiting responses to address shortages and extending the effects

Exhibit 11: Invoice price of select oncology shortages and Herfindahl-Hirschman Index (HHI), 1993–Jun 2023



Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Following brand loss of exclusivity, oncology medicines with shortages have seen overall declines in price despite variable market participants and market concentration.
- Prices for injectable oncology shortages dropped significantly after generic entry, stabilizing at prices of less than \$1.00 per extended unit in recent years.
- These pricing dynamics make it difficult for manufacturers to get a return on the investment needed to increase production when a shortage is ongoing, often leading to prolonged shortages.
- Despite four to ten manufacturers for these injectable generic medicines, the markets have remained moderately to highly concentrated with one or two of these manufacturers maintaining a majority of the market share.
- Oral capecitabine has seen a similar rapid decline in price with generic entry and an increasing number of competitors — up to 19 in 2021 and 2022 — but the market has remained moderately concentrated with a few manufacturers.
- The low prices and high degree of market concentration exposes the market to significant disruptions when a major player experiences a manufacturing disruption or exits. These factors reduce resiliency, as other manufacturers in the market and new entrants would need to invest in increasing manufacturing capacity in a low margin product.

Notes: 2023 data shown here is based on sales data from the first six months of 2023. See Definitions for more information about Herfindahl-Hirschman Index (HHI).

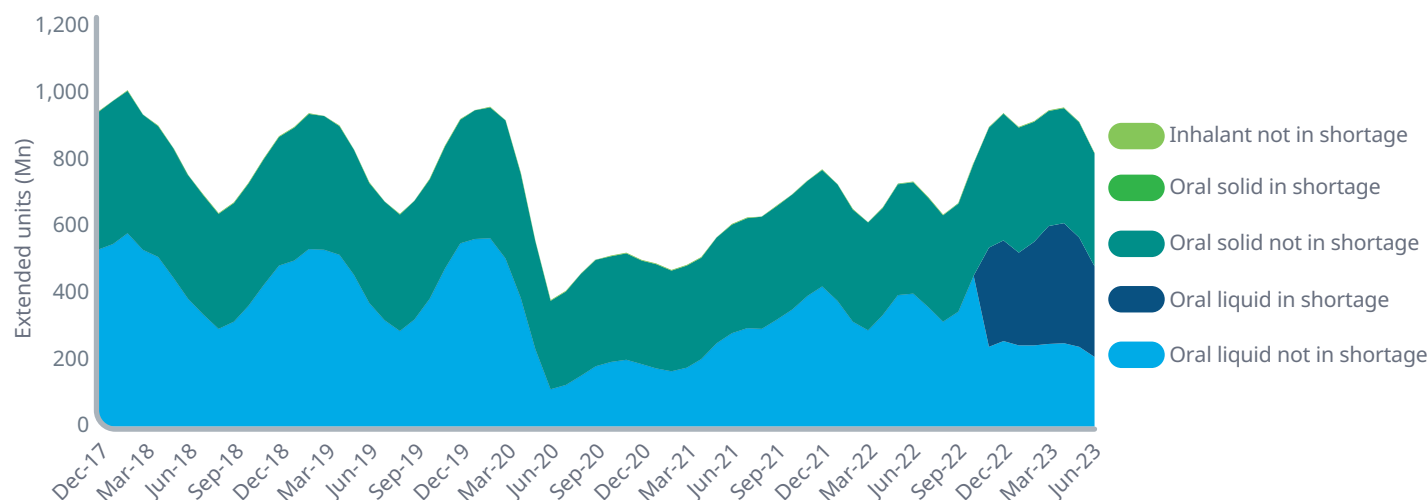
Shortages across other therapy areas

- Shortages have occurred across a number of other therapy areas with causes ranging from increased demand to manufacturing disruptions, meaning a single solution may not prevent or resolve future shortages.
- Public health measures during the COVID-19 pandemic disrupted the seasonal pattern of bacterial infections, particularly in children, and a return to historic infection levels in late 2022 led to a shortage in oral pediatric antibacterials.
- Increasing injectable antibacterial shortages began in late 2021 when market share leaders experienced manufacturing delays and have yet to be resolved.
- Anesthetic shortages have been persistent since 2017, with local anesthetics particularly affected and general anesthetics impacted with successive waves of COVID-19 hospitalizations.
- Overall ADHD medicine volume has increased 12% since 2017, leading to shortages due to increased demand, despite available manufacturing capacity.
- Despite growth in overall mental health prescriptions, shortages have been confined to a limited number of molecules and generally resolved quickly.
- GLP-1 agonist use has more than doubled since the end of 2020, driven by new patients in both diabetes and obesity and contributing to ongoing shortages in these novel medicines.

Shortages have been the result of various causes, including increased demand and manufacturing disruptions.

Oral antibacterial shortages driven by increased pediatric use in late 2022 following lower demand during the pandemic

Exhibit 12: Non-injectable antibacterial volume by form and shortage status, Dec 2017–Jun 2023, 3-month rolling avg extended units (Mn)



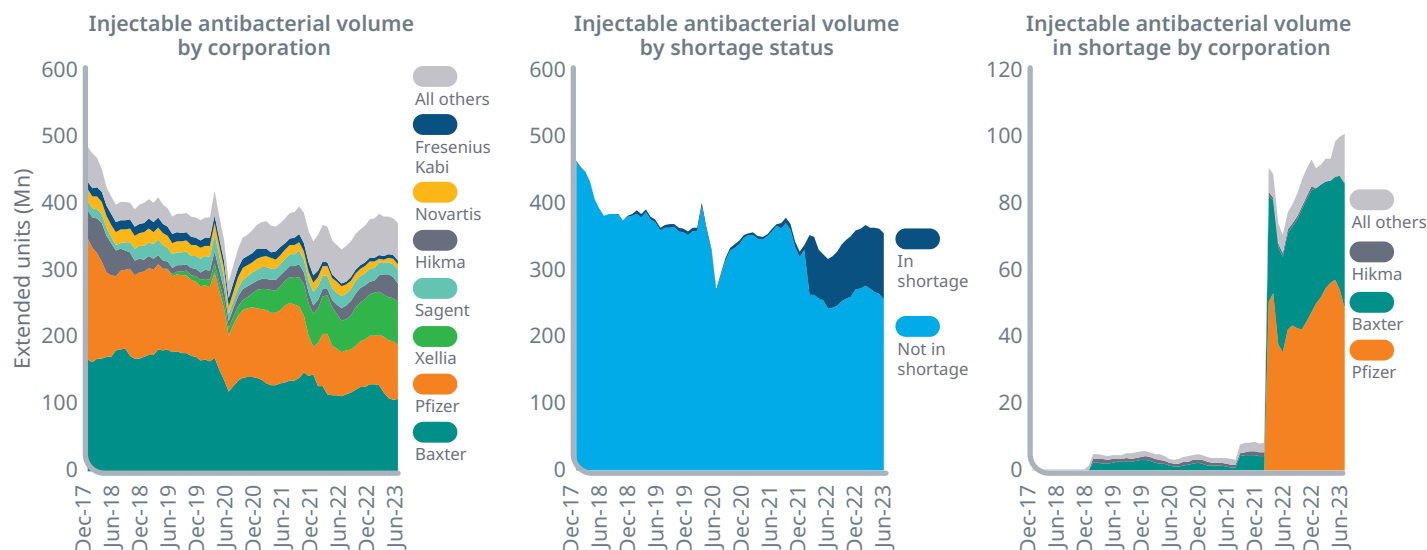
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Antibacterial usage was down over 20% during 2020 and 2021 as social distancing and other public health measures used to combat COVID-19 were effective at decreasing bacterial infections. As these measures were phased out, antibacterial use began to rise again in 2022 and was up 2% in the first half of 2023 compared to pre-pandemic levels.
- Children under the age of 19 saw the most dramatic changes in usage throughout the pandemic, with a 50% decline in prescriptions early on followed by a significant increase as children returned to school and other activities, ending 2022 with prescriptions 8% above pre-pandemic levels.⁵
- The significant disruption during the pandemic in pediatric use of antibacterials led to a shortage in oral liquid formulations starting in October 2022 as the health system was not able to predict demand for the fall/winter respiratory illness season, which was more severe than prior years.
- One consequence of antibacterial shortages, reported by researchers at Boston Children's Hospital, is a shift in prescribing to more broad spectrum antibacterials, which can increase the likelihood of antimicrobial resistance.⁶

Notes: Shortages are determined at the pack level and included only during the period for which the pack was in shortage.

Increasing injectable antibacterial shortages began in late 2021 when market share leaders experienced manufacturing delays

Exhibit 13: Injectable antibacterial volume by corporation and shortage status, Dec 2017–Jun 2023, 3-month rolling avg extended units (Mn)



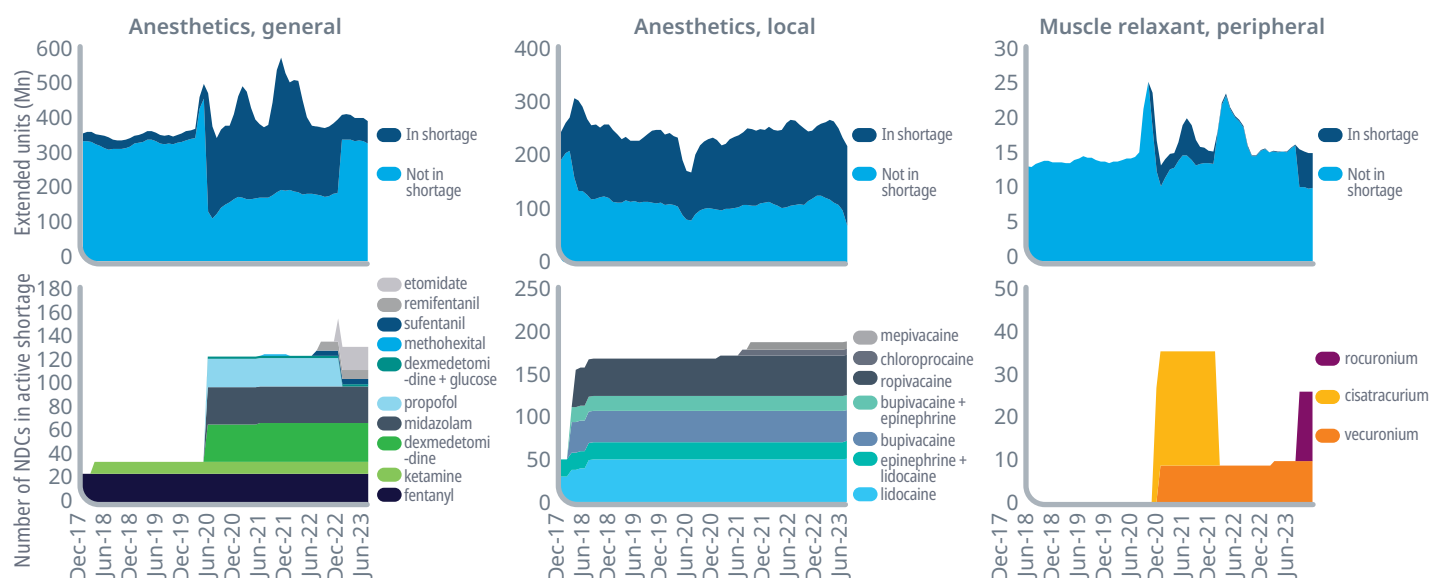
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Injectable antibacterials have seen declining volume over the last five years as efforts have been made to more appropriately use antibacterials to reduce the development of antimicrobial resistance.
- Baxter Healthcare and Pfizer account for more than half of the injectable antibacterial volume in the U.S., with Xellia Pharmaceuticals the next largest manufacturer at 17% of the market.
- Shortages of injectable antibacterials have been ongoing since 2017 but have impacted less than 3% of volume until early 2022 when a shortage of injectable metronidazole began, and shortages now impact 28% of overall volume.
- Injectable metronidazole shortages accounted for 91% of injectable antibacterial volume in shortage as of June 2023, with Pfizer and Baxter Healthcare shortages contributing the most.
- Additionally, Pfizer, which accounts for 38% of the injectable penicillin market, warned of a shortage in June 2023 due to manufacturing delays and rising syphilis infections, with the shortage expected to last through 2024,⁷ adding further stresses on healthcare providers trying to navigate the injectable antibacterial market.

Notes: Manufacturers with less than 3% of total volume and repackagers are included in all others. Shortages are determined at the pack level and included only during the period for which the pack was in shortage.

Anesthetic shortages have been persistent since 2017 with local anesthetics particularly affected

Exhibit 14: Anesthetic volume by shortage status and molecules in shortage, Dec 2017–Jun 2023



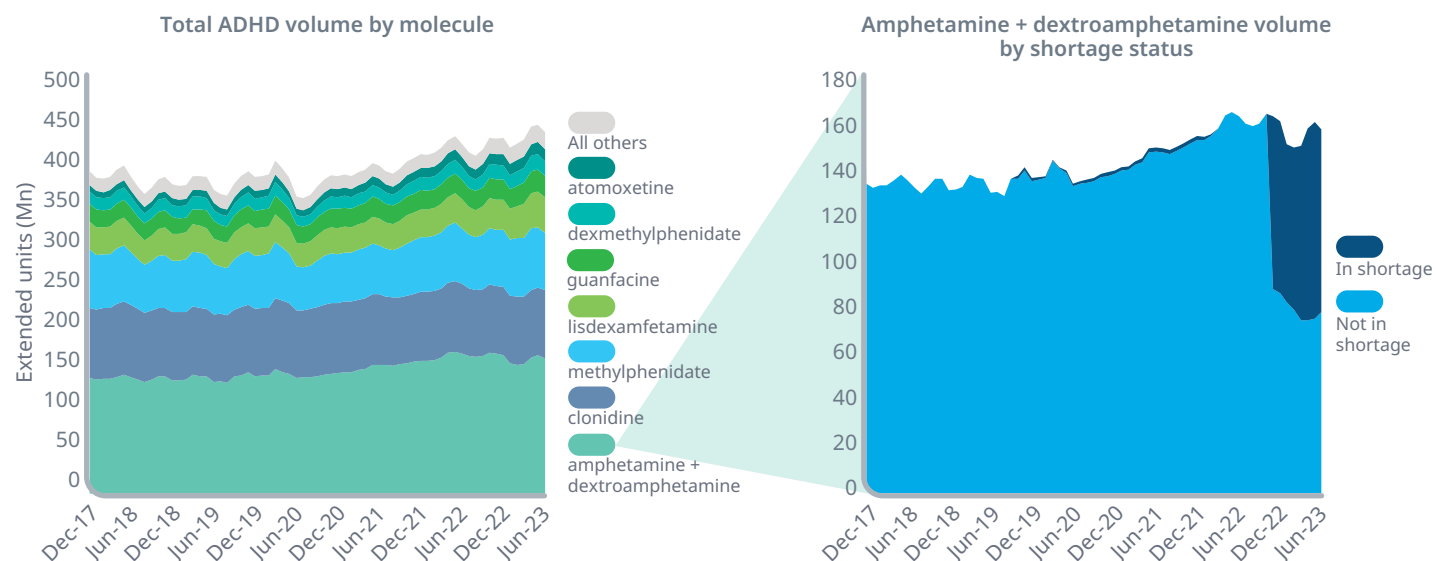
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Anesthesia medicines, including general, local, and muscle relaxants, are foundational to inpatient and outpatient surgical procedures, and shortages in these medicines can result in delays for patients receiving procedures and hospitals making prioritization decisions based on available supply.
- General anesthesia has had shortages for many years for fentanyl, which as a controlled substance has additional supply chain complications.
- At the start of the COVID-19 pandemic, reported shortages for medicines needed for ICU patients resulted in supply-chain shocks that drove volumes up substantially and then had seasonal spikes for several years.
- Local anesthesia has been dominated by a many-years-long lidocaine shortage, which in turn has its roots in companies' challenges in manufacturing sufficient supplies of long-acting versions such as bupivacaine, resulting in shortages of both molecules.
- Muscle relaxants are a common medicine for intubating patients, among other uses, and the pandemic surge in demand generated shortages which were resolved, despite annual spikes in volume.
- Shortages across these medicines complicate scheduling of a wide range of procedures and surgeries, which may be part of a broad-based reduction observed in elective procedures in post-pandemic periods.

Notes: Includes prescription medicines only; OTC medicines are not included. Shortages are determined at the pack level and included only during the period for which the pack was in shortage.

Overall ADHD volume has increased 12% since 2017 leading to shortages due to increased demand

Exhibit 15: ADHD volume by molecule and shortage status, Dec 2017–Jun 2023, 3-month rolling avg extended units (Mn)



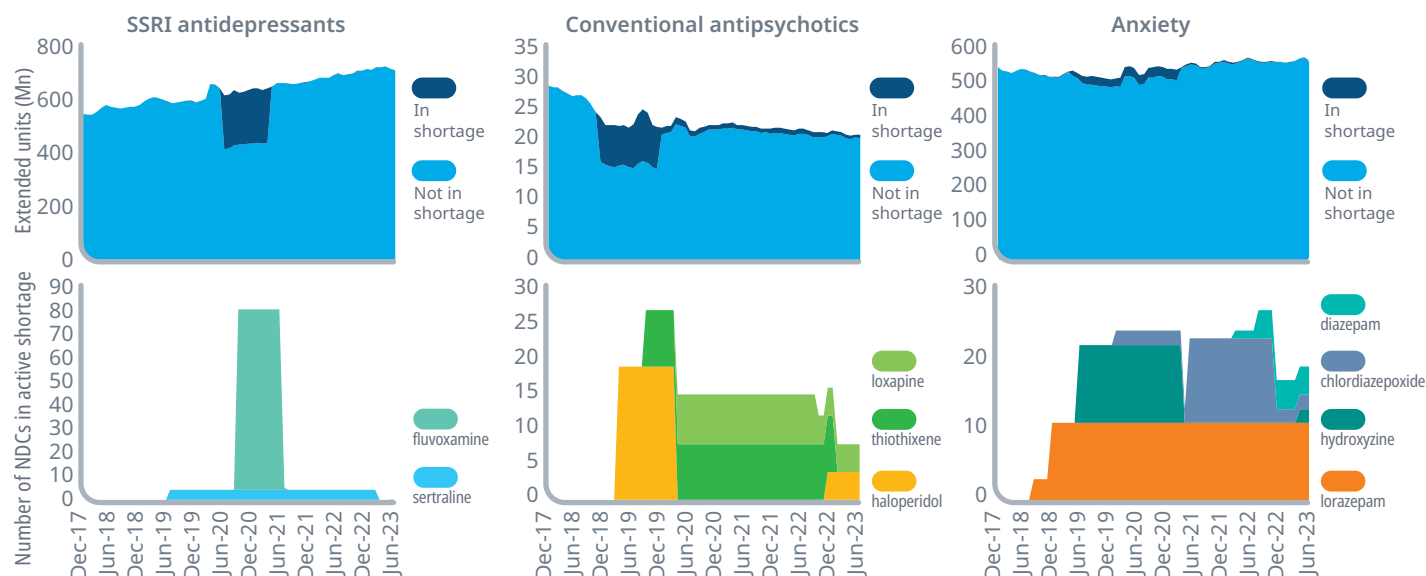
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Overall use of medicines for attention-deficit/hyperactivity disorder (ADHD) has grown 12% since 2017 and amphetamine + dextroamphetamine (amphetamine salts) account for 37% of ADHD medicine use.
- Use of ADHD medicines rose significantly throughout the pandemic, particularly in women aged 20–64, with an increase in remote work and clinician awareness contributing and continued use from previously diagnosed patients.⁵
- Shortages in ADHD have primarily impacted amphetamine salts, where half of volume was in shortage as of June 2023. Other ADHD medicines, including novel treatments Qelbree and Azstarys launched in 2021, remain available.
- Because amphetamine salts are Schedule II drugs, their manufacturing is highly controlled, however the FDA and Drug Enforcement Administration (DEA) have indicated that manufacturers produced only 70% of their amphetamine salt quota in 2022, leaving nearly 1 billion additional doses that could have been supplied.⁸
- An additional complicating factor is the spring 2022 opioid crisis settlement, which required drug wholesalers to exercise more scrutiny over the volumes of controlled substances they ship to pharmacies. Most affected organizations implemented algorithmic volume caps, with some pharmacies and/or prescribers with volatile prescription demand resulting in canceled orders and patients unable to acquire prescribed medications.⁹

Notes: Includes prescription medicines only; OTC medicines are not included. Shortages are determined at the pack level and included only during the period for which the pack was in shortage.

Mental health molecules have been on shortage since 2018 with some classes showing sharp increase in shortage due to demand

Exhibit 16: Mental health volume by shortage status and molecules in shortage, Dec 2017–Jun 2023



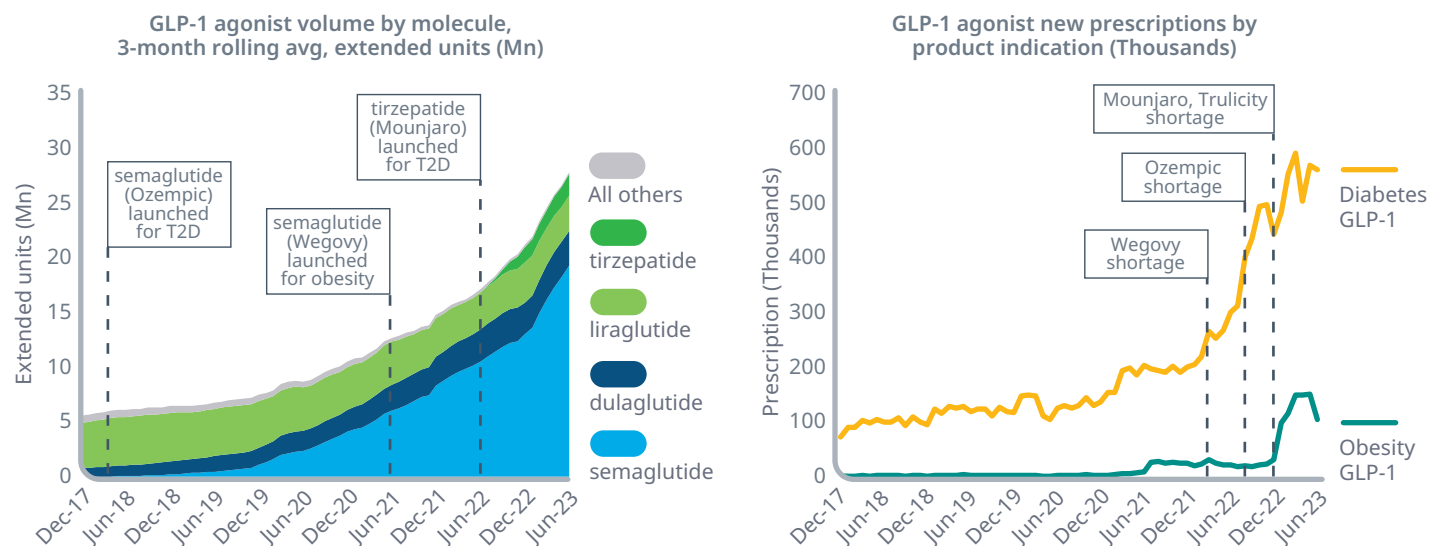
Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

- Despite significant growth in overall mental health prescriptions since 2019,⁵ shortages have been confined to a limited number of molecules and generally resolved quickly.
- For the most part, antidepressants are dispensed as oral solids, and oral medicines can be characterized as lower complexity for manufacturing and thus more easily addressed by a company increasing supply compared to injectable drugs.
- The lack of substantial impact on the market level trend suggests there may be other therapeutic alternatives, which could include newer branded therapies that may benefit from shortages of older generic drugs.
- Anxiety drugs have seen a notable increase in volume over the past five years, particularly during the pandemic, and while there have been shortages, the impacts have been relatively isolated and resolved within a couple of years.
- Notably, an ongoing shortage in injectable lorazepam could have impacts on patients undergoing surgeries, experiencing seizures, or admitted in the ICU, however other benzodiazepines for injection are available as therapeutic alternatives.¹⁰

Notes: Shortages are determined at the pack level and included only during the period for which the pack was in shortage.

GLP-1 use has more than doubled since the end of 2020 driven by new patients in both diabetes and obesity

Exhibit 17: GLP-1 agonist volume by molecule and new prescriptions by indication, Dec 2017–Jun 2023



Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, IQVIA National Prescription Audit, Jun 2023; IQVIA Institute, Oct 2023.

- The first GLP-1 agonist for treatment of type II diabetes launched in 2005, however GLP-1 agonist use has increased rapidly since the launch of Ozempic in 2018 and the subsequent launch of Wegovy for treatment of obesity in 2021, with current GLP-1 agonist volume nearly four times that in 2017 and GLP-1 agonists the fastest growing mechanism in diabetes.⁵
- Since the launch of Wegovy, new prescriptions are up 181% for diabetes GLP-1s and 257% for obesity GLP-1s as increasing awareness of these medicines has increased patient demand.
- Wegovy, Ozempic, Trulicity, and Mounjaro are all experiencing shortages as new patient demand across both diabetes and obesity outpaces supply, potentially causing difficulties in filling prescriptions for patients already on therapy.
- Novo Nordisk, the manufacturer of Wegovy, indicated in May 2023 that it was limiting supply of lower doses of Wegovy used as starting doses to ensure adequate supply of higher doses for existing patients.¹¹
- New data highlighting the effectiveness of GLP-1s in preventing cardiovascular events¹² and the early termination of a trial for chronic kidney disease due to efficacy¹³ indicate a likely expansion of use of GLP-1s, further increasing demand.

Notes: GLP-1 agonist products are grouped based on indication listed on latest FDA label and do not reflect off-label use.

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

NATIONAL PRESCRIPTION AUDIT (NPA):

NPA is the industry standard source of national prescription activity for all pharmaceutical products. It measures demand for prescription drugs, including dispensed pharmaceuticals to consumers across three unique channels: retail, mail service, and long-term care pharmacies. From sample pharmacies, IQVIA collects new and refilled prescription data daily. NPA represents and captures over 92% of all outpatient prescription activity in the United States and covers all products, classes, and manufacturers.

NATIONAL SALES PERSPECTIVES (NSP) measures revenue within the U.S. pharmaceutical market by pharmacies, clinics, hospitals and other healthcare providers. NSP reports 100% coverage of the retail and non-retail channels for national pharmaceutical sales at actual transaction prices. The prices do not reflect off-invoice price concessions that reduce the net amount received by manufacturers.

THIRD-PARTY INFORMATION:

FOOD AND DRUG ADMINISTRATION DRUG

SHORTAGES DATABASE is a searchable database to provide stakeholders with easy access to information about drugs in shortage and includes information about current drugs in shortage, resolved shortages, discontinuations of specific drug products, and other relevant product information. Information in the database is predominantly provided to FDA by manufacturers and the database is updated daily. For this report, the information analyzed from the database was that provided as of June 8, 2023. The database can be accessed from: <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.

Defintions



HERFINDAHL-HIRSCHMAN INDEX (HHI) is a measure of market concentration and is often used to measure the impact of mergers on competitiveness in a market. The HHI is the sum of the squares of each market participants market share. The U.S. Department of Justice and Federal Trade Commission define markets as unconcentrated when the HHI is below 1,500, moderately concentrated when the HHI is between 1,500 and 2,500, and highly concentrated when the HHI is above 2,500.¹⁴

SALES AT INVOICE PRICES are used throughout this report and reflect sales at prices paid by outlets (i.e., pharmacies, hospital, clinics), whether purchased directly from a manufacturer or indirectly via a wholesaler. Invoice line-item discounts are included. Other discounts and rebates are not reflected.

EXTENDED UNITS are the number of tablets, capsules, milliliters, ounces, etc. of a product shipped in each unit and can be used to measure volume. For oral solid formulations, extended units are equal to the number of tablets or capsules. For wet vials, extended units are equal to the number of milliliters. For dry vials, extended units are equal to the number of vials.

NATIONAL DRUG CODES (NDCS) are assigned by the FDA and serve as universal product identifiers for prescription drugs. Each NDC code is a 10-digit number that identifies the labeler, product, and package. The labeler code identifies the firm that manufactures, repackages or distributes a drug product. The product code identifies the specific strength and form for a product. The package code identifies the trade package size.

Methodologies

DEFINING SHORTAGES

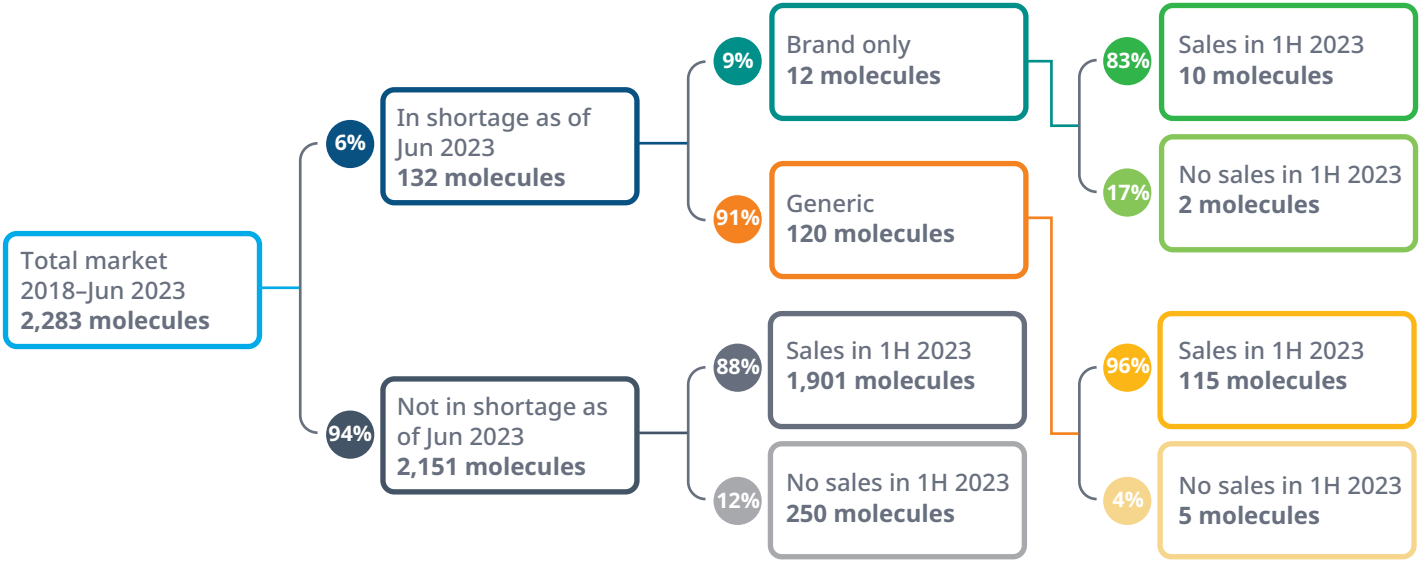
Shortages are defined throughout this report based on information provided in the FDA Drug Shortages Database as of June 8, 2023. NDCs are provided in the Drug Shortages Database and were matched to NDCs available in IQVIA National Sales Perspective. Volume and product characteristics were assessed for shortages at the NDC level.

Shortages were determined and further characterized at the molecule, or active ingredient, level. Molecules with “current” or “resolved” statuses in the Drug Shortages Database were determined to be shortage molecules, regardless of the presence of discontinuations within that molecule. Molecules that had only “discontinued” statuses were not included as shortages and are reported as discontinuations.

For “current” shortages, shortages were considered active from the initial posting date included in the Drug Shortages Database. For “resolved” shortages, shortages were considered active from the initial posting date to the date of update included in the Drug Shortages Database.

Shortages were only included in volume and sales analyses where sales occurred in the observed period. For current shortages, volume and sales analyses are based on 1H 2023 data (Jan–Jun 2023). Total market analyses are based on prescription drugs only where volume/sales were observed in the period. The segmentation of molecules in the market is provided in Exhibit 18.

Exhibit 18: Molecules in U.S. market segmented by shortage status and sales in 1H 2023



Source: FDA Drug Shortages Database, IQVIA National Sales Perspective, Jun 2023; IQVIA Institute, Oct 2023.

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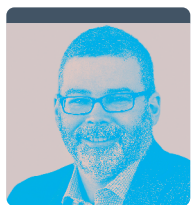
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Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.

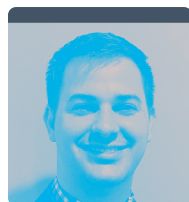


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Michael Kleinrock serves as Research Director for the IQVIA Institute for Human Data Science, setting the research agenda for the Institute, leading the

development of reports and projects focused on the current and future role of human data science in healthcare in the United States and globally. Kleinrock leads the research development included in Institute reports published throughout the year. The research is focused on advancing the understanding of healthcare and the complex systems and markets around the world that deliver it. Throughout his tenure at IMS Health, which began in 1999, he has held roles in customer service, marketing, product management, and in 2006 joined the Market Insights team, which is now the IQVIA Institute for Human Data Science. He holds a B.A. degree in History and Political Science from the University of Essex, Colchester, UK, and an M.A. in Journalism and Radio Production from Goldsmiths College, University of London, UK.



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About the Institute



The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry, and payers.

Research agenda

The research agenda for the Institute centers on five areas considered vital to contributing to the advancement of human health globally:

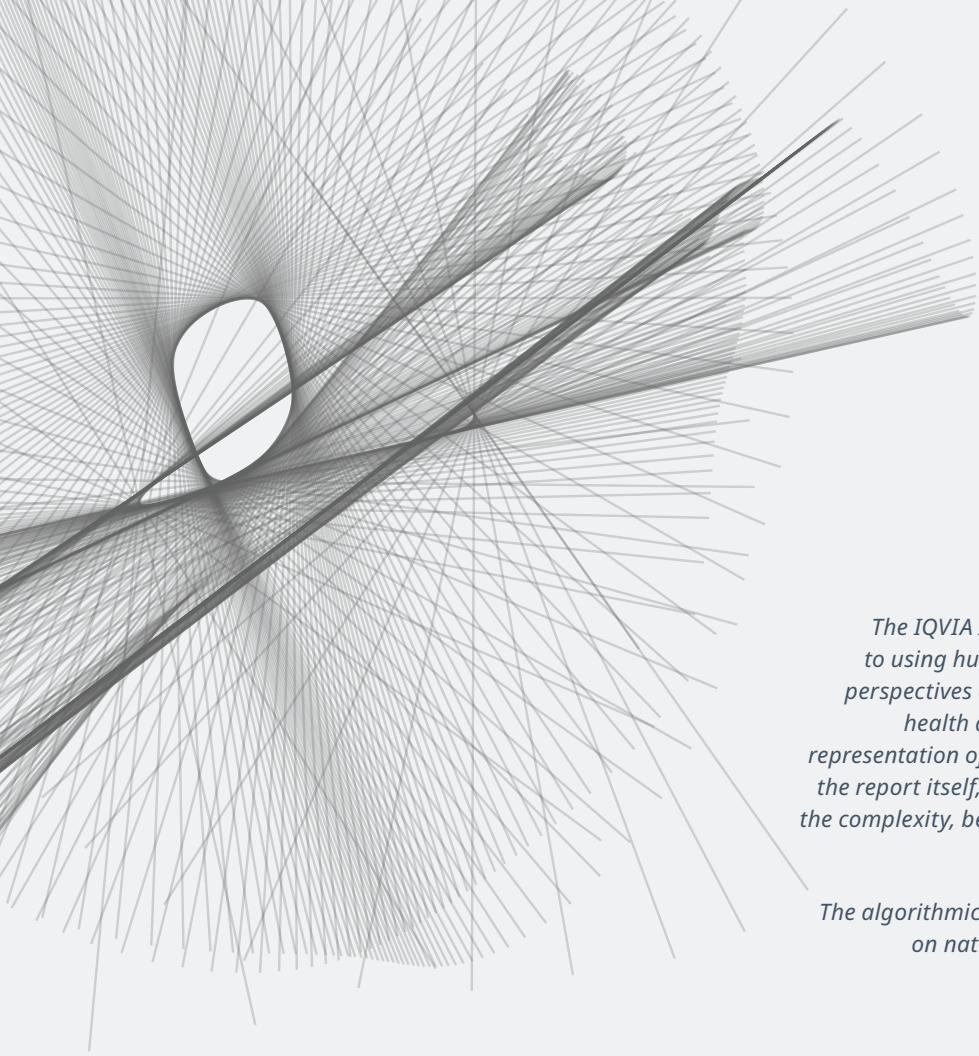
- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.

- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding principles

The Institute operates from a set of guiding principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.



The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

The algorithmic art featured on this report is generated based on national drug codes (NDCs) in shortage in the U.S. across therapy areas, Dec 2017–Jun 2023.



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