vizient®

Evaluating the impact of the oncology drug shortage

August 2023

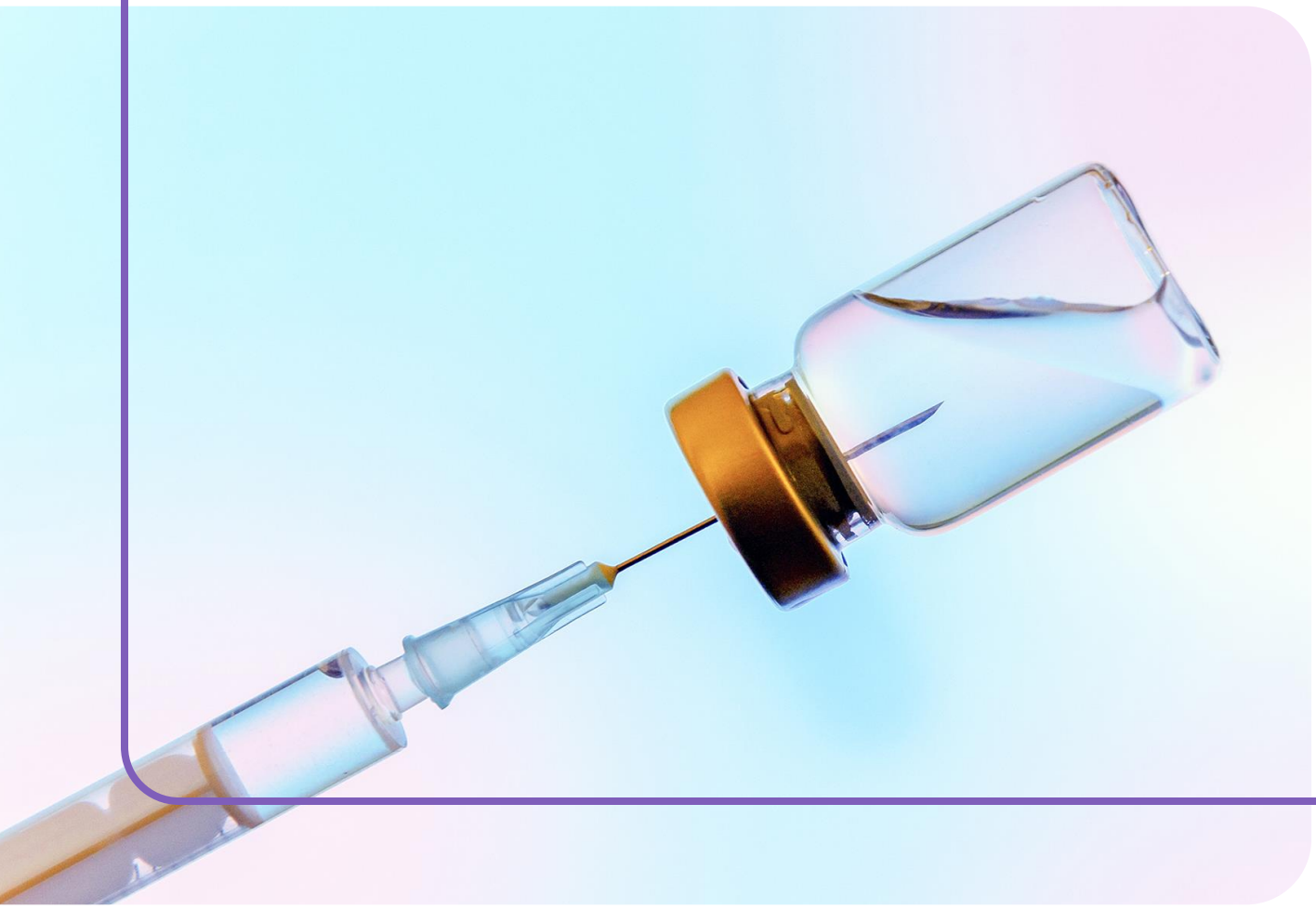


Table of contents

Executive summary

For many patients with cancer in the United States, the generic injectable medications preferred for treatment may not currently be available. This challenge is in part due to a national shortage of various oncology medications including: **capecitabine, carboplatin, cisplatin, docetaxel, fludarabine, fluorouracil and methotrexate**. These seven medications are traditional cytotoxic antineoplastics that serve as a foundation of standard of care treatment for a wide variety of cancer types including but not limited to breast, bladder, endometrial, head and neck, lung and ovarian cancers.

This paper analyzes the current suppliers and market conditions for each of these seven oncology drugs and the factors contributing to their shortage status in the U.S. Survey data from Vizient pharmacy program participant health systems noted the majority of patients that require these medications have had their treatment courses impacted in some way, ranging from 85% of patients requiring cisplatin to 70% of patients requiring carboplatin, fludarabine or fluorouracil.

Suppliers for six of the drugs including capecitabine, carboplatin, cisplatin, docetaxel, fluorouracil and methotrexate, include Accord Healthcare, the U.S.-based distributor for international manufacturer Intas Pharmaceuticals, Pfizer, Fresenius Kabi and Hikma based on 2022 sales data. The market for these products became significantly disrupted in December 2022 when Intas Pharmaceuticals made the voluntary decision to temporarily cease manufacturing and distributing products manufactured at their facility in the Special Economic Zone (SEZ) near Ahmedabad, India after a U.S. Food and Drug Administration (FDA) inspection discovered multiple issues pertaining to their quality control program.

Due to the sudden suspension of products from the Intas Pharmaceuticals SEZ plant, a shift to non-majority manufacturers for these six drugs began to occur in early 2023 resulting in a national drug shortage. Since January 2023, these products began to be included on drug shortage lists; additionally, these medications have had a two-fold increase in units ordered by providers.

From this analysis, two primary findings have emerged as probable causes to the development of national oncology drug shortages for certain drugs:

- The lack of quality and resiliency in the drug supply chain, which is an ongoing challenge.
- Recent medication approvals in oncology have enhanced our ability to treat advanced cancers and prolong remission and/or patient survival. However, older, generic drugs remain the standard of care for numerous treatment regimens in oncologic disease states and are frequently subject to drug shortages.

The lack of transparency into the magnitude and duration of shortages, in addition to how manufacturers and distributors help mitigate or otherwise respond to the shortage, can result in significant uncertainty for providers regarding whether order fulfillment will meet patient care needs. This uncertainty may translate to ordering higher quantities than normal and/or ordering from alternate sources, further stressing the supply for workhorse oncology agents. Increasing transparency in the supply chain could prevent situations of over-ordering during periods of order fulfillment uncertainty and mitigate downstream consequences. Opportunities to increase transparency include the following:

1. **Manufacturers** could provide frequent and more detailed updates on product availability and estimated release dates for products and invest resources into their quality management programs.
2. **Wholesalers** could contribute to transparency in the supply chain by implementing their allocation process for drugs during periods of shortage when order quantities exceed certain thresholds.
3. **Providers** could evaluate their inventory management practices and align ordering practices based on necessary par levels determined by their patient volume.
4. **Group Purchasing Organizations (GPOs)** could share market insights on current and future demand to help manufacturers, wholesalers and providers gain insight into ways to optimize supply distribution and purchasing behaviors.
5. **FDA** could increase access to information related to drug shortage mitigation efforts, information related to the drug shortage cause, such as notices received from manufacturers regarding supply chain disruptions, and information regarding Form 483 findings and resolution efforts. In addition, ongoing development of FDA's Quality Management Maturity (QMM) program could foster commitment to quality in pharmaceutical manufacturing business practices and potentially preventing significant manufacturing interruptions.

Together, these efforts toward increasing transparency and visibility aim to strengthen the pharmaceutical supply chain in the U.S. and minimize disruptions to healthcare operations and patient care.

Background

Shortages of medications have plagued the U.S. healthcare system for more than two decades, hindering the ability of health systems to provide care to their patients and creating a serious public health concern. FDA has recognized the extensive disruption that drug shortages create and published various resources regarding drug shortages, including the agency's Strategic Plan for Preventing and Mitigating Drug Shortages (2013), Drug Shortages: Root Causes and Potential Solutions (2019) and Report to Congress: Drug Shortages CY 2022 (2023), to help analyze the causes and devise strategies to prevent and mitigate drug shortages. However, drug shortages have persisted and, in some cases, worsened, with the peak number of shortages recorded at 309 in the second quarter of 2023.

For this report, Vizient pharmacy program participants identified seven oncology medications that have scarce availability and require initiation of mitigation protocols to sustain patient care. These medications are **capecitabine, carboplatin, cisplatin, docetaxel, fludarabine, fluorouracil and methotrexate**. Notably, fludarabine has a longstanding history of being on shortage dating back to 2019; due to the longevity of this shortage, its characterization will be presented separately. These are traditional cytotoxic antineoplastics that serve as a foundation for the standard of care treatment for a wide variety of cancer types.

To better characterize the driving forces behind these shortages and identify probable solutions to minimize patient care disruptions, an analysis of the **supply** and **demand** for these seven oncology products was conducted using Vizient data and publicly available materials. Additionally, Vizient conducted a survey of our health system and hospital pharmacy program participants to gather feedback on the severity and impact of the oncology drug shortage on operations and patient care.

Supply insight

Six of the seven identified oncology medications – capecitabine, carboplatin, cisplatin, docetaxel, fluorouracil and methotrexate – can be sourced through multiple suppliers including Accord Healthcare, the U.S.-based distributor for Intas Pharmaceuticals, Pfizer, Fresenius Kabi and Hikma based on 2022 U.S. sales data.

In December 2022, the Intas Pharmaceuticals facility located at Pharmez Special Economic Zone (SEZ) near Ahmedabad, India was cited for incomplete procedures detailing lab and environmental monitoring, insufficient monitoring of aseptic processing and stability testing processes as well as blatant destruction of documents pertaining to their quality control program. FDA issued FDA Form 483, notifying Intas Pharmaceuticals of deviations from good manufacturing practices and data integrity requirements. The full 11-observation inspection report can be found online. Intas Pharmaceuticals made "the immediate and voluntary decision in December 2022 to temporarily cease manufacturing and distribution of products manufactured at the SEZ facility that were destined for the U.S." At that time, Accord Healthcare shared with customers that products already manufactured, on hold or pending distribution by Intas Pharmaceuticals could undergo triplicate testing by an independent third-party laboratory prior to being imported to the U.S. market.

On June 2, 2023, Intas Pharmaceuticals was officially issued a letter from FDA that references an import alert (Import Alert 66-40) notifying Intas Pharmaceuticals that they may continue to supply certain products previously manufactured at the cited SEZ facility in India that are medically necessary and in short supply in the U.S. At the time of this publication, Accord Healthcare officials have not provided guidance on when production and distribution of medications from the Intas SEZ facility in India may resume.

Currently, a national shortage of these six oncology medications exists in the U.S., affecting the treatment of numerous patients across multiple disease states. Of note, there are different definitions of a drug shortage. FDA defines a drug shortage as "a period of time when the demand or projected demand for the drug within the U.S. exceeds the supply of the drug," whereas the American Society of Health System Pharmacists (ASHP) defines a drug shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent."

- *Listed as a shortage via ASHP*: capecitabine, carboplatin, cisplatin, docetaxel, fludarabine, fluorouracil and methotrexate
- *Listed as a shortage via FDA*: capecitabine, carboplatin, cisplatin, fludarabine and methotrexate

Medications often appear on the ASHP shortage list earlier than the FDA shortage list due to the need for providers to obtain different product formulations or alternative products to ensure continuity of care. Given the ability of FDA to authorize importation of pharmaceutical products and employ other mitigation strategies for drugs currently on shortage, Vizient submitted a letter in April 2023 sharing insights regarding various oncology agents, including those already identified as being on shortage, and encouraging FDA to add certain agents to their drug shortage list. Figure 1 details the timeline of these citations and the subsequent shortage identification for these six agents.

Figure 1. Timeline of events related to 2023 oncology shortage

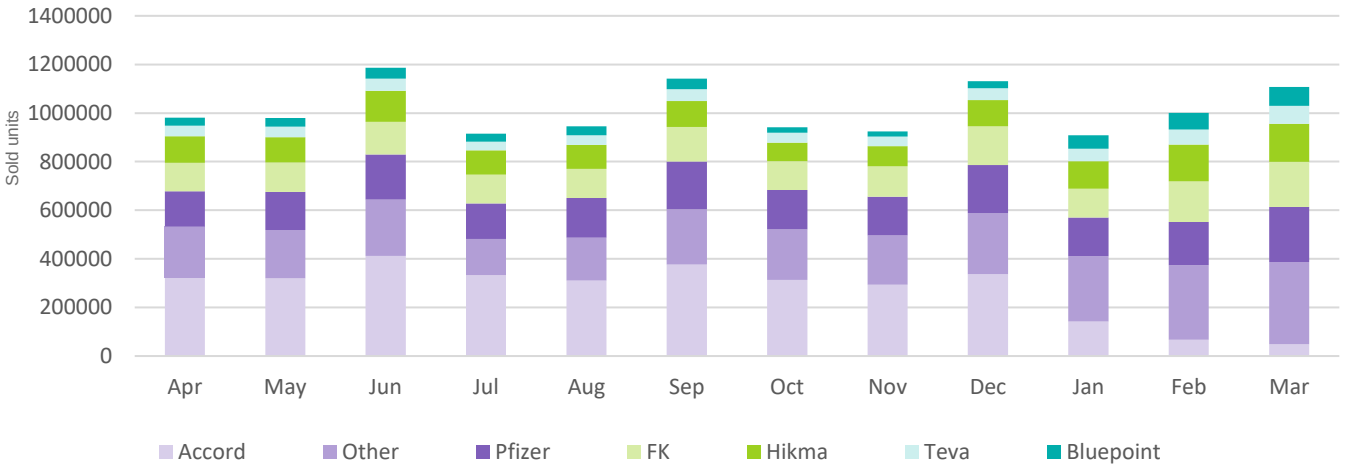
December 2022
• Nov. 22 - Dec. 2: FDA inspection of Intas Pharmaceuticals manufacturing facility in Pharmez Special Economic Zone (SEZ) near Ahmedabad, India • Dec. 2: Intas received notification of FDA Form 483 • Intas Pharmaceuticals leadership voluntarily halts manufacturing and production of agents at its SEZ facility
January 2023
• Jan. 9: Fluorouracil listed on ASHP shortage list • Jan. 10: Cisplatin listed on ASHP shortage list • Jan. 11: News of Intas Pharmaceuticals Form 483 citations appear in lay press
February 2023
• Feb. 1: Capecitabine listed on ASHP shortage list • Feb. 2: Methotrexate listed on ASHP shortage list • Feb. 9: Capecitabine listed on FDA shortage list • Feb. 10: Cisplatin listed on FDA shortage list • Feb. 27: Docetaxel listed on ASHP shortage list
March 2023
• March 13: Methotrexate listed on FDA shortage list • March 28: Carboplatin listed on ASHP shortage list
April 2023
• April 21: Society of Gynecologic Oncology releases statement regarding carboplatin and cisplatin shortages • April 28: Vizient sends advocacy letter to the FDA in response to oncology drug shortages • April 28: Carboplatin listed on FDA shortage list
May 2023
• May 24: Cisplatin product approved for importation from China through Qilu Pharmaceuticals
June 2023
• June 2: FDA issued Intas Pharmaceuticals an import alert • June 7: National Comprehensive Cancer Network (NCCN) Best Practices Committee releases carboplatin and cisplatin shortage survey results and statement on mitigating the impacts of anti-cancer drug shortages

National sales data for these six oncology agents was obtained from IQVIA. The unit of measure for sales volumes throughout this analysis is a unit, defined as the smallest package sold of a particular drug, such as a vial, to dispensing outlets. From April 2022 to December 2022, the manufacturer market share is stable for capecitabine, carboplatin, cisplatin, docetaxel, fluorouracil and methotrexate, then begins to shift to non-majority manufacturers in early 2023 as depicted by the graph in Figure 2.

As a result of the Intas Pharmaceuticals supply chain disruption, the market share for Accord Healthcare in the U.S. has experienced an overall decrease from 31% in 2022 to 10% in 2023 to date, representing a deficit of 684,000 units between Q4 2022 and Q1 2023 across these six medications.

Of note, an overall increase of 12% in total number of units sold for these medications was observed when comparing January through May 2023 with January through May 2022.

Figure 2. Market share of six affected oncology products from April 2022 to March 2023



Source: IQVIA 2023

Quarterly peak fluctuations during the months of June, September and December are also seen in Figure 2. Numerous factors could influence these trends including seasonal patterns in patient visit volumes and/or distribution models where central locations are replenished once inventory levels are distributed to satellite campuses.

Other suppliers producing the affected oncology products have gained market share since the Intas Pharmaceuticals supply chain disruption. All have attempted to increase the amount of product available in the supply channel including through the release of emergency stock. However, the supply of certain agents has been more dramatically affected than others.

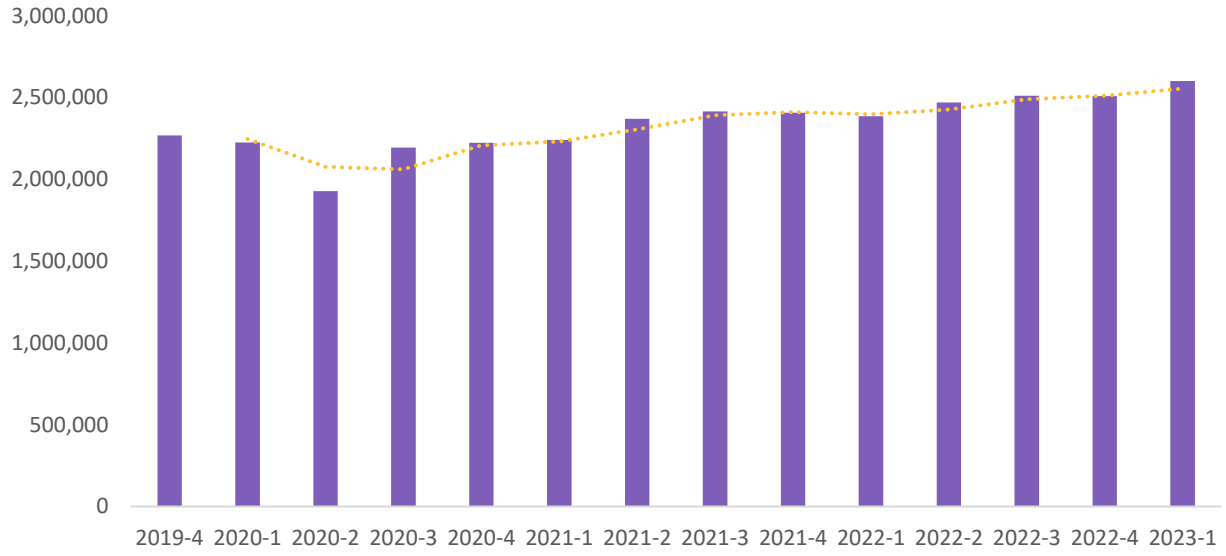
- **Capecitabine**: Accord Healthcare has been the majority market share supplier since at least 2017. Accord Healthcare market share decreased year-to-date (2023) from 42% to 17% while other suppliers for this product have provided additional supply 2023, increasing their market share.
- **Carboplatin**: Sales of carboplatin have been increasing, with more sales in March 2023 than the prior 15 months (43,000 units vs. previous monthly sales maximum of 35,000 units) as providers transitioned some patients to carboplatin during the cisplatin shortage. Pfizer has retained majority market share, which increased supply and gain of market share from 36% in 2022 to 44% in 2023 to date.
- **Cisplatin**: The most dramatic market share change due to the Intas plant closure was for cisplatin, for which Accord Healthcare market share dropped from 51% in 2022 to 11% in 2023. Cisplatin sales peaked in January 2023 (approx. 25% above 2022 average monthly sales), with Bluepoint Labs and Teva increasing their supply and market share in 2023 (10% to 21% and 14% to 29%, respectively).
- **Docetaxel**: Sales for docetaxel were higher in first quarter 2023 than any quarter in 2022, with Teva and Sagent picking up market share at 22% and 15%, respectively. Accord Healthcare market share dropped from 40% in 2022 to 22% for year-to-date 2023.
- **Fluorouracil**: There was a slight dip in fluorouracil sales during first quarter 2023, representing approximately a 5% decline from fourth quarter 2022. The market share for Accord Healthcare declined from 28% in 2022 to 12% in 2023 to date.
- **Methotrexate**: Accord market share dropped substantially from 33% to 9%, with a significant dip in sales in January 2023 that has since increased over the past few months. Pfizer has retained majority market share of 47% in 2023.

On May 24, 2023, Qilu Pharmaceuticals, a Chinese pharmaceutical manufacturer, announced they had been authorized by FDA for temporary importation of cisplatin 50 mg/50-mL vials in conjunction with Apotex Inc. This product is not FDA approved and has non-U.S. labeling and barcodes that may not register in U.S. scanning systems. A Dear Healthcare Professional letter distributed by FDA is available that details these considerations. Appendix A details the safety and operational considerations for healthcare institutions and providers utilizing this product.

Demand insight

To better characterize the demand trends for individual oncology medications, the Vizient Clinical Data Base (CDB) was queried to understand the overall growth in the oncology service line and identify if more individual patients were being diagnosed and treated in 2023. The report quantified unique patient cases receiving antineoplastics by quarter from Q1 2020 to Q1 2023. Inpatients receiving antineoplastics in the oncology service line showed flat volume (i.e., no growth) compared with 2019 baseline, while outpatients receiving antineoplastics grew 20% compared with 2019 baseline. **However, the number of unique outpatient oncology patients receiving chemotherapy has only slightly increased over time at approximately 1.5% growth quarter-over-quarter between January 2022 and March 2023** as shown in Figure 3. This relatively flat trend in unique patients would not be expected to drive substantial growth in demand for traditional antineoplastic medications such as those currently on shortage.

Figure 3. Trend in outpatient cases using antineoplastic agents in oncology service line shows 1.5% quarterly growth

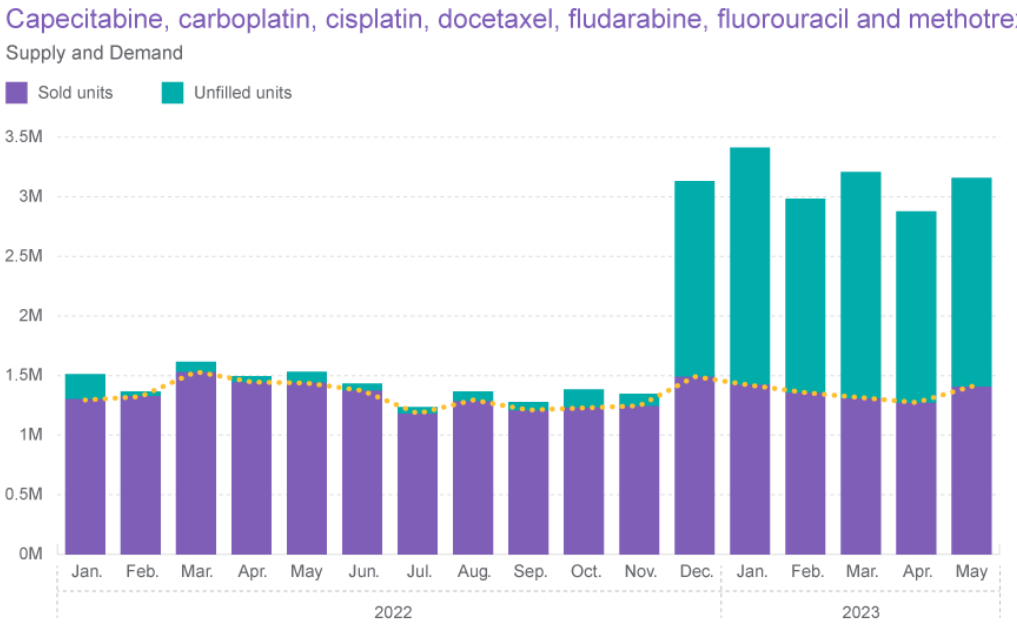


Source: Vizient Clinical Data Base/Resource Manager™. Vizient, Inc.; 2023. January 2020-March 2023.

Next, wholesaler data was evaluated to identify trends in Vizient pharmacy program participant ordering and order sales volume for the seven identified oncology products between January 2022 and May 2023. These data do not include any orders placed or purchases made directly from pharmaceutical suppliers.

When aggregating all seven products and viewing the data by number of units, there was a stable ordering pattern with a minimal unfulfillment rate from January to November 2022 (Figure 4). Beginning December 2022, the total orders placed dramatically increased and has continued with a higher-than-usual demand into 2023. **Overall, demand increased by over 136% when the six-month period of December 2022 through May 2023 was compared with June 2022 through November 2022.**

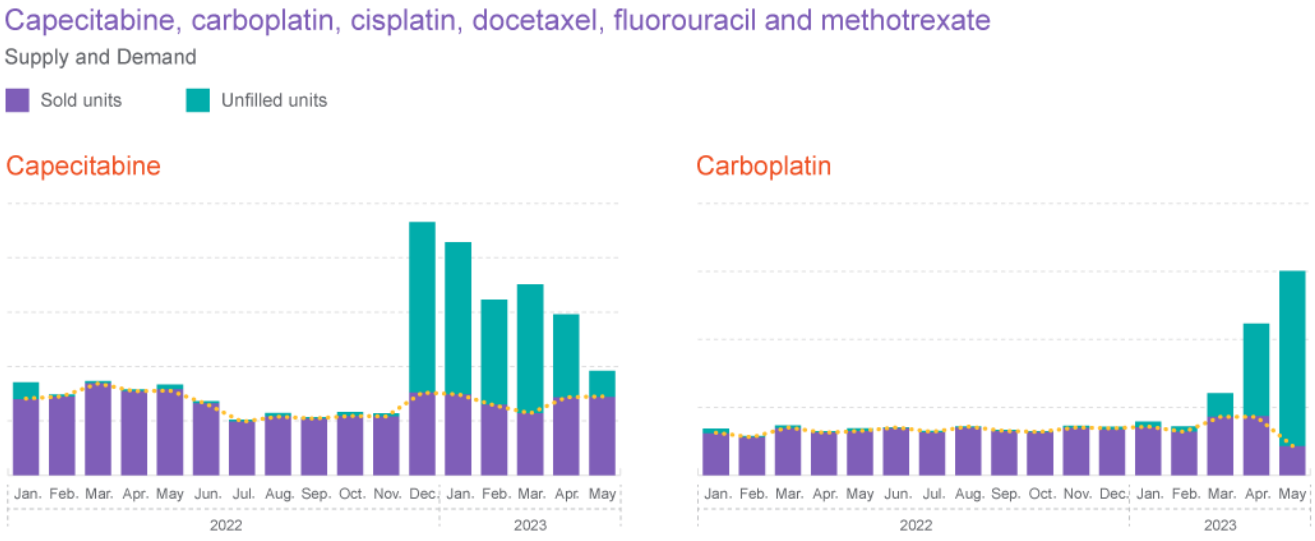
Figure 4. Units ordered and sold through wholesalers, January 2022-May 2023



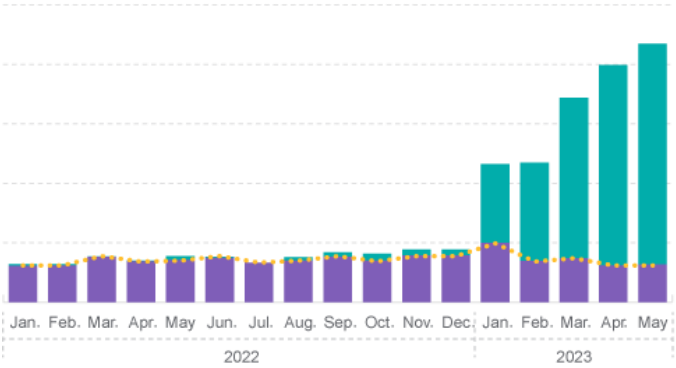
Source: Vizient internal data, January 2022-May 2023

The demand patterns for each of the affected oncology medications was quantified over the same period. Each medication has slightly different timelines and degrees of severity (Figure 5). The magnitude of increased demand was quantified as the percent increase in demand for December 2022 through May 2023 (active drug shortage period) compared with the prior six-month period of June through November 2022. Of note, during periods of increased demand or supply chain disruptions, manufacturers and/or wholesalers may implement allocation procedures to serve as a supply stability tool by potentially adjusting the quantities that an individual purchaser can receive to align with historical ordering volumes.

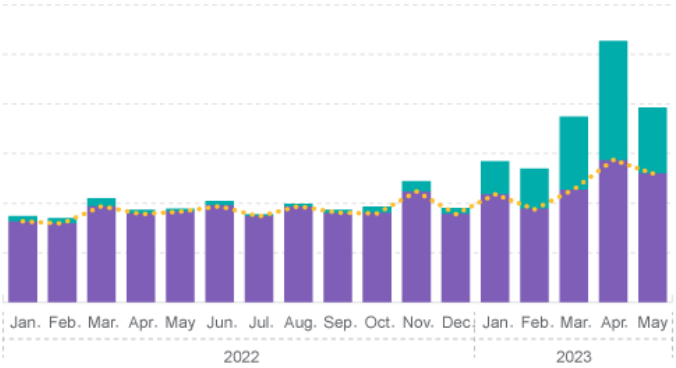
Figure 5. Units ordered and sold through wholesalers, January 2022-May 2023



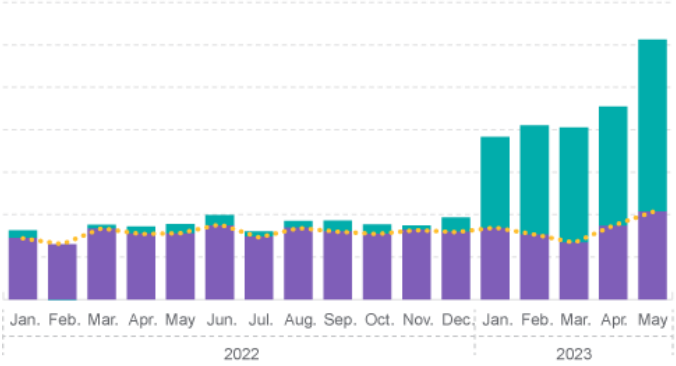
Cisplatin



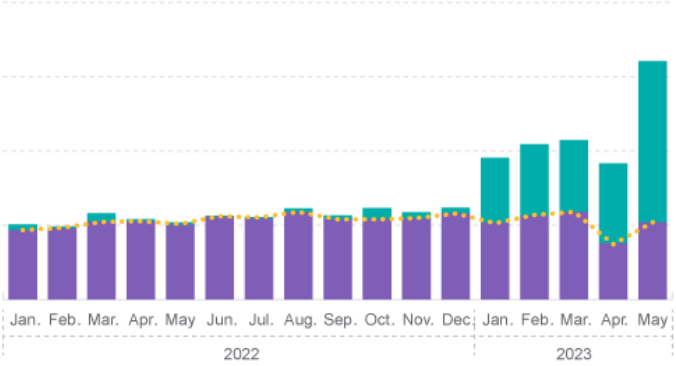
Docetaxel



Fluorouracil



Methotrexate



Source: Vizient internal data, January 2022-May 2023

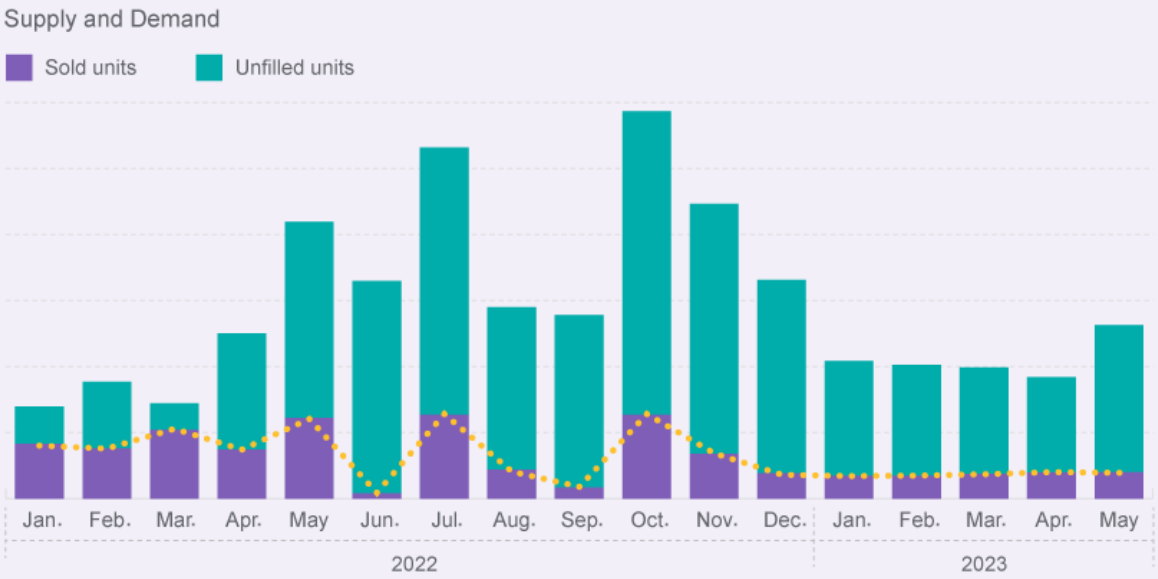
- **Capecitabine** experienced an almost three-fold increase in demand of 197%. Of note, the labeling of capecitabine was updated on December 14, 2022, to include use in gastric, esophageal, gastroesophageal junction and pancreatic cancers as a part of the FDA Project Renewal, an Oncology Center of Excellence initiative. The expanded indications for this agent would have also resulted in an increase in utilization and quantity ordered. Demand appears to be normalizing and approaching baseline levels as of May 2023.
- **Carboplatin** is a therapeutic alternative for cisplatin included in many National Comprehensive Cancer Network (NCCN) treatment guidelines. ASHP listed carboplatin on the drug shortages list on March 28, 2023. The demand for carboplatin began to climb in April 2023, with an overall 110% increase in demand.
- **Cisplatin** has seen an almost four-fold increase in demand of 273%.
- **Docetaxel, fluorouracil,** and **methotrexate** have seen increases in demand of 69%, 127%, and 77% respectively, during the active drug shortage period.

Fludarabine – an exception

Fludarabine has been on shortage since 2019 and is an outlier in this analysis. Fresenius Kabi and Teva currently hold the majority of market share at 76% combined in 2023. Intas Pharmaceuticals did not produce fludarabine at the SEZ facility near Ahmedabad; they have since started production at other facilities in 2023 and have been gaining a portion of the market share up to 13% in 2023 to date. Areva Pharmaceuticals entered the fludarabine market from Q4 2020 to Q2 2021 but only gained less than 1% market share at the time. Areva Pharmaceuticals entered the market a second time in 2023 and to date has gained 7% of the market share. The Areva product has a wholesale acquisition cost (WAC) 10 times higher than competitors, which may hinder its uptake in the market.

One factor related to the increases in demand of fludarabine is attributed to the increase in utilization of chimeric antigen receptor T-cell therapy (CAR-T). Fludarabine serves as one of the primary conditioning agents given prior to the administration of CAR-T. Of note, there was a 45% decrease in quantity ordered of fludarabine in 2023 compared with the previous three quarters (Figure 6), and quantity fulfilled has remained steady in 2023.

Figure 6. Fludarabine units ordered and unfulfilled through wholesalers, January 2022-May 2023



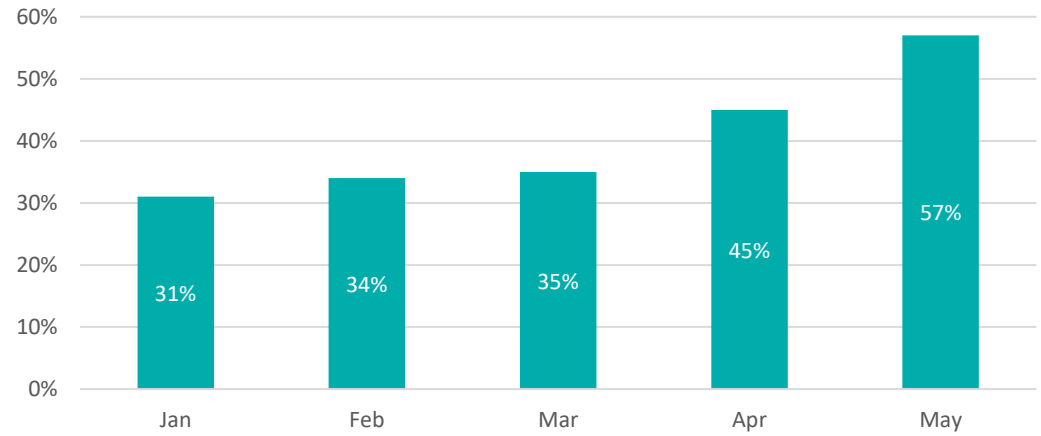
Source: Vizient internal data, January 2022-May 2023

Demand distributions

To further describe the impact of these increases in demand for the seven identified oncology agents, an additional analysis was conducted to identify the Vizient pharmacy program participants who received less than 50% of their historical benchmark quantity ordered. Historical benchmark quantity ordered was defined as the average monthly volume purchased by a Vizient pharmacy program participant in calendar year 2022. In January 2023, 31% of Vizient pharmacy program participants received less than 50% of historical order quantities. **By May 2023, the proportion of Vizient program participants who received less than 50% of historical order quantities increased to 57%** (Figure 7).

With a lack of transparency into how long the supply chain disruption will continue, providers may consider order quantities that exceed historical levels because of uncertainty regarding whether order fulfillment amounts and timing would meet patient care demands. Figure 7 displays a trend of increasing rates of insufficient order fulfillment, suggesting that longer durations of drug shortages may contribute to a greater impact on product distribution.

Figure 7. Proportion of Vizient Pharmacy Program Participants receiving less than 50% historical benchmark quantity ordered, January 2023 to May 2023



Source: Vizient internal data, January 2023-May 2023

As the agents in question are all antineoplastics, it would follow that the primary stakeholders for demand and stewardship of these agents would be major cancer centers, such as those belonging to the National Comprehensive Cancer Network (NCCN). The majority of NCCN member institutions are also Vizient program participants. When purchasing patterns for Vizient member providers who are major cancer centers are compared with those who are not, several interesting trends emerge:

- Quantities ordered appear to double in December 2022 for non-cancer center participants and remain elevated through at least May 2023.
- Quantities ordered by major cancer center members begin to increase significantly in February 2023 once alternatives were depleted (e.g., cisplatin/carboplatin) but appear to have moderated in April and May 2023.

These trends may be due to the ability of major cancer center member providers to identify therapeutic alternatives for agents currently on shortage and order products not currently on shortage and stocked by the wholesaler as well as leveraging their wholesaler allocations based on historical order quantities.

Vizient provider insight

In April 2023, Vizient conducted a survey of its health system and hospital member providers to better characterize the severity of the oncology drug shortage and impact on daily operations and patient care capacity. An eight-question survey was developed and distributed to the Vizient Oncology Network (VON), Vizient Oncology Clinical Council and Vizient Pharmacy Network Cancer Care Committee during the time frame of April 21–28, 2023.

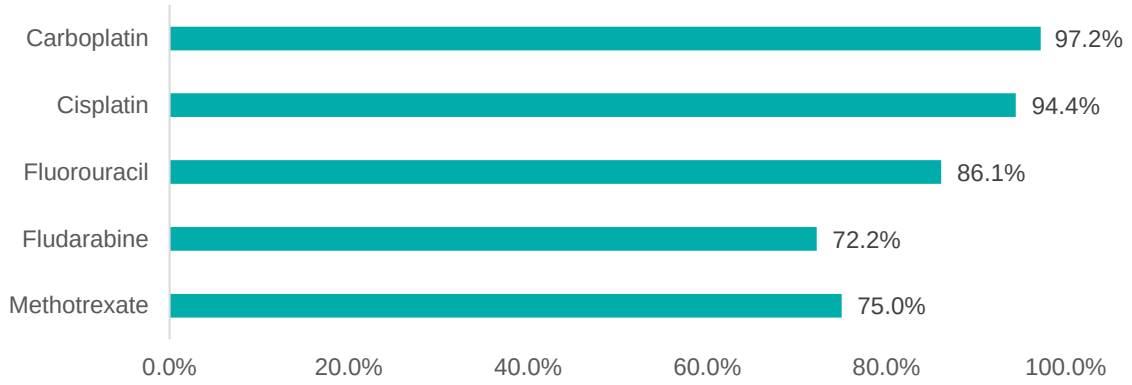
Survey demographics

A total of 32 unique Vizient oncology member providers gave complete responses to the survey for analysis. These responses represent health systems throughout the U.S. and include 10 of the 33 NCCN-designated cancer centers (30%).

Oncology drug specifics

Respondents were asked to quantify which oncology agents were causing the greatest challenge in supply for their institution. Drug selection options included carboplatin, cisplatin, fludarabine, fluorouracil and methotrexate based on the feedback from Vizient member providers in early April 2023. A free text option was also provided to add additional drugs of greatest challenge not listed. The drugs demonstrated as having the greatest impact for Vizient member providers were reported as both carboplatin and cisplatin (Figure 8). Additional medications most frequently reported as a challenge were capecitabine and docetaxel.

Figure 8. Proportion survery respondents impacted by oncology drug shortages

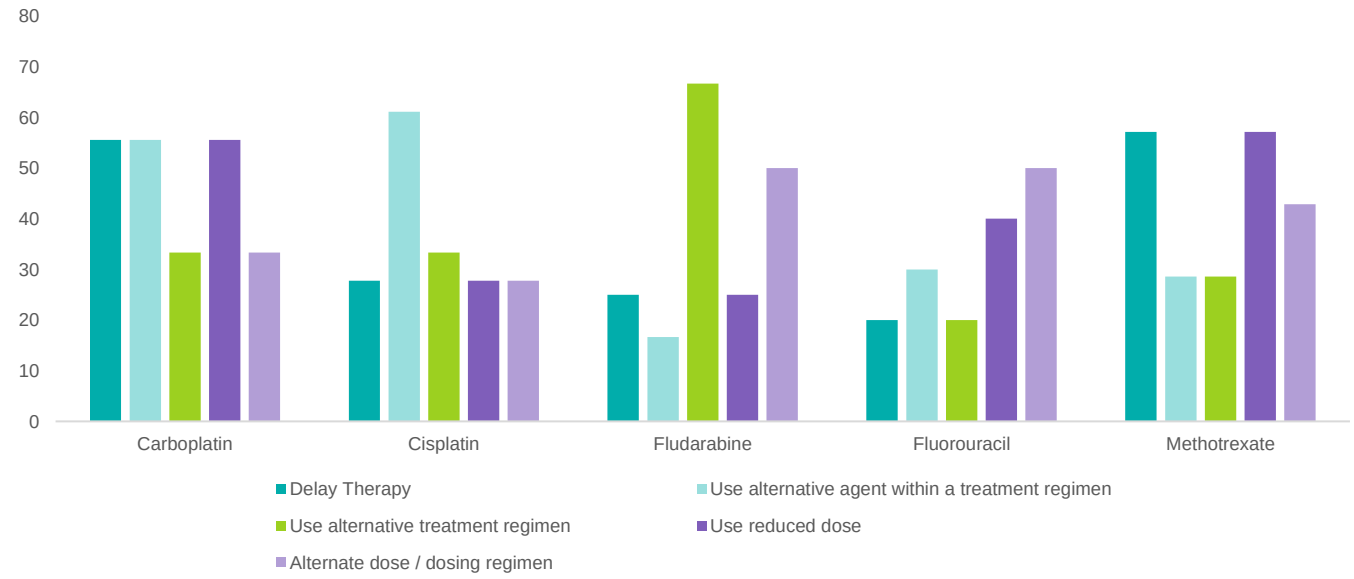


Mitigation strategy implementation

During periods of drug shortages, mitigation strategies are developed and implemented by health systems to optimize their response to the shortage and minimize impacts to operations and patient care. These multi-faceted strategies are intended to prolong the existing inventory, optimize patient treatment and ensure healthcare team members are aware of these strategies.

Figure 9 represents number of survey respondents who implemented mitigation strategies for carboplatin, cisplatin, fludarabine, fluorouracil and methotrexate as well as what proportion used the specific strategies listed in the survey. Given its widespread use in a variety of cancer types, the majority of respondents (56%) implemented some type of mitigation strategy for cisplatin. The most common strategy was to substitute carboplatin for cisplatin within a treatment regimen (11 responses, 61%), while for those managing the fludarabine shortage the strategy was to switch patients to an alternative myeloablative conditioning regimen including cyclophosphamide, busulfan or melphalan.

Figure 9. Specific mitigation strategies implemented at survey institutions for impacted drugs



Patient impact

Overall, more than half of patients that required any of these seven medications at surveyed Vizient member provider organizations are being affected by shortages, ranging from 85% of patients requiring cisplatin and 70% of patients requiring carboplatin, fludarabine or fluorouracil. By substituting individual drugs within treatment regimens or switching to a different treatment regimen entirely, the ability to treat patients with cancer is being significantly affected by these current shortages. Both capecitabine and carboplatin are part of this shortage situation due to their ability to be used instead of fluorouracil and cisplatin, respectively.

In addition to substituting these antineoplastic agents with other medications, respondents reported via free-text responses the following necessary actions to manage these shortages:

Procurement

- Buying from alternative sources
- Investigating possibility of alternative manufacturers
  - Requiring purchase of higher cost manufacturers (e.g., Areva brand fludarabine)
- Sourcing alternative presentations and vial sizes of drugs
- Managing inventory within health system / integrated delivery network (IDN) across various sites
- Purchasing ahead when available/increasing par levels
- Leveraging allocations across multiple wholesaler accounts to procure doses when urgently needed

Conservation of supply

- Restricting administration to certain indications
- Omitting drug from regimens when possible
- Batching patients
- Dose-rounding; rounding down doses by 10% (carboplatin), lowering doses to use preservative-containing product (methotrexate)

Prioritizing patients

- Not starting certain patients on consolidation therapy / prioritizing immunotherapy
- Identifying lists of patients with upcoming treatment appointments to determine who should be prioritized, which treatments can be delayed, which patients could receive an alternative agent or switching treatment locations
- Creation of a prioritization schema for situations where a drug shortage progresses to the point of not being able to treat all patients

Communication

- Holding interdisciplinary meetings (twice weekly or weekly) to assess if drug inventory can meet patient needs
- Sending out frequent updates to pharmacy and provider team members on the status of supply

Under Vizient's Novaplus® Enhanced Supply (NES) program, suppliers maintain additional inventory of essential products to mitigate supply disruptions. Vizient member providers can request access to NES products through Vizient's Advanced Access Hub in cases where they are unable to obtain product through normal distribution channels for products covered under the program. Vizient also offers participating member providers access to additional dedicated inventory for Essential medications through its NES Reserve program including some of the oncology products mentioned in this analysis with requirements to manufacture and warehouse additional supply based on provider's historical purchases. In Q1 2023, 291 requests were made for these NES products through the Advanced Access Hub.

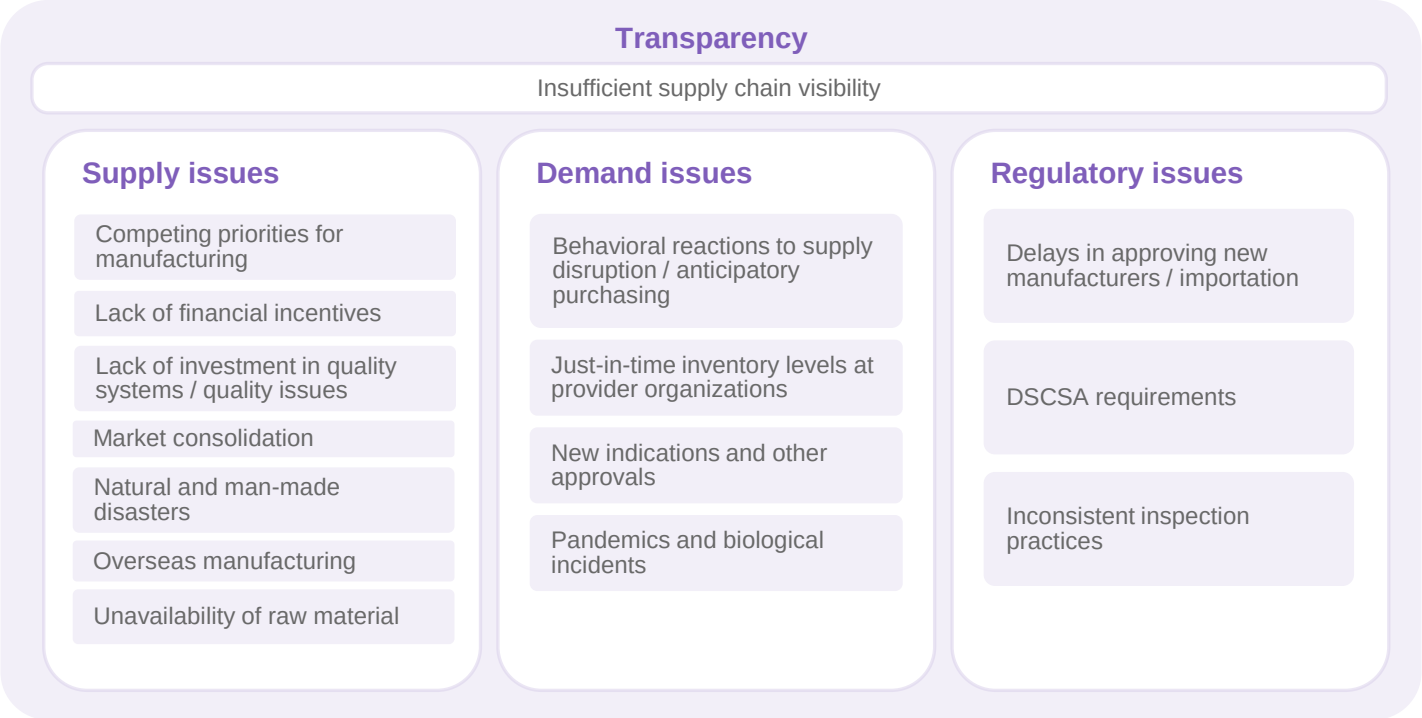
Vizient was able to facilitate fulfillment of over 12,800 units of carboplatin, methotrexate and methotrexate PF for its member providers through the NES program in Q1 2023.

Factors influencing drug shortages

The FDA Drug Shortages Task Force published Drug Shortages: Root Causes and Potential Solutions (2019), in which they found, among other causes, that economic forces contributed to the ongoing challenge of drug shortages. Specifically, one area needing the most attention was quantification of the harms of drug shortage, particularly those that lead to worsened health outcomes for patients, and better characterization of shortages.

This report aims to serve as a tool to assist in providing transparency into current supply and demand dynamics for Vizient member providers and the impact on hospital operations and direct patient care during shortages of multiple oncology drugs. To identify probable solutions that may help temper the impact of future drug shortages, Figure 10 details the various attributes that initiate, potentiate or otherwise influence the magnitude and duration of drug shortages.

Figure 10: Influences on drug shortages



Resources

- Drug Shortages: Causes, Impact, and Mitigation Strategies. Frontiers in Pharmacology. 2021 July;12:1-18.
- Drug Shortages: Root Causes and Potential Solutions, 2019. U.S. Food & Drug Administration.
- Factors Involved in U.S. Generic Drug Shortages. U.S. Pharmacist. 2020 June;45(6):19-24.
- Short Supply: The Health and National Security Risks of Drug Shortages, March 2023. United States Senate Committee on Homeland Security & Governmental Affairs.
- Strategic Plan for Preventing and Mitigating Drug Shortages, October 2013. U.S. Food & Drug Administration.

Regarding the root cause of drug shortages related to mature quality management systems, Vizient continues to support FDA development of a quality management maturity (QMM) program. While still in its early stages, this program was created on the principle that drug manufacturers with advanced quality systems can proactively detect vulnerabilities, thus reducing the likelihood of supply disruptions or interruptions. Establishing participation and incentivizing higher levels of QMM at manufacturing facilities and sharing this information with purchasers will increase transparency and enable purchasers to more effectively consider both price and quality of a pharmaceutical product.

Conclusion

The lack of consistent supply for high quality, lifesaving drugs has plagued the healthcare industry for far too long. The impact of drug shortages has reached every level of the healthcare system and most importantly has directly affected the patients that require these therapies. Hospital and health system personnel responsible for ensuring supply of these agents for their organizations have more than two decades of experience in combatting drug shortages with strategies such as increasing par levels and/or increased ordering quantities for medications in limited supply to the extent that their institution's fiscal and physical constraints allow.

Overall, the data indicate an overall increase of 12% in total units sold for these seven agents during this period of active drug shortages. When evaluating the quantities of these medications ordered, there has been a 136% increase in demand based on order quantities with only a slight increase in the number of patients with new diagnoses of cancer (1.5% quarter-over-quarter growth between January 2022 and March 2023). There is an increasing proportion of Vizient pharmacy program participants receiving less than 50% of historical benchmark order quantities during this same period (reaching 57% in May 2023)

The shortage situation is further exacerbated by the lack of public information and transparency into the timeline for recovery and product availability to meet market demand. Hospitals and health systems are unaware if a drug shortage will improve or deteriorate at any given time for the duration of the shortage.

Carboplatin and cisplatin have received the most attention in the press during the current oncology shortage. Cisplatin experienced the greatest disruption to its supplier landscape, with a drop in market share for Accord from 51% to 11% following the Intas citations. As a result of this supplier disruption, FDA has approved importation of cisplatin from China through Qilu Pharmaceuticals; operational and safety implications should be considered by providers who purchase this product. Interestingly, total sales for cisplatin have remained stable despite some shifting in the supplier landscape.

The National Comprehensive Cancer Network (NCCN) Best Practices Committee recently published a survey regarding the carboplatin and cisplatin shortage; responses indicated 93% and 70% of centers were experiencing a shortage of carboplatin and cisplatin, respectively. Additionally, the Society of Obstetrics and Gynecology and the American Society for Clinical Oncology have developed recommendations on how providers can address the current shortage of carboplatin and cisplatin (Appendix B).

Call to action to reduce the impact of future shortages

One overarching theme emerging from this analysis is the lack of transparency in the supply chain for healthcare organizations, regulatory bodies such as FDA and even the suppliers themselves. The Homeland Security and Governmental Affairs Committee publication Short Supply: The health and national security risks of drug shortages provides the following insight: *"Neither the federal government nor industry had end-to-end visibility of the pharmaceutical supply chain – from the key starting materials, APIs, finished dosage and various other manufacturers that are "upstream" – to the "downstream" suppliers, which include purchasers and providers. This lack of transparency limits the federal government's ability to proactively identify and address drug shortages."*

Vizient and our member provider organizations strive for full transparency into the health and performance of the supply chain for pharmaceuticals. Additionally, the End Drug Shortages Alliance (EDSA) was established by Vizient in 2022 (now an independent organization with over 170 participants from across the industry) and seeks to "end drug shortages through focus on transparency, quality, redundancy and production of additional supply to achieve measured and sustainable results."

Given the insights related to the supply and demand for the seven oncology agents analyzed, increased transparency could lead to a reduction in over-ordering during periods of stress in the supply chain and could improve the downstream effects that occur with acute increases in demand. Opportunities to increase transparency include the following:

1. **Manufacturers** could provide frequent updates on product availability and estimated release dates for products and invest resources into their quality management programs.
2. **Wholesalers** could contribute to transparency in the supply chain by communicating their allocation process for drugs during periods of shortage when order quantities exceed certain thresholds.
3. **Providers** could evaluate their inventory management practices and align ordering practices based on rational par levels determined by their patient volume.
4. **Group Purchasing Organizations (GPOs)** could share aggregated historical purchase data to help manufacturers, wholesalers and providers gain insight into ways to optimize supply distribution and purchasing behaviors.
5. **FDA** could increase access to information related to drug shortage mitigation efforts, information related to the drug shortage cause, such as notices received from manufacturers regarding supply chain disruptions, and information regarding Form 483 findings and resolution efforts. In addition, ongoing development of FDA's Quality Management Maturity (QMM) program could foster commitment to quality in pharmaceutical manufacturing business practices and potentially preventing significant manufacturing interruptions.

Together, these efforts to increase transparency and visibility could strengthen the pharmaceutical supply chain in the U.S. and minimize disruptions to healthcare operations and patient care.

Appendix A: Cisplatin importation

FDA is allowing temporary importation from China of cisplatin 1 mg/mL, 50-mL vials from Qilu Pharmaceutical through Apotex authorized distributors. This product is not FDA-approved. For ordering information, reach out to your distributor or contact Apotex Corporation customer service at 1-800-706-5575.

There is a Dear Healthcare Professional Letter describing the differences between the U.S. products and the Chinese product. Some of the most notable differences are that the Chinese box and labels are printed in Chinese, there is no NDC, and the linear barcode may not track appropriately. Refer to the letter for detailed information.

Safety checklist for using cisplatin from China (Qilu Pharmaceutical)*	
☐	Distribute the Dear Healthcare Professional Letter to staff and others in the organization who may be involved in administering cisplatin. Ensure review of the information.
☐	Review the ISMP article on FDA authorization of cisplatin importation from China.
☐	Preemptively enter the Qilu Pharmaceutical product into your EHR.
☐	Preemptively update the master formulation record to reflect Qilu product-specific instructions when this product is used for compounding.
☐	Verify the product received was imported by either Qilu or Apotex Corp.
☐	Ensure product matches the U.S. NDC, one of the lot numbers and one of the expiration dates listed in the Dear Healthcare Professional Letter.
☐	Visually inspect the carton and vial to compare and match to image in Appendix 2 of the Dear Healthcare Professional Letter.
☐	Consider creating a label that includes the translated lot number and expiration date to apply to both the vial and carton. **Note:** The carton contains both a production and expiration date.
☐	Implement a visual product verification process at every step in the medication use process when the linear barcode would normally be used because the barcode may not register on U.S. scanning systems. Consider adding an organization-specific barcode for continuity and safety.
☐	Refer to the FDA-approved cisplatin injection package insert for full prescribing information. The Dear Healthcare Professional Letter contains a side-by-side comparison between the U.S. FDA approved and imported product.
☐	Report adverse events and/or quality problems to FDA's MedWatch adverse event reporting process.

*In addition to usual medication safety and medication use processes.

Appendix B. Shortage mitigation strategies

Society of Gynecology and Oncology – Cisplatin and Carboplatin (i.e., platinum-based antineoplastic agents)

- **Minimize ordering of non-essential platinum**. If an alternative agent with comparable efficacy and safety is available, then cisplatin or carboplatin should not be ordered.
- **Increase the interval between cycles and reduce the total platinum dose when clinically acceptable to do so**. Where National Comprehensive Cancer Network (NCCN) guidelines state a range for cycle duration, default to the longer end of that range (e.g., if platinum is recommended every three to four weeks, then default to every four). Where guidelines state a range of dosing, default to the lowest therapeutically appropriate dose.
- Consider **minimizing or omitting cisplatin or carboplatin for recurrent platinum-resistant ovarian and other cancers**.
- **Ration dosing by rounding doses down to the nearest vial size** as a first step to ensure efficient use. If the shortage becomes more critical, consider reserving carboplatin and cisplatin for curative intent treatment.
- **Consult with your oncology pharmacy** to determine your healthcare system's current supply of these platinum agents and **escalate any shortages promptly along the supply chain and to your clinical teams**. We encourage our oncology community to communicate with other local providers regarding drug availability and to consider referrals for select patients if clinically indicated.
- If adequate supplies are unavailable, **select an alternative, evidence-based regimen** and consider a consultation with oncology / hematology colleagues.

American Society of Clinical Oncology – Clinical guidance

- **Re-prioritize non-essential use of antineoplastic agents in limited supply.** If an alternative agent, intervention, or sequence with comparable efficacy and safety is available, then the limited agent should not be ordered.
- **Increase the interval between cycles and/or reduce the total treatment dose when clinically acceptable.** Where nationally recognized guidelines (e.g., ASCO, NCCN, etc.) state a range for cycle duration, default to the longer end of that range (e.g., if platinum is recommended every 3 to 4 weeks, default to every 4). Where guidelines indicate a range of dosing, default to the lowest therapeutically proper dose.
- **Minimize** or **omit** the limited agent for recurrent agent-resistant cancers.
- **Minimize waste by optimizing vial size, dose rounding and using multi-use vials.**
- **Institutions should establish a working multidisciplinary utilization committee** to monitor drug shortages, **provide and communicate internal policies on utilization**, and act as an independent arbiter to **promote equitable use of drugs in short supply**.
- **Select an evidence-based alternative regimen** if adequate supplies are unavailable and **consider a second opinion consultation** with oncology/hematology colleagues to discuss disease site-specific options.
- Providers should **offer counseling referrals (if available) to patients affected by shortage-related distress.**

  This guidance was adapted from the Society of Gynecologic Oncology (SGO) communique on cisplatin and carboplatin shortages and reviewed by SGO representatives.

Resources

Vizient Strategies for Drug Shortage Management

Participants in the Vizient pharmacy program have access to resources and expertise to help navigate drug shortages, including the following:

- **Advanced analytics**: With real-time visibility into expense management across all care settings, organizations rely on Vizient analytics to help hospitals reduce pharmaceutical spend while improving outcomes. An algorithm identifies products at risk of going short, influences engagement and drives sourcing strategies.
- **Advocacy**: Vizient supports legislative and regulatory efforts to proactively address the systemic causes of the drug shortage crisis. Vizient also hosted a series of congressional briefings on hospital providers' drug shortage management and mitigation strategies, participated at multiple events hosted by the FDA and other healthcare partners on drug supply chain resiliency, pharmaceutical quality and a competitive marketplace for biosimilars.
- **Clinical engagement**: Provider members collaborate with Vizient to develop strategies that minimize the impact of shortages on the workflow.
- **Drug shortages resources**: Vizient member provider webpage provides I.V. Shortages Resource Guide, drug shortage alerts and drug-specific mitigation strategies.
- **Drug Shortages Task Force**: Vizient team focused on development of solutions and resources to support member providers with drug shortages.
- **Novaplus® private label**: Offers 200+ drugs representing 900+ NDCs. Vizient member providers that use Novaplus see the highest fill rates in the industry.
- **Novaplus Enhanced Supply (NES)**: Sourcing strategy for essential medications to create up to six months of additional inventory based on historical purchases warehoused in the United States by the suppliers, covering more than 120+ drugs representing 480+ NDCs and 130 million units of additional inventory. Vizient member providers have accessed more than 1.4 million units of additional inventory in the last 12 months. The NES Reserve program is an enhanced sourcing program that dedicates additional inventory only for the reserve member's pharmacy to access.
- **Partnership with the University of Utah**: Enables collaboration and provides daily alerts on the latest drug shortages.
- **Sourcing resources**: Includes our failure-to-supply program, which brought $25 million in value back to provider members in 2022; wholesale fill-rate monitoring and damages; wholesale agreement support; and effective contracting strategies (e.g., contracts with commitments and allowing price increases to give manufacturers flexibility if there are challenges).
- **Vizient Essential Medications List**: Vizient pharmacy experts continually identify essential medications where, if not available, they would prove the greatest threat to a hospital's ability to provide immediate and high-quality patient care. Also included are accompanying mitigation strategies.
- **Vizient member provider drug shortage mitigation group**: Collaboration opportunity to offer guidance to Vizient regarding drug shortages and the associated mitigation strategies to address them.

Vizient, Inc.
290 E. John Carpenter Freeway
Irving, TX 75062-5146
(800) 842-5146

To learn more, please contact
pharmacyquestions@vizientinc.com.

Vizient, Inc. provides solutions and services that improve the delivery of high-value care by aligning cost, quality and market performance for more than half of the nation's healthcare providers. Vizient provides expertise, analytics, advisory services, and a contract portfolio representing more than $130 billion in annual customer purchasing volume, to improve patient outcomes and lower costs.
www.vizientinc.com