Drug Shortages: Root Causes and Recommended Solutions

With McKesson's deep expertise in pharmaceutical distribution, supply chain analytics, and market access dynamics, we are committed to helping address the multitude of issues contributing to drug shortages.

While each drug shortage is unique, we can build supply chain resiliency by understanding root causes and deploying targeted solutions to **enhance the reimbursement and market access landscape, incentivize supply preservation programs, and improve supply chain visibility.**

Introduction

Drug shortages can prevent or delay access to necessary treatments, disrupting medical care and compromising patient health. The average drug shortage impacts at least half a million patients. Of those impacted, one-third are over the age of 65[1]. Shortages can lead to higher prices and, even when resolved, impact a patient's ability to fill their prescriptions.[2] Additionally, providers (e.g., community pharmacists, physicians, hospitals, health systems) must expend resources to manage or mitigate shortages - roughly $359 million per year in labor resources and $200 million per year in purchasing of alternative treatments.[3]

While brand drugs are also impacted, generic drugs face specific market dynamics increasing the risk of shortage. Generics are often more susceptible to production issues, as they typically share a production line. Waning economics often prohibit manufacturers from building critical redundancies. Researchers examined the Food and Drug Administration (FDA) drug shortage list in January 2023 and found that shortages impacted 4-6% of generic/brand and generic-only markets compared to approximately 3% of brand-only markets.[4]

2022 drug shortage data indicates equal impact to injectable and non-injectable drugs.[5] However, this varies by drug class. The top 5 classes of drugs currently in shortage include those to treat central nervous system conditions, anti-microbials, fluids/electrolytes, chemotherapy, and hormones; except for antimicrobials, these categories are dominated by injectables. [6]

[1] ASPE Report to Congress Impact of Drug Shortages on Consumer Costs. May 2023. https://aspe.hhs.gov/sites/default/files/documents/87781bc7f9a7fc3e6633199dc4507d3e/aspe-rtc-costs-drug-shortages.pdf
[2] ibid
[3] ibid
[4] Association for Accessible Medicines. Drug Shortages: Causes & Solutions. June 2023. https://accessiblemeds.org/sites/default/files/2023-06/AAM_White_Paper_on_Drug_Shortages-06-22-2023.pdf
[5] https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics
[6] ASHP. Drug Shortages Statistics. https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics

Common supply chain drivers of prescription drug shortages

The U.S. drug supply chain is globally fragmented, vastly complex, and contains limitations on the availability and sharing of manufacturing information. [7]As a result, any number of factors along the supply chain can spark a shortage. The FDA has noted ongoing challenges due to COVID-19 disruptions, which may have also exacerbated quality issues and capacity constraints for U.S. and global manufacturers.[8]

The supply of both generic and branded drugs may be interrupted by events in any of three key categories: market-wide supply constraints, product-specific issues, and reimbursement and market access limitations. Within those categories, some of the most common causes of shortages include:

- **API issues**: Availability of active pharmaceutical ingredients (API) can be impacted by multiple factors including geographic concentration of API manufacturing, changes in testing requirements, and a limited or disrupted supply of key starting materials. The substantial geographic concentration of API manufacturing globally heightens geo-political supply risk, in particular regions such as China, India, and Eastern Europe. Adequately assessing API risk is difficult for direct purchaser organizations, as crucial information around specific API sources[9] for many products is considered proprietary.
- **Manufacturing and Quality issues**: Manufacturing and quality challenges are among the most common drivers of shortages. Limited production capacity for injectables, highly potent compounds, and complex formulations can impact supply of these products. In addition, quality-related issues such as product recalls due to inadequate manufacturing controls, contaminated raw materials and patient adverse events can cause shortages. Similarly, quality inspections by regulators such as the FDA may lead to Warning Letters or Import Bans that impact product supply. At times, the cost of remediating quality issues can lead to product discontinuations and/or plant closures.
- **Generic economic deflation**: In aggregate, the generic drug market operates at lower margins. Shrinking profitability on individual products occurs due to declining sell prices, escalating input costs, or inadequate production volumes. Sell prices predominantly reflect the level of competitive

Currently in Shortage: Cisplatin

Cisplatin is a generic oncology medicine used to treat a variety of cancers, with high manufacturing costs and razor thin margins.

In February of 2023, Cisplatin fell into shortage due to quality issues associated with a manufacturer's facility. This facility was responsible for a majority of the global supply of the drug.

Despite FDA's efforts and work with manufacturers and API suppliers to increase supply, quality assurance issues remain, and Cisplatin is still in shortage.

[7] "ASHP Guidelines on Managing Drug Product Shortages." American Society of Health-System Pharmacists, 2018; 75: e593-601.
[8] Food and Drug Administration. Tenth Annual Report on Drug Shortages. 2022. https://www.fda.gov/media/169302
[9] "We Still Don't Know Who Makes This Drug." Health Affairs. February 7 20220. https://www.healthaffairs.org/content/forefront/we-still-don-t-know-makes-drug

intensity (number of competitors and their pricing strategy) and reimbursement. As competitors seek share (and adequate production volumes) in a highly competitive market, the sell price and margin can quickly erode and lead to supplier exits.[10] In markets with limited competitors the supply chain may lack enough redundancy to support unexpected shocks. Maintaining a healthy balance of competition, price, cost, and reimbursement are critical to support a robust supply chain. In addition, Medicaid inflation penalties have limited the ability for generic manufacturers to raise prices, even when other manufacturers have exited the market due to lack of profitability.

- **Discontinuing products**: Much like generic economic deflation, ongoing product rationalization in the context of a manufacturer's full product portfolio is simply a fact in the U.S. drug market. Suppliers may eliminate name-brand or generic products from their portfolios altogether or discontinue certain pack sizes, which eliminates some natural redundancy in the supply chain.
- **Disasters**: When hurricanes, fires or other disasters sweep through an area where drugs or APIs are produced, the effects to the drug supply chain can be devastating. For example, when Hurricane Maria struck Puerto Rico, the powerful storm affected roughly 50 pharmaceutical manufacturing sites, including makers of top-selling biologics and components.[11]

McKesson's Public Policy Recommendations

A diverse set of root causes means that there is no single "silver bullet" solution to ending drug shortages. We believe all stakeholders should work together to address the problem, and we are advocating for public policy proposals that will prevent or mitigate shortages in the future.

Reimbursement and Market Access Incentives

A robust, competitive market is one that naturally buffers against drug shortages.[12] The right incentives could make it financially appealing for new market entrants or existing manufacturers to invest in the necessary redundancies and quality programs to guard against supply disruptions. This will require significant investments to bolster the market and economic opportunity for historically competitive, low margin drug classes and those which rely on a limited number of global manufacturers (e.g., two or less). Determining drugs eligible for such programs and the duration of such efforts is imperative. Initiatives must not generate misaligned incentives to create or maintain a drug shortage. Programs must have a clear guardrails and metrics to ensure market correction and program exploitation are prioritized. Efforts must be led through public-private partnerships between federal agencies (e.g., FDA, CMS) and key stakeholders across the supply chain, including but not limited to manufacturers, distributors, patient advocacy organizations, and impacted physician specialty organizations. We outline key opportunities below:

[10] Association for Accessible Medicines. Drug Shortages: Causes & Solutions. June 2023.
[11] "Hurricane Maria's Lessons for the Drug Industry." Jarvis, L.M., Chemical & Engineering News, September 17, 2018. https://cen.acs.org/%20pharmaceuticals/biologics/Hurricane-Marias-lessons-drug-industry/96/i37
[12] Experience with the Generating Antibiotic Incentives Now (GAIN), passed in 2012, demonstrates that without the appropriate reimbursement and market access incentives, manufacturers are reticent to invest in the development and marketing of drugs when presented with incentives focused on expedited FDA reviews and extended exclusivity alone. Source: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-reports-its-progress-advancing-policies-developing-next-generation-antibiotics

- **Enhance Medicare Access and Reimbursement:** Mandatory equitable or favorable formulary placement under Medicare Part D could fuel greater competition, especially for biosimilars and competitive drugs classes. Formulary exclusivity contracts can make it difficult for new market entrants to secure enough patient volumes to make manufacturing investments. Mandatory coverage could level the playing field and address some access barriers. Additionally, enhanced reimbursement for drugs across therapeutic classes with a history of shortages or risk of shortage within Medicare programs can create economic favorability to support investment or reinvestment in manufacturing capabilities.
- **Limit Federal Program Rebate and Pricing Requirements:** We should consider modifying current policies and contemplate when it is best to allow manufacturers to 'reset' prices[13] to reflect the current cost of producing goods, or at minimum buffer against additional penalties that make necessary price increases disadvantageous.
    - Inflation Reduction Act (IRA) Inflationary Rebate Penalties: The IRA[14] does contain some level of safeguards to protect eligible inflationary rebatable Medicare Part D and B drugs that may be susceptible to shortage. However, this discretion is left to the Health & Human Services (HHS) Secretary and does not define the parameters for a drug becoming "eligible" for exemption, the market data/criteria needed to make such assessments, or the duration of a drug being excluded. We recommend codifying exclusions more clearly to create better economic safeguards for drugs in shortage and those at risk of shortage.
    - Medicaid Drug Rebate Program (MDRP) Average Manufacturer Price (AMP) Cap Penalties: Manufacturers of brand and generic covered outpatient drugs must pay each state Medicaid program a statutory rebate to participate in the program. The Medicaid Rebate is currently capped at AMP. Starting January 1, 2024, drugs facing Medicaid rebates higher than AMP will no longer by capped at 100% of the drug's AMP. This is likely to create considerable market constraints and may further drive manufacturers out of the market. We recommend suspending all MDRP rebate requirements for an established period of time to allow manufacturers to invest in the production of drugs in or at risk of shortage. We recognize the magnitude of impact will depend heavily on which drugs are eligible for such a safe harbor, and therefore recommend that at a minimum, penalties remain capped at 100%.
        - Inclusion of inflationary penalties on generic drugs in the MDRP: As a result of these penalties, when generic manufacturers pull their drugs from the marketplace due to pricing economics, the remaining manufacturers have no flexibility to raise prices when they are adversely impacted by the MDRP inflation rebates. We recommend suspending inflation penalties on generic drugs that are in shortage.
    - Modify the 340B Program: Federal pricing programs, such as a 340B ceiling price, can deter market entry of new generic manufacturers. We recommend temporarily excluding certain drugs (e.g., low-cost generics, critical drugs in or at risk of shortage) from the program or

[13] "Resetting" price in this context means allowing a manufacturer to establish a once in a lifetime "new" price for a drug for the purposes of Federal drug reporting programs, such as 340B and the MDRP. As such, 340B ceiling price and MDRP Average Manufacturer Price (AMP) calculations would start anew and not be subject to the restrictions of predecessor market dynamics.

[14] U.S. Congress. HR 5376 Inflation Reduction Act of 2022.

limiting the ceiling pricing to avoid "penny pricing" challenges (e.g., make ceiling price equal to AMP). This exclusion should accompany specific quality and production goals for manufacturers.

- **Quality-Based Incentives:** Ensuring quality of medicines is paramount to a safe and stable drug supply chain. In addition to requiring minimal quality requirements, rewarding manufacturers that adopt quality best practices is a sensible and worthy pursuit. Integrating quality within drug manufacturing is not a new concept. For years, FDA has contemplated the need for a Quality Management Maturity (QMM) program for greater manufacturer transparency and is currently soliciting public comments on how to create a voluntary program[15]. Lack of appropriate incentives may limit manufacturer investments in the quality management systems necessary to get ahead of disruptions.[16] Integrating business and manufacturing incentives is foundational to building global supply chain resiliency. As such, quality-based incentives such as accelerated approvals, vouchers, and enhanced payments for manufacturers demonstrating exceptional quality practices are appropriate. We support incentivizing a culture of quality, and whether done through FDA or industry-prescribed metrics, believe that improving global quality will favorably impact drug shortages. It is important to note that direct purchaser organizations conduct their own quality due diligence during sourcing. Such diligence may include a review of prior FDA inspections, product recalls, site inspections, and other quality assurance assessments. These activities will likely expand in response to ongoing quality-related shortages and a growing focus of direct purchasers on quality as a crucial factor in product selection.

Supply Preservation Programs

Improving access and preservation of API bolsters global supply chain resiliency. This requires creating and aligning incentives across the supply chain that go beyond on- or near-shoring manufacturing capabilities. For maximum benefit, all efforts must be contemplated in coordination with federal and state Strategic National Stockpile (SNS) efforts.

- **Incentives for Buffer Stock Programs:** If implemented with the appropriate safeguards, creating incentives for manufacturers to maintain a 3 to 6-month reserve capacity of critical medicines could be another solution for drug shortages in certain therapeutic categories. Manufacturers should further be encouraged to maintain reserve capacity of APIs and other necessary ingredients for emergency production, if needed.

  In order to prevent against inadvertently aggravating a drug shortage, these programs should made available to both hospital and community providers. While we support CMS's overall goal of creating a buffer stock incentivization program for hospitals as early as CY 2024, we believe that the current proposal could further exacerbate access gaps if additional sites of care are not included. As the recent cancer drug shortage has demonstrated, creating safeguards in only one part of the care

[15] Food and Drug Administration. Quality Management Maturity Program for Drug Manufacturing Establishments; Request for Comment. Sept 15 2023.
[16] U.S. Food and Drug Administration. Drug Shortages: Root Causes and Potential Solutions. 2019. https://www.fda.gov/media/131130/download?attachment

delivery ecosystem disproportionally disrupted access for patients unable to seek care in hospitals or Cancer Centers of Excellence. Buffer stock programs should include core capabilities to support the safe and efficient storage (e.g., temperature controls), management (e.g., staffing, record keeping), and rotation of supply (e.g., virtual vendor managed inventory). Additionally, since demand can fluctuate regionally and by individual customers, the ability to seamlessly pass product both regionally and nationally should be a key attribute for entities facilitating buffer stock programs.

Most providers and manufacturers may not have the infrastructure and core capabilities necessary to operationalize buffer stock programs. Distributors are ideally positioned to serve in this role and should be recognized as preferred partners to entities working on behalf of providers or manufacturers. Should CMS elect to move forward with permitting a buffer stock program(s), it is important that the agency has methods for evaluating impact to the supply chain, and tactics ready to deploy should unintended consequences be observed.

Supply Chain Visibility

Enhancing the integrity of our global supply chain necessitates greater visibility and insight into the original source of excipients (inactive substances that serve as the vehicle or medium for a drug or other active substance), APIs, and finished dosage products. We continue to support efforts to improve data collection from manufacturers to improve our understanding of potential supply chain vulnerabilities. The ongoing collaboration between distributors and FDA and Administration for Strategic Preparedness and Response (ASPR) continues to provide valuable insights.

Where FDA and ASPR may see market softness across distributors, early warning signals should be shared with distributors to optimize our ability to respond. For example, while distributors continue to diversify our supply sources, lack of “origin” insights prohibit us from ensuring our efforts are truly creating safeguards or simply new sourcing routes to the same “origin” source. Additionally, while distributors conduct their own partner evaluations to ensure suppliers meet core quality metrics, these may not uncover the same vulnerabilities as identified in FDA evaluations.

We recommend the private sector and federal agencies maintain an open dialogue - one that encourages sharing data and insights while protecting commercial interests. The focus should be on the exchange of required information, rather than onerous reporting requirements. We must continue to build trust across public-private partnerships in order to effectively identify early warning signs that a shortage may be on the horizon.

To avoid unnecessary burdens, there should be clarity on the criteria for inclusion of APIs or finished product(s) on the critical medication shortage list. Similarly, when that drug is no longer on the shortage list and there is evidence that market supply has stabilized, then reporting requirements should be rescinded.

Conclusion

McKesson believes solving supply chain disruptions is an “all hands on deck” effort that requires the cooperation and collaboration of all the stakeholders in the supply chain. By better understanding and addressing the often highly variable root causes, bolstering supply preservation efforts, and improving communication between stakeholders, we can make meaningful progress in protecting the health of our nation.

About McKesson

McKesson is a global leader in healthcare supply chain management solutions, retail pharmacy, community oncology and specialty care, and healthcare information solutions. McKesson partners with pharmaceutical manufacturers, providers, pharmacies, governments, and other organizations in healthcare to help provide the right medicines, medical products, and healthcare services to the right patients at the right time, safely and cost-effectively. As a mission-driven company, we are focused on working with our customers and partners to advance health outcomes for all.

McKesson has been a long-time supporter of Angels for Change, a global nonprofit on a mission to end life-saving drug shortages since its inception in 2019. The nonprofit was inspired by founder Laura Bray’s work with McKesson to access life-saving medication for her daughter who was diagnosed with leukemia. Bray then made it her mission to help other patients in similar positions.

In July 2021, the McKesson Foundation awarded Angels for Change with a grant that enabled the nonprofit to expand its staff, lease office space, support education programs, and help cover general operating costs.

Building on our shared momentum, McKesson joined Angels for Change in the summer of 2023 at their annual SummitONE event and again at the White House for a special Cancer Drug Shortage Roundtable to help create equal access to critical life-saving treatments.