Your Generics & Biosimilars Industry

Association for Accessible Medicines

Drug Shortages: Causes & Solutions

Executive Summary

I. Background

U.S. Patients Rely on Generic Medicines / Generic Sustainability is at Risk

Generic medicines are the backbone of the U.S. prescription drug market, supplying more than 9 out of every 10 prescriptions. And the availability of generic medicines overall is remarkably stable – even during challenges such as the COVID-19 pandemic.

Nonetheless, drug shortages, which hit crisis proportions between 2010 and 2011, can be a challenge for manufacturers, providers, and patients. Due to aggressive efforts by industry and the Food and Drug Administration (FDA), the incidence of shortages has declined, but recent reports suggest a rise in shortages in 2023.

Drug shortages are not limited to generic markets. They affect roughly 3% of brand-only markets and 4-6% of generic/brand and generic-only markets.[1] Nonetheless, evidence suggests that some generic drugs may be particularly susceptible to drug shortages, due to challenges facing the generic marketplace.[2] Manufacturing generic drugs is a highly competitive, low-margin industry. External measures including disruptions in the supply chain, regulatory delays, or changes in competitive intensity can make producing certain products financially unsustainable.

In fact, the risk of drug shortages is increasing as the long-term sustainability of generic manufacturing faces threats. Generic prices are decreasing, drug purchasers are becoming more concentrated, new generics are not adopted as quickly, some generics are never launched due to limited commercial opportunities, and registered manufacturing sites are declining.[3][4] These changes force generic manufacturers to reconsider production of lower-margin, often older, medicines to ensure continued financial sustainability of the overall pipeline.[5] Generic product discontinuations have numbered over 3,000 since 2010 and appear to be on the rise.[6]

At the core, shortages reflect challenges to the long-term sustainability of generic medicines. While each drug shortage is unique, most stem from the increasing fragility of the generic drug market. This fragility is caused by (1) market and pricing factors that undermine the

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[1] Food and Drug Administration. "Analysis of the FDA Drug Shortage List". (January 4, 2023). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages

[2] Stromberg, C. "Drug Shortages, Pricing, and Regulatory Activity Working Paper". (2014). National Bureau of Economics. Available at http://www.nber.org/chapters/c13102.pdf

[3] Association for Accessible Medicines. "AAM Comments in Response to Administration's Blueprint on Drug Pricing" (July 26, 2018) Available at: https://accessiblemeds.org/sites/default/files/2018-07/AAM-HHS-Blueprint-to-Lower-Drug-Prices-RFI-71-16-18.pdf

[4] Long, D. "US Pharmaceutical Trends, Issues and Outlook" (February 2023) Presentation at Access!2023.

[5] For example: 1) Swetlitz, I. "Teva Plans to Cut Back Generic Drug Production Even As Shortages Intensify," (May 18, 2023) Bloomberg. Available at: https://www.bloomberg.com/news/articles/2023-05-18/teva-plans-cuts-to-generic-drug-production-amid-shortages#xj4y7vzkg and 2) PR Newswire "Lannett Company, Inc. Enters Into Restructuring Support Agreement" (May 1, 2023). Available at: https://www.prnewswire.com/news-releases/lannett-company-inc-enters-into-restructuring-support-agreement-301811795.html

[6] Raffat, U. Evercore ISI Research. (July 16, 2018)

sustainability of low-cost generic manufacturing and (2) government policies that compound challenging market dynamics. These leave generic markets vulnerable to shortage, often as a result of (3) regulatory and manufacturing challenges.

The result can strain supply chains and leave providers without sufficient supply for patients. As FDA Commissioner Dr. Robert Califf recently noted, "We have got to fix the core economics if we're going to get this situation fixed."[7]

II: What are Drug Shortages - Why Definitions Matter

Any discussion of drug shortages requires clarity in definitions to address the issue. The FDA defines a shortage as "***a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug***".[8] Otherwise, there are different types of 'drug outages or unavailability':

1. **Drug shortage:** defined by the FDA and based on statutorily mandated reporting by drug manufacturers, drugs appear on the FDA drug shortage list. This signifies that a national shortage is in effect and manufacturer(s) cannot supply sufficient supply. This is the definition of drug shortage AAM is utilizing in this paper.

2. **Out-of-stock:** The American Society of Health-Systems Pharmacists (ASHP)/University of Utah 'drug shortage list' includes any drug outage, whether a short-term disruption (usually lasting 1 to 2 weeks) or longer term, but have different causes.[9] While the result is the same – that patients are not able to get their medication – the cause and solutions are different from a formal shortage.

   Out-of-stock --- short term means that the pharmacy or the wholesaler-distributor does not have the drug immediately available but there is drug in the supply channel. This would need to be addressed with the pharmacy community and/or the wholesale-distribution community. This rarely occurs due to manufacturing issues.

   Out-of-stock --- long term means the wholesaler-distributor, pharmacy, and/or the pharmacy benefit manager (PBM) are setting reimbursement or making stocking decisions to maximize revenue, rather than ensure product availability. Even though the drug is available in the supply channel, a pharmacy may not be able to dispense that product. This rarely occurs due to manufacturing issues.[10]

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[7] Jewett, C. "Drug Shortages Near an All-Time High, Leading to Rationing". (May 17, 2023). New York Times, Available at: https://www.nytimes.com/2023/05/17/health/drug-shortages-cancer.html

[8] FD&C Act 506C(h)(2) (21 U.S.C. 356c(h)(2))

[9] American Society for Health Systems Pharmacists. "Drug Shortage Bulletins" Drug Information Service of the University of Utah and provided by ASHP as its exclusive authorized distributor. (March 2023) Available at: https://www.ashp.org/drug-shortages/current-shortages

[10] Kolenich, E. "Richmond Owner: Small Pharmacies Often Lose Money on Drugs, Told to Lie About Supply". (May 2, 2023). Richmond Times-Dispatch. Available at: https://richmond.com/news/state-and-regional/govt-and-politics/richmond-owner-small-pharmacies-often-lose-money-on-drugs-told-to-lie-about-supply/article_2df76e2c-e83b-11ed-b800-771db2bf4431.html

The impact of these different definitions is found by comparing the FDA drug shortage list to that published by the ASHP. As of June 6, there were 138 products listed on the FDA drug shortage list compared to 238 on the ASHP list. Of those on the FDA list, all but 40 were on the ASHP list, whereas the ASHP list contained 141 products not considered to be in shortage by FDA.[11]

These distinctions are critical. When formulating solutions, they must be tailored to true drug shortages, although policymakers should also consider the causes and impacts of practices that result in drugs being out of stock.

III: Factors that Lead to Drug Shortages

At the core, shortages reflect challenges to the long-term sustainability of generic medicines. While each drug shortage is unique, most stem from the increasing fragility of the generic drug market. This fragility is caused by (1) market and pricing factors that undermine the sustainability of low-cost generic manufacturing and (2) government policies that compound challenging market dynamics. These leave generic markets vulnerable to shortage, often as a result of (3) regulatory and manufacturing challenges.

Factor 1: Pricing and market dynamics
Pricing and market factors are disrupting the economic sustainability of generic manufacturing, shrinking product portfolios, and reducing available resources to counter drug shortages.

> **High generic price deflation.** In the past five years, although patients used more generics, the total value of all generic sales fell by $6.4 billion.[12] While generic drug prices have historically declined, the last few years have yielded particularly high rates of price deflation.[12] Generic drugs are launching at a greater discount off the price of their branded counterparts, lowering prices at a faster rate and ultimately reaching a lower price point.[13] These trends provide short-term savings to patients and payers, but they can cause companies to discontinue products, close facilities or shutdown altogether, placing a burden on the market. Not only might this leave a void that, at best, takes time for other manufacturers to fill, but it may be financially unattractive for another manufacturer to attempt to enter a new market or ramp up production to prevent a shortage. Altogether, this "race-to-the-bottom" calls into question the generic market's long-term sustainability.
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> **Supply chain purchasing power.** Price deflation has been driven by unchecked consolidation among generic drug-buying organizations. Three hospital/clinic group purchasing organizations control roughly 90 percent of all generic medicine purchasing

[11] Comparison of FDA and ASHP drug shortage lists as of June 12, 2023.
[12] IQVIA Institute for Human Data Science. "The Use of Medicines in the U.S. 2023 Usage And Spending Trends And Outlook To 2027" (April 2023) Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-use-of-medicines-in-the-us-2023/the-use-of-medicines-in-the-us-2023.pdf
[13] IQVIA Institute for Human Data Science Analysis conducted for AAM. Data reflects pricing trends for newly introduced generic products separated by year.

for hospitals/clinics.[14] In the retail market, three purchasing consortiums (wholesaler/retail chain combinations) collectively control 90 percent of the retail prescription market.[15] Fewer buyers means fewer markets for the more than 200 generic drug manufacturers in the U.S., and can result in unsustainably low prices with as many as a dozen manufacturers making any given product.

Increasing input costs. Manufacturing faces cost inflation as a result of overall inflation and geopolitical re-alignment. This causes margins to be compressed significantly and, coupled with price deflation, can result in product discontinuations.

Slower adoption of new generics. New product launches are the lifeblood of the generic industry, but Medicare policies reward the continued use of higher-cost brands. This results in formulary decisions that block generics or place generics in a higher cost-sharing tier or favor higher-priced brand medicines over generic or biosimilar alternatives. Slower adoption of new generics or biosimilars makes it more difficult to justify the continued production of medicines that are losing money. The business model of many generic companies is to strive to offer a wide array of products, which may include keeping certain drugs in production that are not directly generating positive financial returns. When the ability for generics to recoup their investment in new products is blocked, it becomes more difficult to justify the continued production of revenue-negative products.

Seasonal/cyclical prediction models. Products used on a seasonal or cyclical basis can be affected by unforeseen changes in demand. This means suppliers may not be able to ramp up when another supplier experiences supply disruptions. For instance, because of purchaser consolidation, one manufacturer typically receives Primary Supply status; however, interruptions at Primary Supplier may not be quickly remedied by alternate suppliers. This also occurs when providers purchase and hoard drugs in short supply, or when hospitals and distributors engage in speculative purchasing, creating unpredictable demand and shortage cycles.

Factor 2: Policy Miscues

State and federal policies, while not focused on generics or drug shortages, can harm generic sustainability and exacerbate the potential for shortages.

Medicaid generic drug penalty. In 2015, Congress created a new price inflation penalty in the Medicaid program for generics.[16] But because the program was based on brand medicines, it neglected important differences in market function. For instance, because it holds a monopoly, a brand manufacturer controls its price, but a generic manufacturer's average price fluctuates due to decisions, outside of its control, by purchasers and other

[14] Seeley, E. "The Impact of Pharmaceutical Wholesalers on U.S. Drug Spending" (July 20, 2022) The Commonwealth Fund. Available at: https://www.commonwealthfund.org/publications/issue-briefs/2022/jul/impact-pharmaceutical-wholesalers-drug-spending

[15] Fein, Aj. "The 2022-23 Economic Report On Pharmaceutical Wholesalers And Specialty Distributors" (October 2022) Drug Channels Institute. Available at: https://drugchannelsinstitute.com/products/industry_report/wholesale/

[16] Public Law No: 114-74.

generic competitors. As a result, generic manufacturers now face millions of dollars in rebate "penalties" on generics that have not been subject to a price increase.[17] These unpredictable, onerous payments undermine the financial viability of low-margin generic markets. This was foreseen by a 2017 analysis concluding the penalty would "increase uncertainty, reduce revenues, encourage manufacturers to exit the market, and discourage the entry of new manufacturers… [and would] have the unanticipated and unintended consequence of increasing the likelihood of shortages for generic medicines."[18]

Government payment policies. Payment policies lead to underpricing and cause generic, particularly generic injectables, to leave the market. Medicare reimbursement policies for sterile injectables creates a race-to-the-bottom that drives prices below market equilibrium.[19] And in many cases, this also harms generic or biosimilar adoption by rewarding providers for using higher-cost brand drugs.[20] And mandatory 340B discounts add cost and threaten the sustainability of producing low-margin, high-value generics.

State regulatory burdens. Numerous state legislatures have enacted or considered legislation aimed at regulating the prices of generic drugs.[21] For instance, proposals to create "pricing transparency" for pharmaceuticals or prohibit "price gouging" by generic drug manufacturers disproportionately impact generic drugs and fail to account for the regular price variability that has always existed in the generics market.[22] Likewise, drug takeback mandates often place the bulk of the financial burden on those who make generic drugs, create additional costs for generic manufacturers, and undermine the viability of low-volume generic markets.[23] Manufacturers need the ability to adjust prices to respond to material cost increases and increasing FDA compliance costs.

Factor 3: Regulatory and manufacturing challenges

Regulatory challenges place a burden on generic manufacturers and can delay the entry of drug products to market and delay the supply of materials needed for manufacturers.

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[17] Association for Accessible Medicines. "CPI Penalty on Medicaid Generic Drugs Threatens Patient Access to Affordable Medicine" (September 2017) Available at: https://accessiblemeds.org/resources/press-releases/cpi-penalty-medicaid-generic-drugs-threatens-patient-access-affordable

[18] Manning and Selck, "Penalizing Generic Drugs with the CPI Rebate will Reduce Competition and Increase the Likelihood of Drug Shortages" (September 2017). Association for Accessible Medicines. Available at: https://www.accessiblemeds.org/sites/default/files/2017-09/Bates-White-White-Paper-Report-CPI-Penalty-09-12-2017.pdf

[19] Gottlieb, S. "Drug Shortages: Why they happen and what they mean" (December 2011) American Enterprise Institute. Available at: https://www.finance.senate.gov/imo/media/doc/Gottlieb%20Testimony1.pdf

[20] Ginsburg, P. Lieberman, S. "Medicare payment for physician-administered (Part B) drugs: The interim final rule and a better way forward" (February 2021) USC-Brookings Schaeffer On Health Policy. Accessible at: https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2021/02/10/medicare-payment-for-physician-administered-part-b-drugs/

[21] Avalere Health. "2021 State Drug Pricing Legislation: The Evolution Beyond Transparency", Avalere (April 2, 2021), Available at:https://avalere.com/insights/2021-state-drug-pricing-legislation-the-evolution-beyond-transparency

[22] Including but not limited to: Laws of Minnesota 2023, Chapter 57, Article 2, Section 23; IL HB 3957, 103rd General Assembly, 2023,

[23] Legislative Analysis and Public Policy Association, "Drug Take-Back and Disposal Programs: Summary of State Laws", (February 2022) Available at: http://legislativeanalysis.org/wp-content/uploads/2022/02/Drug-Take-back-and-Disposal-Programs-Summary-of-State-Laws-FINAL.pdf

Inspections and warning letters: Facility inspections are a critical element of FDA's regulation of drug products. Inspections that lead to warning letters, not tied to drug safety or efficacy issues, can cause prolonged manufacturing shutdowns and delays when FDA resources are not dedicated to timely evaluate facility readiness. Recent analyst coverage, trends in FDA Warning Letters, and subsequent manufacturer decisions make clear that this continues to be a contributing factor.[24]

Insufficient supply of available raw materials and components: Raw material used in the manufacturing process, such as active pharmaceutical ingredients (API), glass vials, stoppers, and IV bags may be in short supply.

Ability to obtain DEA quota for API: Manufacturers may experience difficulty obtaining and maintaining an adequate supply of the API due to quota scrutiny by the Drug Enforcement Administration (DEA). The DEA handles quota requests on a case-by-case basis but this process can be slow.

Challenges associated with the manufacturing and release of products: Manufacturers face challenges, including but not limited to:

- Limited number of qualified production lines and/or facilities;
- Increasing costs of API and raw materials;
- Complexity of manufacturing; and
- Guidances, standards and monograph changes.

In addition, products approved with short shelf life (18-24 months) may limit the financial feasibility of producing additional safety stock.

Natural Disasters. Studies have found that some shortages are the result of unforeseen natural disasters that can cause manufacturing facilities to shut down. When this happens, there may be a temporary shortage of certain products, depending on the ability of other manufacturers to ramp up production to fill any shortfall.[25]

Drug Supply Chain Security Act: The looming November 27 Drug Supply Chain Security Act[26] deadline for interoperable exchange, verification, and tracing for all drug products could cause a spike in drug shortages. It is unknown how many generic manufacturers are prepared for this, but some manufacturers will likely not be fully ready for this deadline. And those manufacturers that are fully ready will be asked to supply additional volumes to cover shortfalls when supply may already be constrained.

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[24] Nephron Healthcare Investment Research. (June 15, 2023) "May Generic Price Auditor: Pockets of Inflation Drive Y/Y Deflation Lower at -6.8%" Pharma Supply Chain & Digital Health.
[25] Palmer, E. "Shortages of drugs and saline reported as Puerto Rico hurricane damage lingers" (October 12, 2017). Fierce Pharma. Available at: https://www.fiercepharma.com/pharma/shortages-drugs-and-saline-reported-as-puerto-rico-hurricane-damage-lingers
[26] Pub. L. 113–54

IV: Solutions to Improve Generic Sustainability & Reduce Drug Shortages

Just as multiple factors contribute to drug shortages, addressing this challenge requires a multi-faceted set of solutions. These include:

Ensuring a sustainable generic drug market

- **Update the generic drug Medicaid Inflation Penalty to align with the inflation penalty included in the Inflation Reduction Act (IRA).** The IRA applies the inflation penalty to single-source generics and gives the Department of Health and Human Services authority to exempt products in or at risk of shortage.[27] Applying this to the Medicaid inflation penalty would more appropriately address the unique features of the generic drug market.
- **Expand the drug shortage exemption of the IRA to exempt drugs that are transitioning out of shortage.**
- **Speed new generics to market through legislation (e.g., Q1/Q2) that enables generic manufacturers to receive key quantitative and qualitative formulation information from FDA.**
- **Ensure that Medicare drug plans cover and encourage the use of new generics and biosimilars.**
- **Amend the 340B program to exempt low-cost generics or adjust the ceiling price required of generics (e.g., instead of AMP minus URA, make the ceiling price equivalent to AMP)**

Increasing reserves of critical medicines

- **Review the FDA Essential Medicines List and consider updating and adapting it to support a drug shortage stockpile and reserve capacity program.**
- **Create reserve capacity supply modeled after the Strategic National Stockpile (SNS) program.** Ensuring ample supply to the most critical medicines will improve patient access to essential medicines during national disasters, pandemics, or significant drug shortages.
- **Create incentives for hospitals to purchase reserve supply at predictable, fixed-price multi-year contracts.** GPOs, wholesaler-distributors, and providers must share in the responsibility of preventing shortages by altering their purchasing behavior to reduce the likelihood of shortages. Incentives for GPOs, wholesaler-distributors and providers to make long-term purchasing commitments using predictable, fixed-price and fixed-term contracts, will help both purchasers and sellers sustain a pipeline of continuous inventory, without forcing race-to-the-bottom prices.

Improving generic manufacturing capacity

- **Provide targeted federal grants or contracts, or other direct assistance, to generic manufacturers with excess manufacturing capacity** to upgrade and update existing manufacturing lines; build new lines in existing facilities; or build new facilities to provide additional capacity. These investments should focus on already existing excess capacity, rather than new generic manufacturing, for generic medicines most vulnerable

[27] Pub. L. 117–169

to shortages.

Reducing regulatory and manufacturing challenges

- **Empower the FDA Drug Shortage Staff** to engage with CDER and ORA staff during the inspection planning process prior to the actual inspection to work with manufacturers and build on their track record of successfully mitigating shortages.
- **FDA should improve transparency regarding the status of applications and inspections to allow generic manufacturers to properly project and plan for manufacturing schedules of drugs in shortage.**
- **FDA should enhance the expedited resolution pathway for drugs in shortage by utilizing alternative, inspection tools (e.g., Remote Regulatory Assessments) if inspection status is the only remaining barrier to approval.**
- **Ensure that guidances do not contain policies that will contribute to drug shortages or prevent/discourage submission of applications for products in shortage.** FDA should consider the impact of draft and final guidances on products susceptible to shortages. Several draft and final guidances impede timely access to generic medicines, and specifically drugs in shortage.[28] FDA should review guidances that may contribute to shortages or that may delay the submission of applications that could resolve drug shortage situations.
- **Ensure that new and updated product specific guidances do not block the expedited approval of needed generics.** The approval standards for generic products are often an evolving process. Such standards may change multiple times during the development process, resulting in significant delays. Instead of delaying the approval of a generic application (for which FDA has already approved other generics), FDA should permit generic sponsors to comply with new or updated approval standards changes as a post-marketing commitment (as currently marketed generic products would do). Particularly in the case of products in shortage, FDA should apply these changes flexibly depending on public health impact.
- **Review shelf-life extension programs for products in critical supply or shortage.**
- **Exercise and communicate appropriate enforcement discretion on an as-needed basis for products at risk of drug shortage in the implementation of serialization requirements under the Drug Supply Chain Security Act.** This will allow products to continue to enter the supply chain and avoid shortages.
- **Streamline regulatory processes to expedite facility reviews.** For example, FDA should expand cooperation with the manufacturer to review the facility and tech transfer processes.
- **Direct DEA to more quickly respond to manufacturer requests for quota adjustments.**

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[28] Such guidances include: (1) *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence),* Docket FDA-2017-D-3101, November 3, 2017; (2) *Appendix A of the Food and Drug Administration's July 2018 Guidance Entitled "Abbreviated New Drug Application Submissions-Amendments To Abbreviated New Drug Applications Under Generic Drug User Fee Amendments"* (FDA-2022-N-1633), August 15, 2022; (3) *Elemental Impurities in Drug Products*, Docket FDA-2016-D-1692, August 30, 2016; and (4) *Handling and Retention of BA and BE Testing Samples*, Docket No. 2002D-O350, May 26, 2004.

V. Conclusion

Policymakers, healthcare providers, and manufacturers each play an important role in reducing drug shortages, and all should be cautious of short-term patches that create long-term barriers to robust generic competition and patient access to low-cost medicines. AAM commends Congress, the White House, HHS, and the FDA for their interest in addressing the longstanding concerns surrounding drug shortages. AAM urges the government to consider the unique aspects that differentiate the brand and generic business models and adopt policies that will reduce drug shortages by improving the long-term sustainability of the generic drug market for patient access and savings.