Drug Shortages:
Landscape Assessment of Policy Proposals to Prevent and Mitigate Drug Shortages

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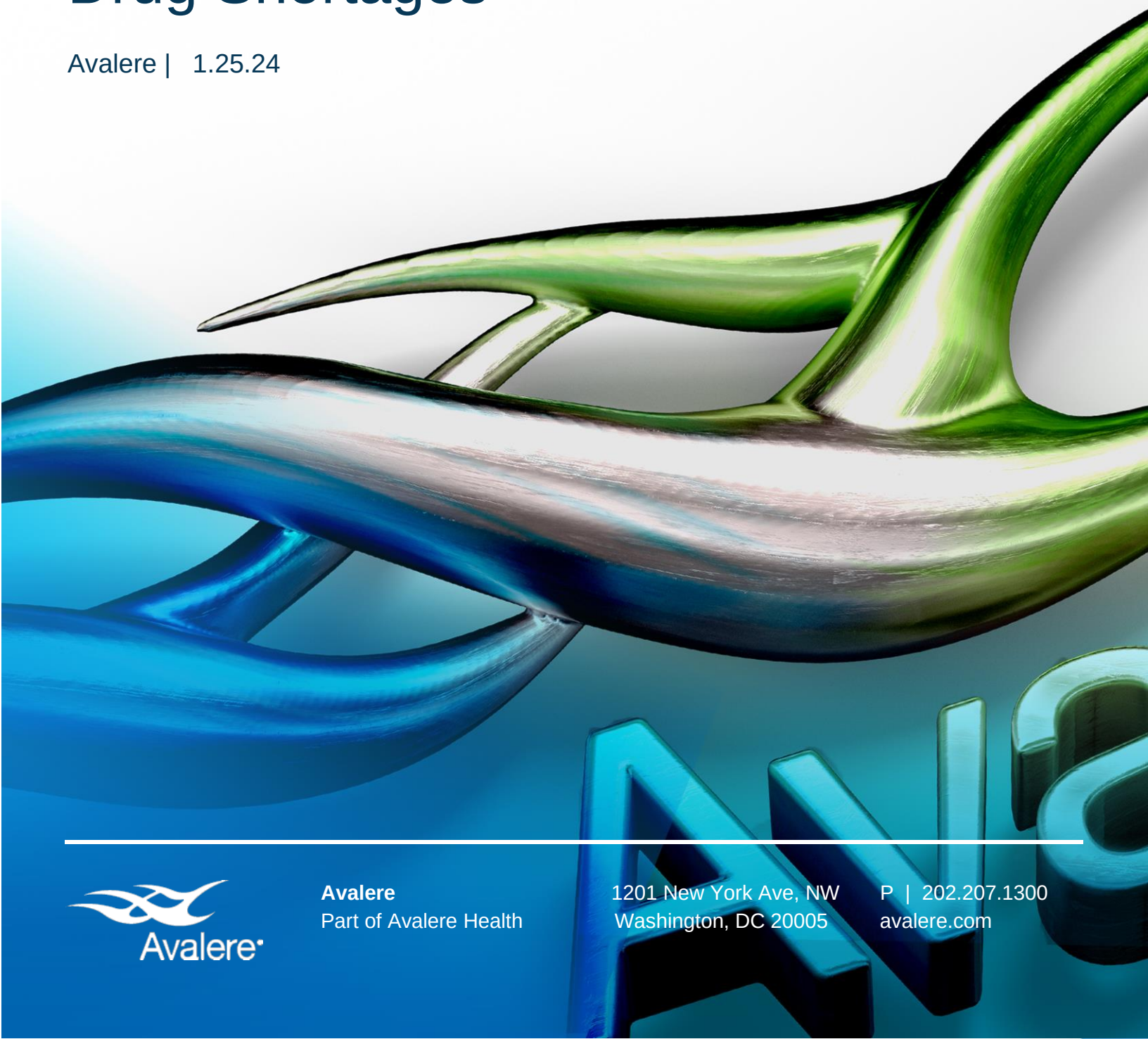

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Background

For the past two decades, prescription drug shortages have been a persistent issue in the United States for a broad range of products including chemotherapies, antibiotics, and anesthetics. The US Food and Drug Administration (FDA) considers a drug in shortage to occur when the total commercially available supply of a medical product is unable to meet current demand.[1] According to the FDA, drug shortages peaked in 2011 with more than 250 new drugs in shortage. Although the FDA worked with manufacturers successfully to avoid 222 shortages in 2022, shortages have persisted, and 49 new drugs in shortage were reported that year.[2] The FDA reports that there are currently 138 drugs in shortage, although the FDA's count may differ from those of other sources based on how they were tabulated (e.g., whether medicines on allocation or stockout are counted). Drug shortages can span across the full prescription drug market, including brand drugs, generics, new products, and established products. However, some products are more susceptible to shortages than others. For example, older, commoditized, and generic drugs, along with sterile injectable formulations with complex manufacturing processes, are highly vulnerable to shortages.[3] In an FDA study of drugs that went into shortage, 67% were drugs with a generic equivalent and 63% were sterile injectables.[4] Similarly, a recent IQVIA report notes that 84% of the drugs in shortage in the past 6 years were generics and 67% were injectables.[5] There is broad agreement that the following combination of root causes contribute to drug shortages:

Manufacturing: Some drug shortages are driven by the complexity of manufacturing processes. Manufacturers may also face constraints such as limited resources, labor shortages, inadequate production capabilities, and outdated manufacturing facilities that could lead to production delays. In an FDA study, 62% of drugs went into shortage because of manufacturing or quality disruptions.[6] Quality issues can include product-specific issues such as sterility problems, and facility-level issues in which production lines fail or experience contamination.

Although some drugs may go into shortage because of issues maintaining supply lines, others go into shortage because of demand surges. Spikes in demand may result from disaster-related or non-disaster-related factors, and shortages result if manufacturing cannot be accelerated to meet demand. For example, in the winter of 2022, demand for oseltamivir was higher than expected due to an influenza outbreak, resulting in a shortage.[7]

Additionally, increasing costs of active pharmaceutical ingredients (APIs) and raw materials, due in part to inflation, may further disincentivize manufacturing of key materials for generic drugs.

[1] FDA. "Drug Shortages: Root Causes and Potential Solutions." (accessed November 9, 2023).
[2] FDA. "Tenth Annual Report on Drug Shortages for Calendar Year 2022." (accessed November 9, 2023).
[3] Office of the Assistant Secretary for Planning and Evaluation. 2011. "Economic Analysis of the Causes of Drug Shortage". (accessed November 9, 2023).
[4] US Food and Drug Administration. "Drug Shortages: Root Causes and Potential Solutions."(accessed November 9, 2023).
[5] IQVIA. "Drug Shortages in the U.S. 2023" (accessed December 4, 2023).
[6] US Food and Drug Administration. "Drug Shortages: Root Causes and Potential Solutions." (accessed November 9, 2023).
[7] University of Minnesota. "Half of US states had antiviral shortages in 2022-23 flu season." (accessed December 19, 2023).

Lengthening Supply Chains: Manufacturers require specific APIs and raw materials to manufacture medicines. A large proportion of these materials come from, and many finished dosage form products are manufactured, outside of the United States, which exposes the supply chain to geopolitical risk. The lengthening of the supply chain also reduces upstream visibility and increases the risk of delays and disruptions.[8]

Regulatory Activity: Regulatory challenges can lead to delayed drug approvals and creation of shortages. In the interest of consumer safety, manufacturers must obtain approvals and maintain current Good Manufacturing Practice (cGMP) compliance with the FDA. If manufacturing and quality requirements are not met, product approvals may be delayed by the FDA, or existing products may become unavailable in the marketplace. The intensity and frequency of FDA inspections may vary based on product-specific characteristics along with sites of production (e.g., overseas vs. domestic inspections).[9]

Economic Incentives: Market and economic factors play a significant role in drug shortages. Market conditions can heavily impact the production of prescription drugs, and there is often fluctuation in investment, capital, and competitive dynamics that determine how manufacturers allocate resources. A 2016 Government Accountability Office (GAO) report noted that low profit margins for generic sterile injectable drugs may limit economic incentives and could cause manufacturers to exit the market.[10] Generic price erosion resulted in a $7 billion reduction in revenue for manufacturers between 2014 and 2019, even as the share of prescriptions filled by generics reached 90% in 2019.[11] [12] Because of this trend, manufacturers are increasingly exiting markets of older, commoditized drugs. Manufacturers of older and generic drugs may shift production based on changes in competition and increased market uncertainty, particularly when generic prices have dropped below economically viable levels. These dynamics can contribute to cyclical shortages; the average drug shortage lasts 1.5 years, but some critical drug products have been in shortage for periods spanning a decade or more.[13]

[8] USP. "Geographic concentration of pharmaceutical manufacturing: USP Medicine Supply Map analysis." (accessed December 19, 2023).
[9] GAO. "FDA Should Take Additional Steps to Improve Its Foreign Inspection Program." (accessed December 19, 2023).
[10] GAO. "Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge." (accessed November 9, 2023).
[11] IQVIA. "Medicine Spending and Affordability in the United States." (accessed December 19, 2023).
[12] AAM. "Roadmaps for Ensuring Patient Access to Generic and Biosimilar Medicines: Securing Sustainable Markets." (accessed November 9, 2023).
[13] US Senate Committee on Homeland Security & Governmental Affairs. "Short Supply: The Health and National Security Risks of Drug Shortages." (accessed November 9, 2023).

The Role of Key Supply Chain Stakeholders and the Impact of Drug Shortages

Shortages impact all levels of the prescription drug supply chain, with negative consequences for a broad range of stakeholders including patients, providers and healthcare facilities, manufacturers, distributors, group purchasing organizations (GPO), and payers.

Patients

Drug shortages acutely impact patients through reduced access to care and/or increased prices.[14] As a result of shortages, patients have faced cost increases and higher rates of medication errors, adverse events, and mortality.[15] A survey conducted by the Institute for Safe Medication Practices (ISMP) found that drug shortages have led to unsafe and compromised care for patients, potentially harmful errors due to the difficulty of obtaining recommended drugs, and delays in treatment.[16] The American Cancer Society Action Network (ACS CAN) conducted a survey of cancer patients and survivors and found that 10% of respondents who had been in active treatment in the past 12 months faced drug shortages during that period. Of patients impacted by shortages, 45% reported a delayed or missed treatment. [17] Pediatric patients face amplified risk during drug shortages because they are administered less effective treatment alternatives and face higher risk of toxicity. [18] Drug shortages are also associated with a higher risk of relapse for children with cancer.[19]

Providers and Healthcare Facilities

A broad range of providers, including hospitals, health systems, physician offices, and pharmacies, act as purchasers of drugs. Individual providers (i.e., physicians and pharmacists) that administer or dispense drugs may have a limited role in product purchasing decisions made by the health system or pharmacy they are affiliated with. Providers face differing impacts from drug shortages based on their buying power, purchasing authority, and the types of products typically utilized.

During drug shortages, providers in all settings must pursue temporary solutions for patients who cannot receive a clinically appropriate drug. The annual labor cost to US hospitals stemming from these activities is estimated at approximately $359 million.[20] A comment letter from the American Hospital Association indicates that drug shortages heighten stress on scarce hospital resources.[21] A 2019 survey found that, on average, hospitals in the United States dedicate more than 8.6 million hours of labor annually to manage drug shortages.[22] Activities

[14] ASPE. "Impact of Drug Shortages on Consumer Costs." May 2023. (accessed November 9, 2023).
[15] Phuong, et al. "The impacts of medication shortages on patient outcomes: A scoping review." PLoS One. 2019 May 3;14(5):e0215837. https://doi.org/10.1371/journal.pone.0215837
[16] ISMP. ISMP survey on drug shortages for hospital pharmacy directors or their designees only. ISMP Medication Safety Alert! 2017;22(17):5-6.
[17] ACS CAN. "Survivor Views: Drug Shortages, Telehealth, & Biomarker Testing." (accessed November 9, 2023).
[18] Butterfield Lindsay. Cash, Jared. Pham, Kathy. "Drug Shortages and Implications for Pediatric Patients." *Journal of Pediatric Pharmacology and Therapeutics* 20, 2 (Spring 2015): 149-152. https://doi.org/10.5863/1551-6776-20.2.149.
[19] Butterfield Lindsay. Cash, Jared. Pham, Kathy. "Drug Shortages and Implications for Pediatric Patients." *Journal of Pediatric Pharmacology and Therapeutics* 20, 2 (Spring 2015): 149-152. https://doi.org/10.5863/1551-6776-20.2.149.
[20] Vizient. "Drug shortages and labor costs." (accessed November 9, 2023).
[21] AHA. Hughes, Stacey. "AHA Responds to Request for Information on Drug Shortages." (accessed November 9, 2023).
[22] Vizient. "Drug shortages and labor costs." (accessed November 9, 2023).

required to manage shortages include time spent on redistributing workloads and accessing therapies through nontraditional distribution channels. Children's hospitals spend more time than other hospital types managing shortages, often needing to compound replacement products into safe pediatric dosage forms.[23] Drug shortages may also lead to hoarding of products in shortage, which can exacerbate shortages and lead to a drug being put on allocation.[24]

Drug Manufacturers

Generic and brand manufacturers are impacted by supply chain disruptions or delays that can compel them to divert resources to address shortages.

Generic Drug Manufacturers

According to the FDA, of the 163 drugs that went into shortage between 2013 and 2017, 67% were generic drugs.[25] Generic drug manufacturers are more likely than brand drug manufacturers to experience shortages because of market consolidation, increased competition, lower prices, and quality-related supply disruptions, which can result in market exit. Sterile injectables are even more susceptible to shortages because of complex manufacturing, limited capacity lines, and high overall production costs, which result in a smaller manufacturing supply base. Shortages can lead to increases in operational costs, downward pressure on margins, and public scrutiny.

Generic manufacturers face challenges with supply chain purchasing power. Currently, three hospital group purchasing organizations control approximately 90% of all generic medicine purchased for hospitals and clinics, which leads to greater competition among manufacturers to attract these buyers.[26] In addition, continuous downward reimbursement trends on generics results in the hospital group purchasing organizations seeking lower prices for their customers from generic drug manufacturers. As prices fall, generic manufacturers that cannot cover production costs may need to exit the market for specific molecules.

Brand Drug Manufacturers

Brand drug manufacturers face unique challenges because brand drugs typically only have a single manufacturer and shortages may occur because of heightened demand for a specific product with limited options for alternative acquisition pathways or increased production. Brand drug shortages occur for a range of reasons, including disruptions in the supply of raw materials (e.g., ethanol during the COVID-19 pandemic), failure of manufacturing facilities to meet regulatory standards, or unanticipated demand surges. These shortages impact manufacturers' financial performance and outlook, but most negative impacts accrue to patients who may not have access to a needed treatment.

[23] Children's Hospital Association and Vizient. "Pediatric Drug Shortage Trends and Best Practices for Mitigation Strategies." (accessed November 9, 2023).
[24] Hantel, Andrew et al. "Prevalence and Severity of Rationing During Drug Shortages: A National Survey of Health System Pharmacists." *JAMA Intern Med*, 179, no 5 (March 2019): 710-711. https://doi.org/10.1001/jamainternmed.2018.8251.
[25] FDA. "Drug Shortages: Root Causes and Potential Solutions." (accessed November 9, 2023).
[26] AAM. "Drug Shortages: Causes & Solutions." (accessed December 6, 2023).

Distributors and Group Purchasing Organizations

Distributors and hospital GPOs play unique roles in the prescription drug supply chain and face different burdens during drug shortages. Distributors often have critical information that can help mitigate or address a shortage, and thus are relied upon by others in the supply chain. Hospital GPOs, like distributors, have visibility into provider demand but also play a role in making sourcing decisions for contracted hospitals. Based on level of visibility, distributors can make decisions about product allocation during drug shortages, hold different levels of inventory based on product risk, and search for alternate sources of product supply. However, supply disruption notifications from manufacturers and regulators are not always timely and can lead to shortages, especially when lacking viable alternative supply channels.

Payers

Drug shortages can require payers to modify their coverage provisions. Pharmacy benefit managers (PBMs) may also play a role in patient access during drug shortages, and continued vertical integration among payers, PBMs, and specialty pharmacies may make it difficult for drug manufacturers to negotiate with PBMs for formulary placement given those PBMs' consolidated market power.[27] Vertical integration may put downward pressure on reimbursement for medicines, and payers may have to cover non-preferred products during shortages and create ways for patients to access their prescriptions through non-traditional means in response to shortages (e.g., medical exemptions). If patients are unable to obtain a clinically preferred product in a timely manner, payers may also face cost-of-care implications.

[27] AHA. "AHA Responds to Request for Information on Drug Shortages." (accessed December 7, 2023).

Overview of Proposed Policy Solutions

In recent years, policymakers and other stakeholders have proposed various policy options to address a range of upstream and downstream factors that contribute to drug shortages. Many of these proposals would require additional funding and resources, and funding requirements vary significantly among proposals. Policy proposals released during the past decade fall into the six categories outlined below.

Incentives for Infrastructure Investment

Multiple proposals have been advanced to incentivize infrastructure investment to build additional capacity and achieve quality maturity. For example, the Brookings Institution and the Association for Accessible Medicines (AAM) have both proposed providing targeted loans and grants to assist small and generic manufacturers, respectively, in upgrading their manufacturer infrastructure.[28,29] Proposals focus on public-private partnerships to incentivize advanced domestic manufacturing technologies for critical generic drugs.[30] Other proposals focus on incentivizing manufacturers to increase their production capacity for essential medicines by offering subsidies or tax incentives.[31]

In its review of domestic supply chains, the Biden administration has also noted that overseas generic API facilities have left the United States at risk for shortages of essential medicines. In response, a White House report recommended that the Department of Health and Human Services (HHS), the Department of Defense (DOD), and other agencies increase funding for advanced manufacturing technologies to foster continuous manufacturing and the manufacturing of APIs.[32] In November 2023, President Biden announced an expansion of HHS authority under the Defense Production Act to allow for investment in domestic manufacturing of essential medicines and critical inputs.[33]

Supply Chain Visibility and Federally Managed Risk and Vulnerability Assessments

Many proposals to address drug shortages have focused on supply chain visibility and broader transparency, often suggesting that the FDA or DOD conduct periodic analyses using the existing drug shortages database to proactively identify risk factors for potential drug shortages. Some proposals suggest that supply chain risk assessments be jointly conducted across HHS, DOD, and the Department of Homeland Security (DHS).[34] [35] [36] [37] Multiple legislative proposals focus transparency efforts on expanding existing API reporting requirements, mapping the

[28] Association for Accessible Medicines. "Drug Shortages: Causes & Solutions." (accessed November 9, 2023).
[29] The Brookings Institution. "Federal Policies to Address Persistent Generic Drug Shortages." (accessed November 9, 2023).
[30] US Senate Committee on Homeland Security & Governmental Affairs. "Short Supply: The Health and National Security Risks of Drug Shortages." (accessed November 9, 2023).
[31] Advanced Regenerative Manufacturing Institute. "Essential Medicines Supply Chain and Manufacturing Resilience Assessment." (accessed December 19, 2023).
[32] The White House. "Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth." (accessed December 6, 2023).
[33] White House. "Fact Sheet: President Biden Announces New Actions to Strengthen America's Supply Chains, Lower Costs for Families, and Secure Key Sectors." Available here.
[34] GAO. "Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability." (accessed November 9, 2023).
[35] US Senate Committee on Homeland Security & Governmental Affairs. "Short Supply: The Health and National Security Risks of Drug Shortages." (accessed November 9, 2023).
[36] US Congress, Senate, *Pharmaceutical Supply Chain Risk Assessment Act of 2023*, S. 1961, 118th Congress. Introduced June 13, 2023.
[37] US Congress, Senate, *MAPS Act*, S. 2364, 118th Congress, Introduced July 18, 2023.

pharmaceutical supply chain, and expanding existing drug shortage notification requirements from manufacturers.[38, 39] To mitigate risk more broadly, some recommendations propose streamlining reviews and regulatory processes to enhance the expedited resolution pathway for drugs in shortage.[40]

Increased FDA Regulatory Flexibility on Compounding and Product Shelf Life

While some proposals focus on drug shortage prevention, others focus more on drug shortage mitigation. One potential solution to mitigating the impact of drug shortages is to increase FDA regulatory flexibility to allow, under certain conditions, a compounder (i.e., a licensed pharmacist or physician) not registered with the FDA to compound drugs under certain conditions (e.g., prescriber certifies that they made reasonable attempts but failed to obtain a related drug with the same active ingredient).[41] Under this proposal, compounders would be allowed to combine, mix, or alter ingredients to create a medication tailored for the needs of an individual patient in limited quantities.

Other proposals focused on extending the shelf life of existing products would authorize the FDA to require manufacturers of life-saving drugs to submit expiration and stability testing studies and make labeling changes based on those studies.[42] These policies would aim to reduce replacement costs for stockpiled products.[43]

Rating Systems to Incentivize Quality Management Maturity and Ensure Adequate Supply

Lack of quality management maturity (QMM) has been cited as a driver of drug shortages. The FDA defines QMM practices as those that support "a more reliable drug supply chain by reducing the occurrence of quality-related failures."[44] Currently, the FDA uses a binary system in which a manufacturing facility either passes or fails inspection. The QMM rating system under consideration by the FDA would assess multiple areas, including leadership (e.g., resource management), business continuity (i.e., supply planning and demand forecasting), technical excellence, advanced pharmaceutical quality system, and employee empowerment and engagement.[45] [46] [47] In September 2023, the FDA released a request for information to solicit comments from stakeholders on developing this QMM program for manufacturers.[48] Multiple stakeholder groups have expressed public support of, or opposition to, QMM. Groups in support of QMM have recommended that the FDA finalize and make public all QMM metrics, noting that QMM will promote greater transparency and help address supply chain issues.[49] [50] Groups in

[38] US Congress, Senate, *MAPS Act*, S. 2364, 118th Congress, Introduced July 18, 2023.
[39] Energy and Commerce. "Health Subcommittee Legislative Hearing: 'Legislative Proposals to Prevent and Respond to Generic Drug Shortages'." (accessed November 9, 2023).
[40] Association for Accessible Medicines. "Drug Shortages: Causes & Solutions." (accessed November 9, 2023).
[41] US Congress, House, *Patient Access to Urgent-Use Pharmacy Compounding Act of 2023*, H.R. 167, 118th Congress. Introduced January 9, 2023.
[42] US Congress, House, *Ensuring Access to Lifesaving Drugs Act of 2023*, H.R. 3783, 118th Congress. Introduced June 5, 2023.
[43] FDA. "Expiration Dating Extension." (accessed December 19, 2023).
[44] FDA. "CDER Quality Management Maturity." (accessed November 14, 2023).
[45] FDA. "Quality Management Maturity (QMM)" (accessed December 6, 2023).
[46] Duke Margolis Center for Health Policy. "Advancing Federal Coordination to Address Drug Shortages." (accessed December 7, 2023).
[47] Vizient. "Re: Food and Drug Administration Quality Metrics Reporting Program; Establishment of a Public Docket; Request for Comments (Docket No. FDA-20022-N-0075)." (accessed December 7, 2023).
[48] FDA. "Quality Management Maturity Program for Drug Manufacturing Establishments; Establishment of a Public Docket; Request for Comments." (accessed December 7, 2023).
[49] ASHP. "Re: ASHP Response to Energy and Commerce Committee Pharmaceutical Drug Shortage Discussion Draft." (accessed December 7, 2023).
[50] Duke Margolis Center for Health Policy. "Advancing Federal Coordination to Address Drug Shortages." (accessed December 7, 2023).

opposition have cautioned that the rating system may be costly and create unintended consequences that could increase or exacerbate drug shortages. [51,52]

To encourage QMM improvements for manufacturers and ensure adequate supply, a different proposal recommends developing a hospital rating system to ensure that major drug purchasers are incentivized to use factors other than price to make purchasing decisions.[53] The hospital rating system has been framed as complementary to the QMM, with supporters proposing that the FDA publicly share inspection facility ratings, and that hospitals that select manufacturers with higher FDA quality scores, or employ other shortage-mitigating tactics, are reimbursed at higher rates than other hospitals. This policy aims to incentivize manufacturers to pursue better quality maturity while also incentivizing hospitals to make better decisions related to drug purchasing.

Reimbursement Reforms

Low reimbursement rates and narrow margins are often cited as challenges for generic manufacturers and can serve as a disincentive for these manufacturers to continue production. Prices for a brand drug product typically undergo a modest decline following market entry of that drug's first generic competitor, and steeper declines when multiple generics enter the market. Stiff competition among generic products may drive prices down until manufacturers begin to exit the market. Generic injectable drugs also generate lower profit margins because of small market sizes and high costs associated with specialized manufacturing processes. Therefore, some proposals focus on reimbursement reform to increase payments for generics in shortage or at risk of shortage. Under Medicaid's generic inflation penalty, manufacturers must pay rebates when drug price growth exceeds the rate of inflation. Some stakeholders contend that inflation penalties result in a market failure in which manufacturers cannot raise prices in response to market conditions, such as when raw material costs increase. In response, some proposals recommend updating the Medicaid inflation penalty to match the Inflation Reduction Act's (IRA's) inflation rebate policy that exempts single-source generics and gives HHS the authority to exempt products in or at risk of shortage.[54] This proposal could also expand the drug shortage exemption within the IRA to exempt drugs transitioning out of shortage.[55]

Government payment policies have also been subject to criticism as low-cost generics may be more susceptible to the effects of shifts in pricing because of the grouping of generic products to calculate average sales price and unit rebate amounts in Medicaid. In response to this dynamic, some proposals aim to exempt low-cost generics or adjust the ceiling price required of generics from the 340B program.[56]

In addition to reforms of existing policy, other innovative reimbursement reforms have been proposed. Some of these reforms include adjusting CMS reimbursement calculations for drugs at high risk of shortage. To ensure that investments in manufacturing are focused on at-risk drugs, the American Society of Health-System Pharmacists (ASHP) has recommended that

[51] AAM. "Re: Docket No. FDA-2022-N-1777, Pharmaceutical Science and Clinical Pharmacology Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments." (accessed December 7, 2023).
[52] Premier. "The Unintended Consequences of a Drug Quality Rating System." (accessed December 7, 2023).
[53] The Brookings Institution. "Federal Policies to Address Persistent Generic Drug Shortages." (accessed November 9, 2023).
[54] Association for Accessible Medicines. "Drug Shortages: Causes & Solutions." (accessed November 9, 2023).
[55] Energy and Commerce. "Health Subcommittee Legislative Hearing: 'Legislative Proposals to Prevent and Respond to Generic Drug Shortages'." (accessed November 9, 2023).
[56] Association for Accessible Medicines. "Drug Shortages: Causes & Solutions." (accessed November 9, 2023).

CMS provide an add-on payment for "critical generic pharmaceutical drugs" at risk of shortage if providers certify that they meet a 50% threshold of procurement (based on historical purchase volume) through long-term contracts.[57]

Drug Inventory Buffer and Stockpiling

One frequently proposed solution to drug shortages is development of drug inventory buffers and stockpiles To ensure ample supply of essential medicines, some stockpiling proposals focus on creating reserve capacity modeled after the Strategic National Stockpile program and establishing incentives for fixed-price multi-year drug purchasing contracts to secure those medicines.[58] [59] These inventories would be based on the FDA's Essential Medicines list, which generally includes medicines needed for patients in acute care medical facilities. [60] Although some proposals focus on the FDA's Essential Medicines List, there are multiple essential medicines lists that could be leveraged as part of a drug inventory buffer and stockpiling solution. For example, HHS's Administration for Strategic Preparedness and Response (ASPR) developed an essential medicines list that could be used.[61]

In the calendar year (CY) 2024 Outpatient Prospective Payment System (OPPS) proposed rule, CMS proposed funding a drug inventory buffer that would cover a hospital's costs to establish a buffer stock of essential drugs (based on the list generated by the ASPR). This policy was originally proposed as an addition to payment under the Inpatient Prospective Payment System and was intended to expand to the OPPS. The proposed payment allocations were consistent with those used in the payment adjustment for domestic National Institute for Occupational Safety and Health-approved surgical N95 respirators. CMS did not finalize the proposal in its final rule and will continue to seek feedback on this policy. However, other stakeholders continue to advocate for buffer stocks as a solution to drug shortages.

Assessment of Policy Solutions' Ability to Address Stakeholder Needs

Given the complex and often intersecting set of factors that contribute to drug shortages, individual policy proposals do not comprehensively prevent or mitigate the widespread impacts of drug shortages. Many of these proposals place administrative and/or resource requirements on drug manufacturers; however, stakeholders across the supply chain are impacted by these proposals. In this section, each policy solution is discussed to determine whether it addresses negative impacts of drug shortages on key stakeholders.

Incentives for Infrastructure Investment

Incentives for public and private investment in supply chain infrastructure would target drug and API manufacturers, but only a subset of manufacturers are likely to be eligible for such

[57] ASHP. "ASHP Response to Energy and Commerce Committee Pharmaceutical Drug Shortage Discussion Draft." (accessed November 9, 2023).
[58] The Brookings Institution. "Federal Policies to Address Persistent Generic Drug Shortages." (accessed November 9, 2023).
[59] Association for Accessible Medicines. "Drug Shortages: Causes & Solutions." (accessed November 9, 2023).
[60] FDA. "FDA Publishes List of Essential Medicines, Medical Countermeasures, Critical Inputs Required by Executive Order." (accessed November 9, 2023).
[61] Advanced Regenerative Manufacturing Institute. "Essential Medicines Supply Chain and Manufacturing Resilience Assessment." (accessed November 9, 2023).

investments. Proposals from AAM and the Brookings Institution generally focus on generic and small manufacturers, respectively.[62] [63] Manufacturers with domestic production and/or essential medicines in their portfolios may benefit, as they would likely be favored for public-private partnerships under these proposals. To the extent that these policies increase capacity for products impacted by shortages, patients and other stakeholders could benefit as well.

Due to the global nature of the supply chain, limitations on funding eligibility may limit the scope of eligible manufacturers and/or sites. According to the FDA, as of 2018, 88% of all APIs were produced outside of the United States and 63% of all drugs were finished overseas.[64] Manufacturers that have mature quality management systems may also be incentivized by increased reimbursement under proposed policies or through financially favorable procurement agreements from HHS. Investments required to incentivize advances in infrastructure will likely place financial liability on the federal government. Outside of government procurement, the public-private investment in infrastructure would be subject to the rules of economics for a commodity. It may be most cost effective for private partners to tie an investment to a long-term commercial contract.

Supply Chain Visibility and Federally Managed Risk and Vulnerability Assessments

Supply chain visibility and assessment proposals could require stakeholders like the FDA, HHS, DOD, and DHS to gather specific types of information from manufacturers and other upstream partners that may not be readily available today, creating a potential administrative burden.[65] [66] [67] [68] Additionally, many supply chain stakeholders consider vendor identities to be competitive information. Under some proposals, this type of information would be made public, which may be undesirable for manufacturers and distributors. Notification systems may also require new or expanded processes for identifying and communicating issues to relevant authorities.

Proposals that aim to increase supply chain visibility would generally require the federal government to analyze collected data to make assessments about where supply chains may be most vulnerable and prone to shortages. Stakeholders along the supply chain could gain access to risk assessments or ratings that would help them make decisions that decrease the likelihood of shortages. However, supply chain stakeholders may be hesitant to provide the federal government with competitive information and may be concerned about how such information might be used.

Increased FDA Regulatory Flexibility on Compounding and Product Shelf Life

Regulatory flexibility to expand availability of compounded drugs and increased product shelf life primarily impacts compounding pharmacies, drug manufacturers, patients, and providers. Expanding the use of compounding pharmacies would impact the physician-administered site of care, including hospital outpatient departments (HOPD) and physician offices, as the proposals require compounded products to be administered by the prescriber. Although compounding may

[62] Association for Accessible Medicines. "Drug Shortages: Causes & Solutions." (accessed November 9, 2023).
[63] The Brookings Institution. "Federal Policies to Address Persistent Generic Drug Shortages." (accessed November 9, 2023).
[64] FDA. "Drug Shortages: Root Causes and Potential Solutions." (accessed November 9, 2023).
[65] GAO. "Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability." (accessed November 9, 2023).
[66] US Senate Committee on Homeland Security & Governmental Affairs. "Short Supply: The Health and National Security Risks of Drug Shortages." (accessed November 9, 2023).
[67] US Congress, Senate, *Pharmaceutical Supply Chain Risk Assessment Act of 2023*, S. 1961, 118th Congress. Introduced June 13, 2023.
[68] US Congress, Senate, *MAPS Act*, S. 2364, 118th Congress, Introduced July 18, 2023.

increase access to certain drugs, it may also introduce the risk of medication errors and sterility issues.[69]

Product shelf-life extensions would require manufacturers to submit studies to the FDA to inform label changes related to product expiry. However, this policy would also allow manufacturers to sell short-dated or slightly expired products that would have otherwise been disposed. Stakeholders largely agree that a sustainable manufacturing base is necessary to prevent shortages in the long-term, and that the impact of these policies on shortages would likely be limited.

Rating Systems to Incentivize QMM and Ensure Adequate Supply

The FDA's QMM program includes measures that go beyond traditional current cGMP, such as shortage risk mitigation measures and company culture. Under various proposals, manufacturers with mature quality systems, including those created under the QMM program, would be rated and granted incentives for drug shortage mitigation actions. Generic manufacturers would be incentivized to invest in quality for older, commoditized products, which may not be attractive under current pricing conditions or if investments outweigh benefits. Brand manufacturers could benefit from this policy, as they are more likely than generic manufacturers to have developed advanced manufacturing and quality systems. However, manufacturer stakeholders have raised concerns about potential issues with the program including metrics that have not been validated or have little utility. In addition, manufacturer investment in infrastructure could raise production costs. Without adjustments in reimbursement and ability to raise pricing, manufacturers that invest in infrastructure may have to discontinue molecules that are no longer sustainable.

A separate but related Brookings proposal suggests a hospital rating system that would incentivize hospitals to prioritize shortage-mitigating activities through increased reimbursement.[70] Hospitals that achieve higher ratings for activities such as using multi-winner procurement practices and long-term contracts, and prioritizing factors other than price would receive additional payment under Medicare. Hospitals that mitigate the likelihood of shortages would likely see an improvement in the availability of needed drug products and would receive higher reimbursement if their actions are deemed eligible for the add-on payments under this proposal, but they may require operational changes related to purchasing and contracting. Although this rating system may incentivize certain hospitals to engage in shortage-mitigating activities, it may also exacerbate treatment inequities among patients as not all hospitals may have the means to shift purchasing to sources that would result in add-on payments.

Reimbursement Reforms

Policies including removing inflation penalties, reforming the 340B program, and altering average sales price (ASP)-based payment all aim to adjust pricing, especially for low-cost products, to a more flexible, market-based system. Reimbursement reforms would impact many stakeholders on the drug supply chain, including providers, patients, and payers, in different ways.

[69] FDA. "Compounding and the FDA: Questions and Answers." (accessed November 14, 2023).
[70] The Brookings Institution. "Federal Policies to Address Persistent Generic Drug Shortages." (accessed November 9, 2023).

Adjusting reimbursement to be market-based, consistent, or higher could improve manufacturer sustainability. For example, current reimbursement dynamics make it difficult for a manufacturer to adjust pricing if the cost of raw materials for a product increases. The manufacturer may have to choose between discontinuing the product or selling it at a loss.

Reimbursement reform would allow manufacturers to invest in shortage-mitigating activities such as manufacturing quality and supply chain diversification. Higher reimbursement may also change the decision-making process for manufacturers who would otherwise exit a product market because of low reimbursement rates. Depending on details of policy implementation, buy-and-bill stakeholders such as HOPDs, physician offices, and infusion centers, may see changes to ASP-based reimbursement.

Drug Inventory Buffer and Stockpiling

Drug inventory buffer proposals primarily target essential medicines, meaning drug inventory buffers would mainly impact manufacturers of a subset of drugs deemed essential for mitigating shortages. Although manufacturers and distributors often hold some amount of inventory, there is no standardized practice across stakeholders.[71] Buffer stocks managed by manufacturers or wholesalers/distributors raise the potential for administrative and capital burdens on entities required to hold managed inventory. Under some proposals, the buffer stock would be purchased in fixed, multiyear contracts, whereas others propose an additional payment above standard reimbursement for buffer stock.

The availability of drug inventory buffers may positively impact providers and patients, who would gain access to buffer stock to mitigate the impact of shortages. Additional stock may reduce the administrative burden that providers currently face when products are unavailable, assuming the stock could be managed in a way that does not trigger or worsen a shortage and that the buffer stock can last through the shortage. However, adding or expanding buffer stocks could also create capacity constraints based on a combination of factors including storage space, specialized storage/handling requirements, and rotation schedule to handle product expiration.

In reaction to the proposed CY 2024 OPPS drug inventory buffer proposal that was not finalized, some stakeholders raised concerns that a drug inventory buffer does not address the root cause of drug shortages and could drive short-term, demand-driven shortages of essential medicines.[72] [73] Whereas proponents of buffer stocks have proposed fixed, multiyear contracts to incentivize supply, other stakeholders have argued that building buffer stocks would increase demand without assurance of requisite increased manufacturing.

The scope of products placed in buffer inventory would have a major impact on whether these policies would help patients and providers. If the FDA Essential Medicines list is used, patients who are facing shortages for medicines not on the list, such as many oncology products, would not benefit from this policy. More expansive drug lists could address a wider range of stakeholders.

[71] ASPE. "Economic Analysis of the Causes of Drug Shortages." (accessed November 14, 2023).
[72] Duke-Margolis. "Centers for Medicare and Medicaid Services, CMS-1786-P." (accessed December 11, 2023).
[73] Brookings. "Comments on CMS hospital payment proposal for maintaining a buffer stock of critical medicines." (accessed December 11, 2023).

Many buffer stock proposals suggest that HHS pay for inventory buffer, placing financial liability on the federal government.

Conclusion

Many of these proposals acknowledge the interconnectedness across stakeholders and the need for multifaceted solutions. Although some proposals target specific stakeholders, stakeholders generally agree that some level of transparency and alignment of incentives will be essential to any solution. No single proposal provides a long-term solution, and it will likely take a combination of multiple policies to address the range of factors across stakeholders that contribute to drug shortages.

Given the complexity of factors driving drug shortages, any viable solution will likely require upstream solutions focused on prevention (e.g., investing in manufacturing, addressing the economics of generics production and payment) and downstream solutions focused on mitigation (e.g., buffer stocks, regulatory flexibility).

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