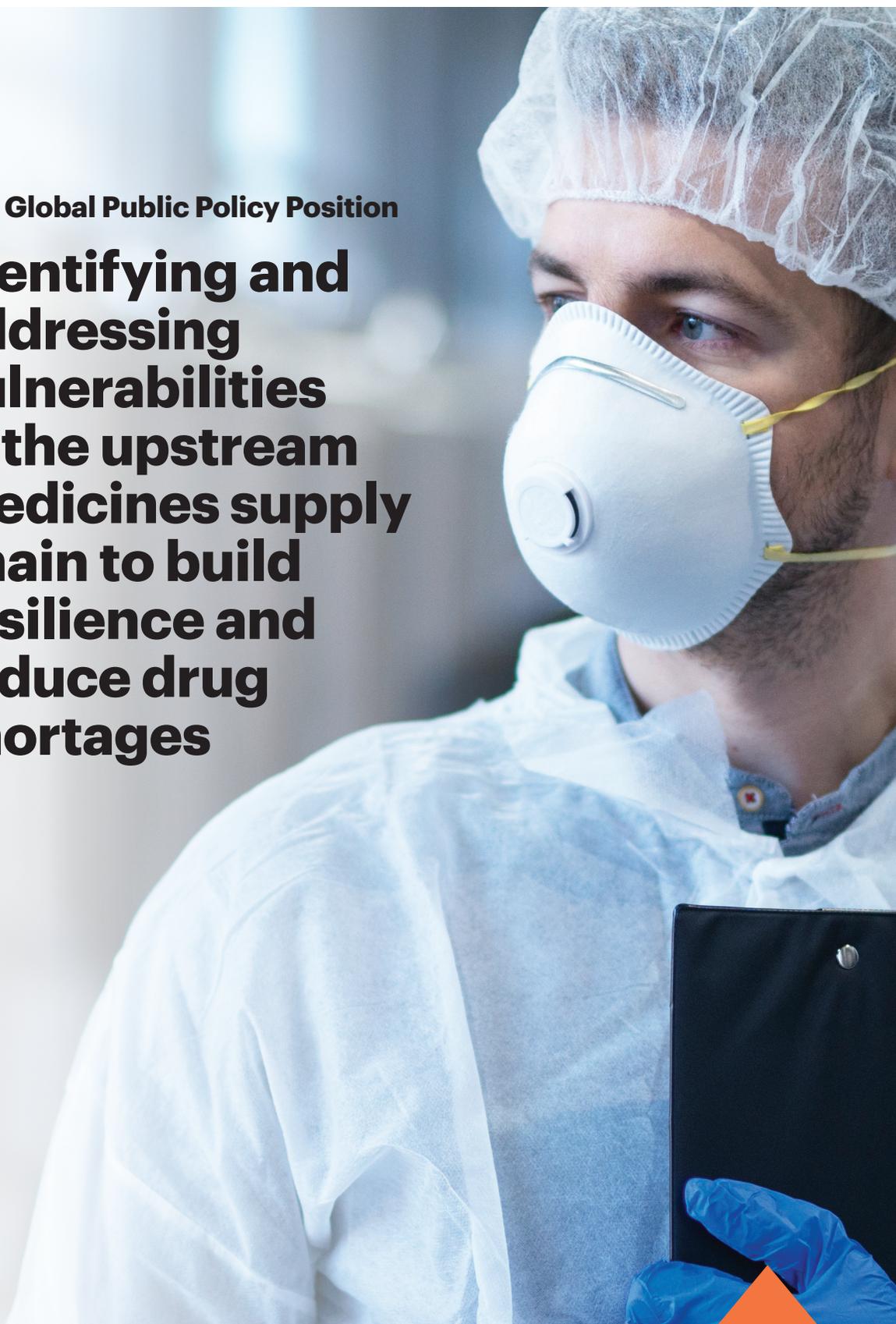


USP Global Public Policy Position

**Identifying and
addressing
vulnerabilities
in the upstream
medicines supply
chain to build
resilience and
reduce drug
shortages**

Policy position



Issue

Identifying and addressing vulnerabilities in the upstream pharmaceutical supply chain are essential to mitigating and preventing drug shortages and to ensuring patients have access to the critical and routine medical care they need. Active and ongoing drug shortages in the United States persist and have reached the highest numbers since 2014.¹ The impact upon patients has been significant, causing treatment delays or the use of less effective treatments, often with unfavorable outcomes.

Supply chain vulnerabilities manifest as shortages when supply is unable to meet demand due to demand spikes, supply disruptions, or both. Currently, there is little insight available into the upstream supply chain for medicines, which refers to the drug manufacturing process where raw chemicals, key starting materials (KSMs), active pharmaceutical ingredients (APIs), and finished dosage forms (FDFs) are produced, refined, packaged, tested, and labeled. For example, a simple factory count is an insufficient gauge of actual production volume, and the task is even harder when it comes to taking inventory of raw materials for drugs. Demand-side medicines supply chain shocks, such as unprecedented need at the point-of-care during emergencies, remain difficult to predict. Addressing upstream supply chain vulnerabilities will build resilience that is essential for mitigating drug shortages, along with additional measures that are necessary for strengthening downstream supply chain reliability.

A wide range of governmental and nongovernmental efforts aim to bolster supply chain resilience and mitigate or prevent drug shortages, however neither a single government agency nor any industry entity has a comprehensive view of the medicines supply chain. This lack of clarity contributes to a limited understanding of the risks to the U.S. medicines supply. Companies and the U.S. Government need a better understanding and mapping of their full supply chains to identify potential vulnerabilities. Additional clarity is needed to identify the root causes of many drug shortages and to effectively deploy resources to improve medicines supply chain resiliency and reduce drug shortages in the United States.

Position

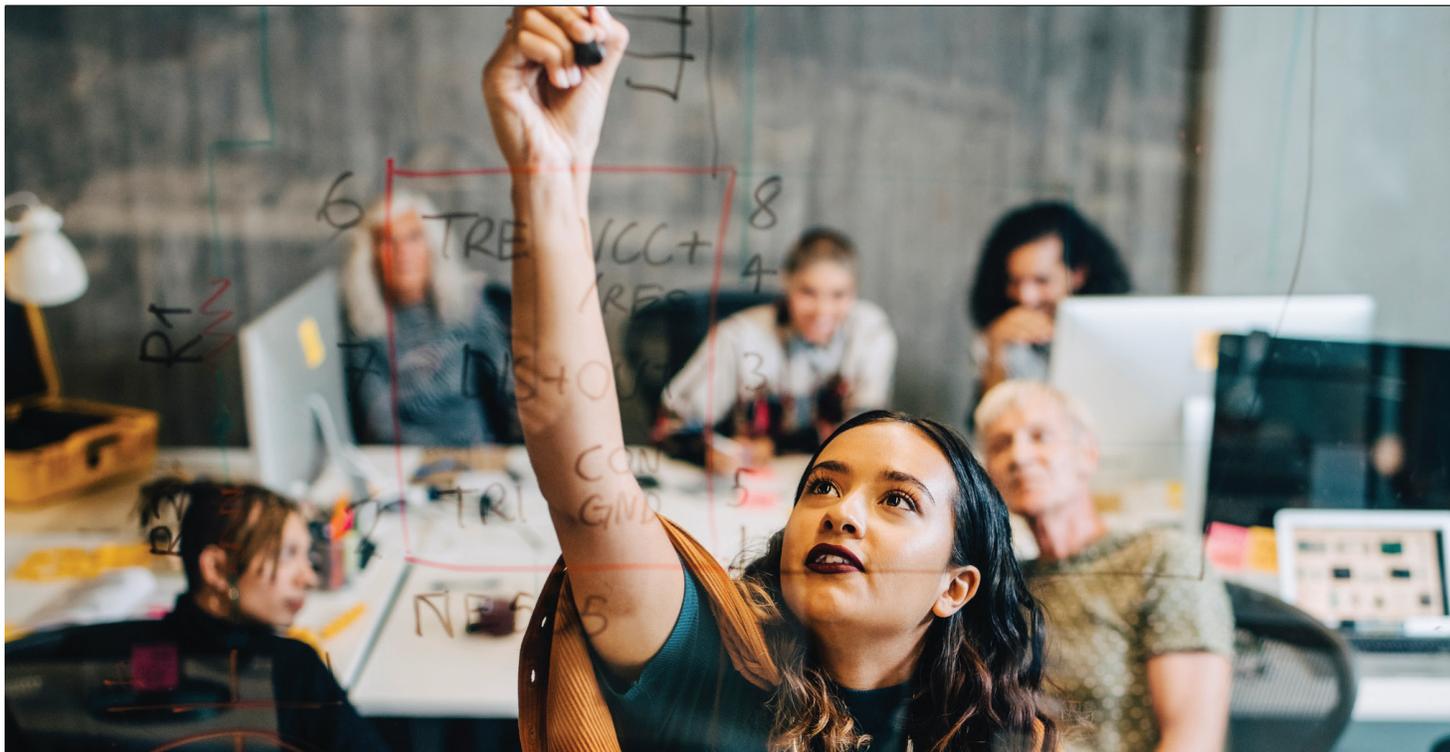
U.S. Pharmacopeia (USP) urges policymakers, regulators, and industry to take further action to identify and respond to risks and vulnerabilities in the upstream pharmaceutical supply chain and reduce medicine supply disruptions. These actions should include risk mitigation strategies, public and private investment, and policy reforms and should be informed by the risks driving drug shortages and a thorough mapping of the U.S. medicines supply chain.

1. Building early warning capabilities

USP calls for the establishment and funding of an Early Warning System and Research Coordinating Center to conduct ongoing surveillance of the pharmaceutical supply chain, provide alerts, and conduct research to fill the gaps in the mapping of the U.S. pharmaceutical supply chain. Such early warning capabilities would enable the U.S. Government and private sector pharmaceutical supply chain stakeholders to adopt a more proactive and informed approach to preventing shortages and mitigating the impact of those that do occur.

2. Establishing a vulnerable medicines list

USP recommends the establishment of a vulnerable medicines list in the United States. This list could either complement or be a component of an essential medicines list, specifically addressing supply chain vulnerabilities. Such supply chain vulnerabilities should include sole or limited number of suppliers, geographic concentration of manufacturers and API, excipient, and KSM suppliers, political and geopolitical risks, climate change susceptibilities, manufacturing complexity, price, and other factors. Creation and utilization of vulnerable medicines lists will help prioritize medicines and properly target policy interventions and finite resources to improve medicines supply chain resiliency and preserve patient access to necessary medicines.



3. Coordinating supply chain resilience and reliability efforts

USP recommends efforts to coordinate medicines supply chain resilience and reliability activities among federal agencies and non-governmental stakeholders. Coordination efforts should include the organization of multi-disciplinary efforts, defining measurable outcome metrics for implementation efforts, and strategic planning activities to maximize the utility of new programs and increase the impact of existing initiatives. Additionally, necessary authorities and sufficient funding should be allocated to lead these cross-cutting efforts to improve drug supply chain resilience and reliability.

4. Strengthening the manufacturing base for drug products

USP supports reforms to foster more security in the manufacturing base for U.S. drug products to reduce the risk of disruptions and shortages, including:

- Economic or other incentive measures that will encourage multiple suppliers for key drugs, geographic diversification of manufacturing

facilities, and manufacturing location and component supply redundancies.

- Economic incentives to encourage increased domestic manufacturing of APIs and finished drug products in the United States, prioritizing specific medicines or ingredients that are most vulnerable to supply disruptions.
- Market-based and pricing incentives that encourage utilization of excess domestic manufacturing capacity: up to 50 percent of manufacturing capacity in the United States has been identified as unutilized.²
- Financial incentives to provide manufacturers with the necessary support to build facilities supporting advanced manufacturing technologies (AMTs) on U.S. soil: manufacturers of low-margin drug products that have a higher likelihood of shortage have insufficient profitability to invest in AMTs.
- The development of tools and standards to help reduce the technical barriers to wider adoption of AMTs.

5. Promoting sustainable prices for generic medicines by valuing supply chain resiliency

The leading and root cause of most drug shortages is unsustainably low prices. Lower margins undermine initiatives to ensure supply chain resiliency by limiting the ability of manufacturers to reinvest in manufacturing facility maintenance and manufacturing updates and quality assurance and management, and causing manufacturers to seek lower-cost geographies for their sourcing and manufacturing. USP understands the necessity for a fundamental shift in the market for lower-priced drugs to guarantee more certainty and predictability of both demand and supply and to increasingly value a drug's supply chain resiliency in addition to its price. As such, USP:

- Supports initiatives to measure and rate manufacturer supply chain resiliency, sustainability, and reliability. Such initiatives are integral to ensure that manufacturer supply chain redundancy and resiliency efforts come to be valued in purchasing and contracting decisions and in regulatory frameworks and efforts.
- Encourages policymakers and public and private drug purchasers to explore:
 - The establishment and utilization of payment and purchasing models that value and incentivize supply chain resilience and reliability.
 - The authorization and use of longer-term guaranteed-volume contracts, in which prices are assured for a defined, guaranteed volume. Such long-term, guaranteed-volume contracts could include provisions to help ensure supply chain resiliency and reliability, including requirements for manufacturing redundancies and diversification of suppliers.

Discussion

Understanding Factors Driving Medicine Supply Chain Vulnerabilities

At the end of 2022, there were 295 active and ongoing drug shortages in the United States, the highest number since 2014.¹ The impact upon patients has been significant, causing treatment delays or the use of less effective treatments, often with unfavorable outcomes. Using the *Medicine Supply Map* (www.usp.org/medicinesupplymap), USP found four risk categories to be correlated with drug shortages, which singularly or in combination can increase a medication's risk for shortage:

- Geographic concentration: drugs with greater geographic concentration of API and/or finished dose manufacturing are more susceptible to shortages.
- Quality concerns: quality failures predict increased vulnerability to drug shortages.
- Low prices: drug products with low prices, common in older drug products, have a higher risk of drug shortage.
- Manufacturing complexity: drugs with higher manufacturing complexity, such as sterile injectables, are more vulnerable to shortage. Examples of manufacturing complexity include the need for dedicated facilities for certain product categories (e.g., certain antibiotics) and complex chemical synthesis of the active ingredient.

These four risk factors are often interrelated, and, in combination, can exacerbate economic challenges for manufacturers of low-margin drug products and impact business decisions about whether to continue manufacturing some drug products. For example, manufacturing complexity increases the cost to manufacture a medicine, which, when combined with low prices of certain drug products, can yield a margin that is unsustainable for a manufacturer. To improve margins, industry stakeholders have sought to reduce manufacturing costs by concentrating production in lower-cost geographies. This concentration creates a range of vulnerabilities, such as those that may arise from natural disasters or geopolitical challenges. Moreover, the

low price, low margin dynamic impedes the industry's ability to create manufacturing redundancies and may lead to underinvestment in quality management systems. Thoroughly accounting for these dynamics is important to increase resiliency of the medicines supply chain.

In determining the four primary factors contributing to drug shortages, the *Medicine Supply Map* used multiple sources of information to identify worldwide sites of pharmaceutical ingredient and finished dose medicine manufacturing. More than 40 datasets from USP, U.S. Food and Drug Administration (FDA), the Centers for Medicare & Medicaid Services, European Medicines Agency, World Health Organization and private sector sources are utilized by the *Medicine Supply Map* platform. These data are enriched with information about risk drivers such as price and ingredients and cover 92 percent of FDA-approved generic prescription drugs. The *Medicine Supply Map* includes over 250 million aggregated datapoints to evaluate indicators of drug shortage risk, including geographic concentration, manufacturing complexity, price, and quality. The model is also informed by insights on the use of USP quality standards in over 80 percent of FDA-registered finished dose and API manufacturing facilities.

Early Warning Capabilities Are Needed to Signal Threats to and Vulnerabilities Within the Medicines Supply Chain to Enable Timely Actions to Prevent or Mitigate Drug Shortages

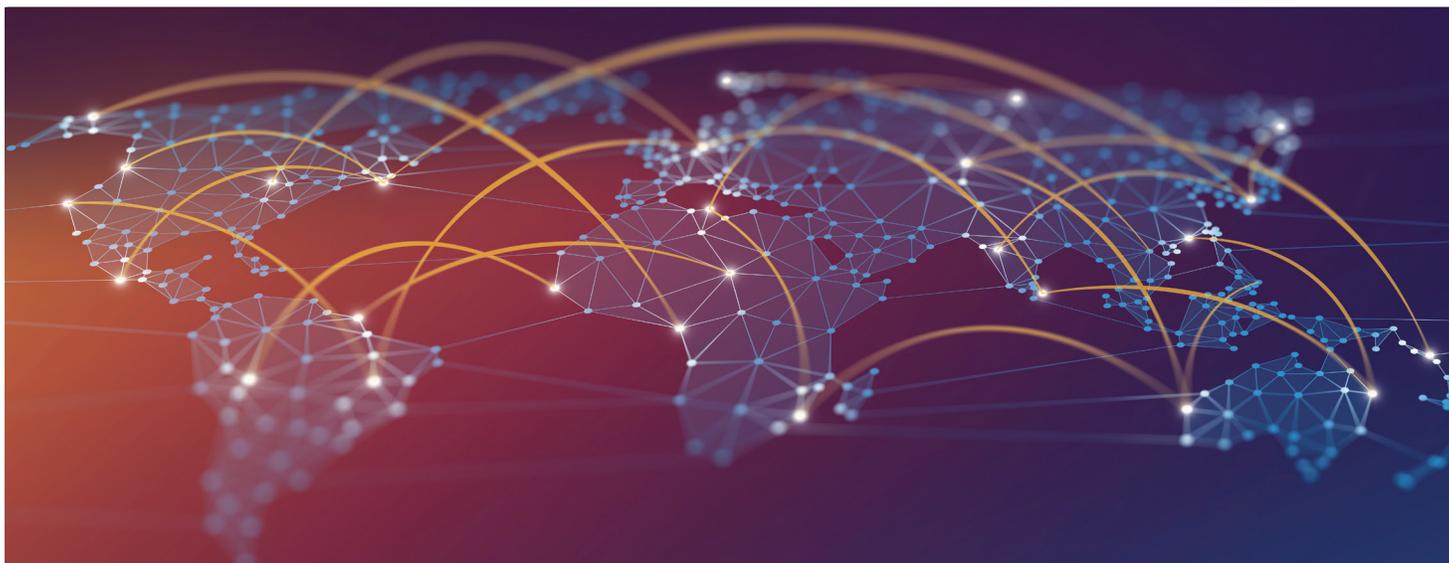
Recent and ongoing shortages in oncology drugs have made clear that while data signals exist that can help predict upstream pharmaceutical supply chain risk, the data are not integrated in a way that can generate actionable insights to prevent or mitigate drug shortages. A USP analysis of shortages of oncology drugs, using its *Medicine Supply Map*, found that carboplatin and cisplatin volume sold during the first quarter of 2023 was higher than in previous years, despite publicized shortages. This demand spike may have been caused by some hospitals' protective purchasing, possibly in response to an FDA Form 483 issued in January 2023 to a key manufacturer of cisplatin and carboplatin.

U.S. Government entities and private sector stakeholders responsible for getting medical products to patients—including manufacturers, wholesalers, and hospitals—need actionable insights that can assist in anticipating and predicting supply chain vulnerabilities and their causes before they result in a drug shortage. A need prevails to integrate already existing data—such as unit volume, supply chain structure, facility quality management maturity, company financial health, epidemiology, and other demand drivers—to prevent drug shortages or mitigate their impact. In the case of recent shortages in oncology drugs, alerts issued by an early warning system could have enabled distributors and manufacturers to act, including by communicating with hospitals and putting carboplatin and cisplatin on allocation or quota until actions could be taken to increase supply. In the case of methotrexate, its market has shown signals of supply vulnerability for more than four years, according to the *Medicine Supply Map*, since long before the most recent shortage. The methotrexate market has experienced significant price declines, market consolidation leading to a concentration of risk, and persistent shortages. These patterns could have been flagged proactively as a concern, potentially guiding preventive actions and policy responses.

Key Starting Materials and Excipients: Medicines Supply Chain Blind Spots

Data blind spots with KSMs and excipients exist. Many supply chain risks associated with the KSMs used to manufacture APIs are largely unknown because no single entity has a grasp on the extent to which the United States relies on foreign countries or facilities for these materials. To characterize the problem and to address nodes of vulnerability, the U.S. Government needs a map of where critical KSMs are made—and at what volume—to reduce those risks to the supply chain.

Excipients, the inactive ingredients in pharmaceuticals, can comprise up to 90 percent of a medicine's volume. Excipients serve important functions in a medicine, including as binders, disintegrants, coatings, preservatives, colors, and flavorings. Like APIs, some excipients are chemicals that have complex manufacturing processes, the potential for contamination, and the potential for stability issues. Some excipients are



particularly vulnerable because they are intended for a variety of commercial purposes (e.g., components of soap, ink, or paint) and may not always be rigorously controlled. Certain excipients are widely used and a breakdown in their supply chains could cause significant disruption. For example, magnesium stearate is used as an ingredient in 33,461 drug products according to the National Institutes of Health (NIH) DailyMed, including those to treat high cholesterol, high blood pressure, diabetes, and bacterial infections.³

Benefits of Identifying and Quantifying Medicines Supply Chain Risks and Vulnerabilities

Foundational mapping of the entirety of the pharmaceutical supply chain to identify vulnerabilities and threats along the links—starting with KSMs and continuing to include excipients, APIs, and finished drug products—is lacking. While certain entities may have access to particular information on where drug products, APIs, and excipients are made, enhanced efforts are needed to ensure key stakeholders along the supply chain have access to this critical information. Establishing comprehensive mapping capabilities of the medicines supply chain would further strengthen and improve the resiliency of the pharmaceutical supply chain and prevent and mitigate drug shortages, while also ensuring pharmaceutical supply chain stakeholders have access to the actionable information they need to get medical products to patients.

Identifying, characterizing, and quantifying risks and vulnerabilities throughout the medicines supply chain—from raw materials and APIs to distribution and administration of drug products to patients—can yield meaningful and timely insights, inform impactful decisions and solutions to avert shortages, and support effective responses to shortages when they do happen. For example, a comprehensive simulated model of the medical product supply chain can enable tactical and training exercises that will help our nation better prepare for the next public health emergency or geopolitical shock by identifying nodes of vulnerability, especially overreliance on one foreign country or any single geographic area. When a shortage does happen, the data and lessons learned can be used to tailor a response and minimize the impact based on an understanding of the shortage’s potential duration and magnitude, supported by insights into root cause(s), market share, and potential alternative suppliers.

A critical need exists to invest in and build early warning capabilities that signal threats to and vulnerabilities within the pharmaceutical supply chain. **USP calls for the establishment and funding of an Early Warning System (EWS) and Research Coordinating Center to conduct ongoing surveillance of the pharmaceutical supply chain, provide alerts, and conduct research to fill the gaps in the mapping of the pharmaceutical supply chain.** Such early warning capabilities would enable the U.S. Government and private sector pharmaceutical supply chain stakeholders to move to a more proactive and informed approach to preventing shortages and mitigating the impact of those



that do occur. Early warning capabilities would also help the U.S. Government increase the return on its investments in strengthening the nation’s medicine supply by targeting investments and resources to the particular vulnerabilities of specific medicines.

Drugs at Risk for Shortage Need to Be Identified to Guide Government and Private Sector Initiatives and Investments

To ensure that finite resources and investments are maximized and have substantial public health impact, efforts are underway in the United States to identify the medicines that should be the primary focus of policy actions and initiatives to improve medicines supply chain resiliency. These medicines, often referred to as “essential medicines,” may be candidates for:

- Onshoring or nearshoring decisions.
- Advanced manufacturing technology investments.
- Transparency requirements, including of the product’s upstream supply chain.
- Stockpiling considerations and incentives.

- Alternative payment and pricing models: guaranteed volume and price contracts, exclusive contracts, exclusion from Maximum Allowable Cost (MAC) lists, waiving Medicaid rebates, bonuses, or other preferential payments to providers.
- Targeted subsidies and tax incentives for domestic production, geographic diversification, supply chain redundancies, and new market entrants.
- Other financial and regulatory incentives to encourage new market entry of manufacturers of essential medicines.⁴⁻¹⁹

There is no common definition of or approach to essential medicines lists within the United States. In August 2020, the Executive Order on Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States (E.O. 13944) was issued, which “directed the U.S. Food and Drug Administration (FDA) to identify a list of essential medicines, medical countermeasures and critical inputs that are medically necessary to have available at all times in an amount adequate to serve patient needs and in the appropriate dosage forms.” The stated goal of the list was “to ensure the American public is protected against outbreaks of emerging infectious diseases, such as COVID-19, as well as chemical, biological, radiological,

and nuclear threats.”²⁰ As a result, in October 2020, the FDA published a list of 227 drug and biological product essential medicines and medical countermeasures, as well as 96 device medical countermeasures.²¹ Essential medicines and medical countermeasures selected for inclusion on the FDA list were those that “are medically necessary to have available in adequate supply which can be used for the widest populations to have the greatest potential impact on public health.”²² Importantly, the criteria for inclusion in the critical inputs portion of the essential medicines list extended beyond active pharmaceutical ingredients to “ingredients or components that possess unique attributes essential in assessing the safety and effectiveness of such products.”²²

Executive Order 14017, Executive Order on America’s Supply Chains, issued on February 24, 2021, focused on the potential and real impacts of pandemics and other biological threats, cyber-attacks, climate shocks and extreme weather events, terrorist attacks, geopolitical and economic competition, and other conditions on manufacturing capacity and supply chain resiliency.²³ The Executive Order also directed relevant Cabinet Secretaries to prepare reports on the supply chain for critical sectors and subsectors within either 100 days or one year of the Executive Order. As part of its review of pharmaceuticals and active pharmaceutical ingredients, the U.S. Department of Health and Human Services (HHS) stated that “the Administration will assemble a consortium of public health experts (including emergency medicine and critical care) in the government, non-profit, and private sector to review the Essential Medicines list and recommend 50-100 drugs that are most critical to have available at all times for U.S. patients because of their clinical need and lack of therapeutic redundancy (Critical Drug List), and determine a potential volume that could be needed, using the surges during COVID-19 pandemic as one metric for that analysis. As a result, the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) contracted with ARMI/NextFAB, entities that worked with clinical stakeholders, to develop a list of prioritized essential medicines most critically needed for typical acute patient care. Acute patient care was defined as: 1) rescue and/or lifesaving use (i.e., Intensive Care Units [ICU], Cardiac/Coronary Care Units [CCU], and Emergency Departments); 2) stabilizing patients in hospital continued care to enable discharge; and 3) urgent

or emergency surgery. As a result, the narrowed down list consisted of 86 critical medicines.⁴

Subsequent to Executive Order 14017, in October 2022 the U.S. Department of Commerce issued a request for public comment on a draft list of critical goods and materials within four of the supply chains assessed under the Executive Order: public health and biological preparedness, information and communications technology, energy, and critical minerals. When finalized, “[t]he list of critical goods and materials will serve as a tool to facilitate ongoing targeted analysis of trade data and the evaluation of policies to strengthen these supply chains.”²⁵ Due to the different objective of the Department of Commerce list, in addition to the different goal of the executive order to which it was responding, the critical goods and materials listed on the Commerce list of the public health and biological preparedness supply chain differ from those included on the FDA list.

While there is no consensus definition of essential medicines, there is a common shortcoming of essential medicines lists: a medicine’s risk of shortage, or supply chain vulnerability, is not adequately factored in to whether a medicine is included on the list. Of the 276 drugs that were in shortage in 2021 in the United States,^{26,27} only 85 were on the FDA Essential Medicines, Medical Countermeasures, and Critical Inputs Essential Medicines List.²¹ Demand-side analysis and supply-side analysis are both necessary to prioritize medicines and target policy interventions to prevent and mitigate drug shortages and improve medicines supply chain resiliency.

As an integral part of the exercise to establish essential medicines lists, medicines with the most vulnerable supply chains must be identified. While medicines with vulnerable supply chains may already be included on essential medicines lists, there must be recognition that shortages of medicines with vulnerable supply chains that may not currently be included on essential medicines lists, like medicines that treat cancer, can cause grave patient harm. The National Academies released a report in 2022 that outlined three components of a framework for including products in supply chain resiliency activities; in addition to considering the harm to product users and the magnitude of a shortage, the framework highlighted the need to assess the risk of a product going into shortage.⁶

USP recommends the establishment of a vulnerable medicines list in the United States, as a complement to or a component of an essential medicines list, which factors in supply chain vulnerabilities. Such supply chain vulnerabilities should include sole or limited number of suppliers, geographic concentration of manufacturers and API, excipient, and KSM suppliers, political and geopolitical risks, climate change and vulnerabilities, manufacturing complexity, price and other factors. Creation and utilization of vulnerable medicines lists will help prioritize medicines and properly target policy interventions and finite resources with the aim to improve medicines supply chain resiliency.

Coordinating Supply Chain Resilience and Reliability Efforts Can Maximize the Impact of New and Existing Initiatives to Reduce the Risk of Drug Shortages

Many governmental and non-governmental efforts have emerged to mitigate or prevent drug shortages and to bolster supply chain resilience. For example, FDA, ASPR, the White House, U.S. Department of Commerce, and others have established programs or outlined recommendations to bolster supply chain resilience and reliability and address drug shortages from different vantage points.^{4,15,28-30} Several non-governmental organizations also have ongoing efforts to inject more transparency and resilience into the medicines supply chain.^{7,31-34} These various efforts have made progress, but gaps and a lack of coordinated, strategic planning remains.

A more effective national strategy to improve drug supply chain reliability should come from a federal government initiative, in collaboration with non-governmental stakeholder organizations. This initiative should coordinate existing programs, reduce siloed work, condense duplicative or redundant efforts, identify gaps in current efforts, view medicines supply chain issues from a holistic perspective that appreciates the complex and multifaceted nature of the issues, and be held accountable for the implementation of programs and measurable results. Sufficient resources, funding, and expertise to confront the challenges associated with the medicines supply chain and coordinate meaningful action across the U.S. government and non-governmental organizations is necessary.

USP recommends efforts to coordinate medicines supply chain resilience and reliability activities among federal agencies and non-governmental stakeholders. Coordination efforts should include the organization of multi-disciplinary efforts, defining measurable outcome metrics for implementation efforts, and strategic planning activities to maximize the utility of new programs and increase the impact of existing initiatives. Additionally, necessary authorities and sufficient funding should be allocated to lead these cross-cutting efforts to improve drug supply chain resilience and reliability.

Promoting Geographic Diversification of the Manufacturing Base for U.S. Drug Products Can Help Reduce Supply Chain Vulnerabilities

USP's *Medicine Supply Map* data show that geographic concentration anywhere—including within the United States—increases the risk of drug shortages. Geographic concentration of the medicines supply chain is generally an outcome of specialization and pricing pressure and can result in drug shortages when a variety of issues occur, including natural disasters (e.g., earthquakes, hurricanes), trade wars, domestic or geopolitical strife, or global public health emergencies, such as the COVID-19 pandemic. While the globalization of the supply chain has generally facilitated access to medicines at a lower cost, it has increased the risk of unreliable supply following sudden or unexpected shocks in specific locations. Potential impacts are difficult to anticipate due to complex and incomplete mapping of manufacturing locations.

In March 2021, nearly three-quarters of FDA-registered API manufacturing facilities and approximately half of all FDA-registered finished dosage form (FDF) manufacturing facilities were located outside of the United States. Within the generic drug market, FDA data indicated that 87 percent of FDA-registered API facilities and 63 percent of FDA-registered FDF facilities were located outside of the United States. While instructive, these figures do not portray the entire spectrum of geographic concentration risk due to the lack of data on the volume each facility produces.¹⁵

Significantly, USP used the *Medicine Supply Map* to assess

U.S. dependence on foreign API, the findings of which are largely consistent with those published by the FDA. USP leveraged machine learning techniques, including Natural Language Processing, on data from the FDA, information from non-U.S. regulatory agencies, and its own proprietary insights to map manufacturing locations associated with approximately 90 percent of active API Drug Master Files (DMFs) around the world. DMFs are submitted to FDA by companies when they intend to supply drug ingredients to another company without disclosing proprietary information; FDA publishes the names of companies filing the DMFs. While DMFs are commonly utilized in the generic drug industry, some manufacturers may choose to make their own API or not use a DMF. Nevertheless, this mapping provided a picture of U.S. reliance on foreign API sources at the end of 2021. The USP *Medicine Supply Map* analysis counted the number of active API DMFs by location, which could have been filed in 2021 or earlier:

- India: 48%
- Europe: 22%
- China: 13%
- United States: 10%
- Other: 7%

USP *Medicine Supply Map* insights also show how U.S. reliance on foreign API sources has changed over time, underscoring the complexity, costs, and length of commitment needed of efforts aiming to foster more security in the manufacturing base for U.S. drug products, including onshoring or nearshoring initiatives. In 2021, India contributed 62 percent of active API DMFs filed that year, up from 20 percent of currently active DMFs that were filed in 2000. Meanwhile, Europe’s contribution declined from 49 percent of active API DMFs filed in 2000 to 7 percent filed in 2021. The United States likewise contributed a lower percentage of 4 percent in 2021. China contributed 23 percent of new API DMFs filed in 2021. Of note, USP’s analysis does not take volume into account, and it is not clear if certain DMF holders are responsible for larger volumes of drugs compared to competitors. Importantly, there is also an insufficient understanding of the sources of

KSMs that are used in the manufacture of APIs for U.S. drug products. However, it is widely known that the geographic concentration of the supply of certain KSMs (e.g., for antibiotics) is a significant vulnerability for the U.S. and global drug supplies.

Advances in manufacturing technologies – collectively referred to as advanced manufacturing technologies (AMT) – could help to strengthen supply chain resilience by reducing the vulnerabilities posed by geographic concentration by helping to bring manufacturing back to U.S. soil and may allow economies that are new to pharmaceutical manufacturing to establish production plants of quality medicines and APIs. However, substantial challenges stand in the way of broader adoption of AMT. These obstacles can include knowledge about the areas where AMT use could be the most impactful and how to best implement it; workforce capacity challenges with an industry-wide shortage of AMT expertise; considerable capital and start-up costs associated with establishment of new facilities; lack of clarity on the return on investment; and ongoing uncertainties regarding regulatory reviews and approvals of medicines made with pharmaceutical continuous manufacturing, (PCM), an AMT, around the world. USP is currently engaging with a broad group of stakeholders, including academic research centers and manufacturers, to identify and articulate appropriate standards and practices that will help make advanced manufacturing more accessible and achievable for industry uptake.

USP encourages policymakers to consider a range of reforms to foster more security in the manufacturing base for U.S. drug products to reduce the risk of disruptions and shortages. Disruptions can occur globally, such as due to a global public health emergency, or locally, such as due to a natural disaster or political unrest. USP urges that policy reforms to promote geographic diversification in medicines manufacturing should include but not be limited to on-shoring and re-shoring initiatives, as geographic concentration—even within the United States—can serve as a significant risk factor for drug shortages.

As such, **USP supports:**

- **Economic or other incentive measures that will encourage multiple suppliers for key drugs, geographic diversification of manufacturing facilities,**

and manufacturing location and component supply redundancies.

- **Economic incentives to encourage increased domestic manufacturing of APIs and finished drug products in the United States, prioritizing specific medicines or ingredients that are most vulnerable to supply disruptions.**
- **Market-based incentives that encourage utilization of excess domestic manufacturing capacity: up to 50 percent of manufacturing capacity in the United States is currently unutilized.²**
- **Financial incentives to provide manufacturers with the necessary support to build facilities supporting advanced manufacturing technologies on U.S. soil: manufacturers of low-margin drug products that have a higher likelihood of shortage have insufficient profitability to invest in AMTs.**
- **The development of tools and standards to help reduce the technical barriers to wider adoption of AMTs.**

Sustainable Prices for Generic Medicines Are Needed to Support Supply Chain Resiliency Efforts

Lower-priced drugs have a higher likelihood of shortage. A 53 percent decrease (\$3.15 to \$1.47) in the average manufacturer price (AMP) for a 30-day supply of high-volume generic drugs consumed was seen in the United States from 2016 to 2022.³⁵ The association between pricing and drug shortages is well documented. For instance, Root Cause 1 in FDA's 2019 drug shortages report was the "lack of incentives for manufacturers to produce less profitable drugs." In that same report, FDA analyzed 163 drugs regulated by the Center for Drug Evaluation and Research (CDER) that went into shortage between 2013 and 2017, and found that "[w]hen compared with all marketed drugs with the same dosage form during the same period, including both generics and brands, the prices of the shortage drugs were at the 36th percentile of prices, while the prices of injectables that were in shortage were at the 33rd percentile and oral products in shortage

were at the 46th percentile."²⁹ Additionally, a 2023 report from the Brookings Institute's Hamilton Project highlighted market dynamics as a root cause of manufacturing quality problems associated with generic sterile injectable drug shortages.³⁴

Lower-priced and margin drug products offer limited incentives for manufacturers to stay in or enter the market. Manufacturers that produce the same low-priced generic drug compete predominantly on price, as the products are interchangeable, and the resiliency of a drug product's supply chain is not currently highly valued in the marketplace. While the number of generic drug manufacturers in the U.S. market has increased by 50% since 2014,³⁶ there are fewer purchasers of drugs, with three purchasing groups accounting for 92% of generic drug purchases.³⁷ The contracting and payment mechanisms for lower-priced drugs that result from this dynamic contribute to demand uncertainty for manufacturers.

The fact that lower-priced drugs have more availability issues should be evaluated within the context of quality and supply chain vulnerability, as unsustainable prices of generic medicines undermine initiatives to ensure supply chain resiliency. Lower margins not only limit the ability of manufacturers to reinvest in manufacturing facility maintenance and manufacturing updates and quality assurance and management, but also cause manufacturers to seek lower-cost geographies for their sourcing and manufacturing. This reality was highlighted in Root Cause 2 of the 2019 FDA report "Drug Shortages: Root Causes and Potential Solutions," which suggested that the market does not recognize and reward manufacturers for mature quality management systems.²⁹ The FDA, in its 2019 drug shortages report, called for the creation of a rating system to incentivize drug manufacturers to invest in quality management system maturity (QMM) – a measure of supply chain resiliency and reliability. Subsequently, in October of 2020, the Agency published two notices in the Federal Register to recruit domestic FDF manufacturers and foreign API manufacturers to participate in the QMM Pilot Programs. The intent of these pilot programs was to inform the development of a QMM rating system. In November of 2022, FDA hosted a workshop that presented the lessons learned from the two QMM pilot programs. The lessons learned were summarized in a paper



published in January of 2023 and included best practices for developing the QMM rating system and conducting QMM assessments.³⁸

Complementing its QMM activities, FDA has proposed to develop and implement a quality metrics reporting program. While the Agency has not yet finalized the direction of the proposed quality metrics reporting program, FDA intends for the program to support its quality surveillance activities. The quality metrics data submitted has the potential to enable the FDA to “[o]btain a more quantitative and objective measure of manufacturing quality and reliability at an establishment.”³⁹

These measures could go further and assess supply chain diversification and maturity, which are important predictors of shortages. If the measures are made public, they could be used in purchasing decisions and price negotiations to favor those manufacturers that can ensure robust supply reliability, rather than only those manufacturers that offer the lowest price. **USP supports initiatives to measure and rate manufacturer supply chain resiliency, sustainability, and reliability. Such initiatives are integral to ensure that manufacturer supply chain redundancy and resiliency efforts come to be valued in purchasing and contracting decisions and in regulatory frameworks and efforts.**

Overall, USP understands the necessity of a fundamental shift in the market for lower-priced drugs to guarantee more certainty, predictability, and sustainability of both demand and supply and to increasingly value a drug’s supply chain resiliency and reliability in addition to its price. **USP encourages policymakers and public and private drug purchasers to promote sustainable prices of generic medicines by valuing supply chain resiliency and reliability. Policymakers and public and private drug purchasers should explore the establishment and utilization of payment and purchasing models that value and incentivize supply chain resiliency and reliability. To insert additional predictability and certainty in the marketplace for lower-priced drugs, USP encourages public and private purchasers to explore the use of longer-term guaranteed-volume contracts, in which prices are assured for a defined, guaranteed volume. Such long-term, guaranteed-volume contracts could include provisions to help ensure supply chain resiliency, including requirements for manufacturing redundancies and diversification of suppliers.**

About USP

USP is an independent, scientific, global non-profit organization founded in 1820 when eleven physicians took action to protect patients from poor-quality medicines. Convening in the old U.S. Senate Chamber, they published a national, uniform set of guidelines for medicines called the U.S. Pharmacopeia. A core pillar of USP's work is to help strengthen the global supply chain so that the medicines, dietary supplements, and foods that people rely on for their health are available when needed and meet quality standards as expected and required.

The Federal Food, Drug, and Cosmetic Act of 1938 created the statutory requirement that medicines sold in the United States generally must adhere to USP's public quality standards to help ensure the quality of medicines and the safety of patients. USP standards are developed by nearly 800 scientific and healthcare experts who volunteer their time on USP's standard-setting committees, which also include over 200 FDA government liaisons. In these and other ways, USP works closely with the FDA, other government agencies, and across health and science communities to develop USP standards (over 6,000 today) that are enforced by the FDA.

In addition to our work on standards, USP is an active participant in many public-private partnerships on supply chain-related issues. This includes work with the FDA, ASPR, and the Biomedical Advanced Research and Development Authority (BARDA). USP also engages with the World Health Organization and the Pan American Health Organization as an officially recognized non-state actor and hosts the USP-APEC (Asia-Pacific Economic Cooperation) Center of Excellence for Securing Medical Product Quality through the Supply Chain, under the sponsorship of the FDA.

USP is governed by more than 500 organizations, including scientific, healthcare practitioner, consumer, and industry organizations, as well as dozens of government agencies, who together comprise the USP Convention.

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