United States Pharmacopeia (USP) Statement for the Record

Submitted to the Senate Finance Committee for the Hearing: "Drug Shortages: Examining Supply Challenges, Impacts, and Policy Solutions from a Federal Health Program Perspective"

December 5, 2023

The United States Pharmacopeia (USP) is pleased to submit the following statement for the record on the hearing "Drug Shortages: Examining Supply Challenges, Impacts, and Policy Solutions from a Federal Health Program Perspective."

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 the first-of-its-kind, national, uniform set of guidelines for medicines and formed the organization now known as USP. Our organization is governed by more than 500 entities, including scientific, healthcare practitioner, consumer, and industry organizations, as well as dozens of government agencies, who together comprise the USP Convention.[1] A core pillar of USP's work is to help strengthen the global supply chain so that the medicines that people rely on for their health are available when needed and meet USP's quality standards as expected and/or 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. Currently, USP standards are developed by nearly 800 scientific and healthcare experts who volunteer their time on USP's standard-setting committees, which also include more than 200 U.S. Food and Drug Administration (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 (more than 6,000 today) that are enforced by the FDA.

Drug shortages continue to pose a significant threat to our nation's patients and public health. Mitigating and preventing drug shortages requires the identification of vulnerabilities in the pharmaceutical supply chain to pinpoint the investments and policy and payment system reforms required to make measurable progress against the continued proliferation of shortages. As policy makers consider solutions to drug shortages, it is imperative to take steps to foster a more resilient supply chain to effectively reduce shortages over the long term. A more resilient medicines supply chain will enhance our national security, improve our ability to respond to medical and public health crisis, and most importantly, will help ensure that patients have access to the quality medicines that are essential for both critical and routine patient care. Now is the time to act.

[1] USP's governing bodies, in addition to the Council of the Convention, include its Board of Trustees and Council of Experts.

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Understanding Factors Driving Medicine Supply Chain Vulnerabilities

Over the past year, there have been more three hundred drugs experiencing ongoing shortages, the highest in a decade. The impact on patients has been significant, causing treatment delays or the use of less effective treatments, often with suboptimal outcomes. Using the *Medicine Supply Map*[2], USP found four risk categories to be correlated with drug shortages, which singularly or in combination can increase a medication's risk for shortage:

1. **Low prices:** Drug products with low prices (most commonly older drug products which are usually generics) have a higher risk of drug shortage.
2. **Manufacturing complexity:** Drugs with more manufacturing complexity, such as sterile injectables, have an increased vulnerability to shortage. Examples of manufacturing complexity include product categories that require dedicated manufacturing facilities (e.g., certain antibiotics) and complex chemical synthesis of the active ingredient.
3. **Geographic concentration:** Drugs with greater geographic concentration of sourcing of active pharmaceutical ingredient (API) and/or finished dose manufacturing are more susceptible to shortages.
4. **Quality concerns:** Quality failures, accounted for in the *Medicine Supply Map* as outcomes of FDA inspections and a history of recalls, predict increased vulnerability to drug shortages.

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. To improve margins, industry has sought to reduce manufacturing costs by concentrating production in lower-cost geographies. This concentration creates a range of vulnerabilities. Moreover, the low price/low margin dynamic impedes industry's ability to invest in increased manufacturing capacity and may lead to underinvestment in quality management systems. To increase resiliency, it is essential to account for these dynamics.

Lower-priced drugs

Lower-priced drugs have a higher likelihood of being in shortage. The association between pricing and drug shortages is well documented. For instance, Root Cause 1 in the 2019 FDA report "Drug Shortages: Root Causes and Potential Solutions" was the "lack of incentives for manufacturers to produce less profitable drugs" which

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[2] 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.

included “unfavorable pricing dynamics” among other market conditions that could limit profitability. 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.”[3] Lower price and margin drug products offer limited incentives for manufacturers to stay in or enter the market. The fact that lower-priced drugs have more availability issues should be evaluated within the context of quality and supply chain vulnerability.

For instance, USP *Medicine Supply Map* analysis shows low price is a significant risk factor for antimicrobial shortages, the impacts of which we recently experienced. During the winter of 2022-2023, with multiple respiratory viruses circulating, drug shortages were experienced among certain antimicrobial drug products. Previously, in the summer of 2022, USP’s *Medicine Supply Map* found that antibacterial drug products were 42 percent more likely to be in shortage than the average drug product. Out of the 128 antibacterial drug products approved in the United States, 20 were in shortage (15.6 percent compared to 10.9 percent for all drug products).[4]

Manufacturing complexity

There are numerous ways to assess the complexity of pharmaceutical manufacturing, including the type and variation of dosage forms, the number of underlying ingredients and key starting materials, the expertise needed to synthesize the molecule, storage requirements, and the size and molecular structure of the active pharmaceutical ingredient. A USP *Medicine Supply Map* analysis shows that the injectable dosage form and certain specifics of the manufacturing and API synthesis processes are predictive of drug shortages. Injectables are particularly vulnerable to supply chain disruptions when compared to solid oral dose medications. Injectable medicines often undergo a manufacturing process called lyophilization, which is expensive and complex, and therefore medicines made with this process have lower supply chain resilience. The complexity of the chemical synthesis of the API was also found to be correlated to drug shortages.

As an example, while not currently in shortage, vincristine sulfate injection, which is used for the treatment of cancer, has been in shortage in previous years and remains highly vulnerable to shortage. This drug requires plant-based starting materials that can be difficult and expensive to obtain. Moreover, its cytotoxic active ingredient is hazardous, expensive to manufacture, and requires dedicated facilities. Manufacturers of vincristine sulfate injection also cannot take advantage of economies of scale due to the low dose/strength of the drug and the low total API needed.

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[3] FDA. 2019. Drug Shortages: Root Causes and Potential Solutions. Available at: https://www.fda.gov/media/131130/download.

[4] Supply chain vulnerabilities exist for antimicrobial medicines: USP Medicine Supply Map analysis | Quality Matters | U.S. Pharmacopeia Blog.

Geographic concentration

USP's *Medicine Supply Map* data show that geographic concentration anywhere – including within the United States – increases the risk of drug shortage. While the globalization of the supply chain has generally facilitated access to medicines at a lower cost, it poses the risk of unreliable supply following sudden or unexpected shocks in specific locations, followed by a lack of understanding of what might be impacted because the mapping of where products are made is complex and incomplete. 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 pandemics such as COVID-19.

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, 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 account for the volume produced within these facilities.[5]

USP used the *Medicine Supply Map* to assess U.S. dependence on foreign API. USP leveraged machine learning techniques, including Natural Language Processing, on data from 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 generics 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:

- 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. 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. This increase is consistent with India's well-publicized national ambition to enhance API manufacturing capabilities. 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 in 2021: 4 percent. China

[5] The White House. Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth: 100-Day Reviews under Executive Order 14017 2021 [cited 2021 August 20]; Available from: https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf.

contributed 23 percent of new API DMFs filed in 2021. USP data suggest that China produces a wide variety of APIs for medicines marketed in the United States.

Understanding these data could give leaders an opportunity to prepare for a potential disruption caused by a shock event, such as an emerging public health, political, or trade crisis. Questions remain from the current analysis, however, when thinking about facets of U.S. reliance on foreign API manufacturers. For example, 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, we also do not understand U.S. reliance on other countries for key ingredients that are used in the manufacture of API.

Quality concerns

USP underscores that medicines supply chain resilience and medicines quality are inextricably linked; issues with medicines quality can threaten medicines supply chain resilience, and medicines supply chain failures, vulnerabilities and disruptions can lead to medicines quality issues, increasing the risk of substandard and falsified medicines. It is well documented that quality issues remain a primary contributor to drug and medical product shortages.

USP *Medicine Supply Map* analysis found that poor FDA inspection outcomes at a facility and products with a history of recalls were correlated with a higher likelihood of shortage. This is consistent with FDA's findings: for example, of the 163 drugs that went into shortage between 2013 and 2017, the FDA found that 62 percent went into shortage due to quality issues.[6] Root Cause 2 outlined in FDA's 2019 drug shortages report suggested that the market does not recognize and reward manufacturers for mature quality management systems.

USP Policy Recommendations

A fundamental shift in the market for lower-priced drugs is needed to align supply and demand forces to create a predictable, sustainable, and quality supply chain that can reliably provide critical drugs to patients. Policymakers and public and private drug purchasers must value quality and resilience through sustainable prices of drugs that demonstrate these characteristics. While the programs and policies to achieve this are being developed and implemented, it is imperative in the near term to utilize and expand tools to assess supply chain vulnerabilities and shortage risks, and to use these insights to proactively intervene in a coordinated manner. USP urges policymakers, regulators, and industry to take further action to identify and respond to risks and vulnerabilities and reduce medicine supply disruptions. While we recognize that drug shortages span various Congressional Committees due to both public health and national security concerns, we urge the Committee to work across committee jurisdictions to ensure that meaningful reforms are enacted and implemented.

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[6] *Ibid.*

1. **Promote 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, 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 the development of initiatives to assess manufacturer supply chain resiliency, sustainability, and reliability. Such initiatives will provide information that can support purchasing and contracting decisions that financially recognize and reward manufacturer supply chain capacity and resiliency 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 capacity that accounts for potential disruptions and diversification of suppliers.

2. **Advance broader geographic diversification of the manufacturing base including incentives to advance more U.S.-based medicine production**

USP supports reforms to foster more resilience in the manufacturing base for U.S. drug products—especially for medicines or ingredients that are most vulnerable to supply disruptions—and to reduce the risk to patients of potential disruptions and shortages that result from the concentration of drug manufacturing in limited geographies. USP supports:

- Economic or other incentive measures that will encourage multiple suppliers for key drugs, geographic diversification of manufacturing facilities, and broader component supply.

- 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.

- 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 and support medicine quality.

3. Utilize existing early warning capabilities and invest to fill gaps in the supply chain map

Both government and non-governmental stakeholders should utilize the full range of early warning capabilities developed for the U.S. drug supply chain. In particular, the U.S. Government should further leverage information platforms that provide actionable data-based insights into medicines supply chain vulnerabilities, while also funding additional initiatives to fill information gaps on a broad range of vulnerabilities including for key starting materials and critical excipients. These capabilities can be housed in a funded Early Warning System and Research Coordinating Center and 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. 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.

U.S. Government entities and the 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. Moreover, a need exists 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.

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.

4. **Utilize a vulnerable medicines list to guide policy interventions and investments**

A vulnerable medicines list that highlights medicines that are vulnerable to shortage based on a range of indicators would provide both government and non-government stakeholders with insights to inform policy and purchasing decisions. Factors that would inform a vulnerable medicines list could include the 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 information.

5. **Coordinate supply chain resilience and reliability efforts**

USP supports efforts to coordinate medicines supply chain resilience and reliability activities among federal agencies and non-governmental stakeholders. We encourage the coordination 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-functional efforts to improve drug supply chain resilience and reliability.

Conclusion

USP thanks the Committee for considering USP's recommendations and for the thoughtful, bipartisan attention to the underlying causes of drug shortages and to the policy and payment system reforms required to improve medicine supply chain resilience. We look forward to working with the Committee and Congress to seek solutions to drug shortages that will help ensure that patients have access to the quality medicines they need.