

Statement of the U.S. Pharmacopeia

Submitted to the Senate Homeland Security and Governmental Affairs Committee

**For the Hearing “Drug Shortage Health and National Security Risks:
Underlying Causes and Needed Reforms”**

March 20, 2023

The United States Pharmacopeia (USP) is pleased to submit the following statement for the record on the hearing “Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms.”

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 Cosmetics 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 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 (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, the Administration for Strategic Preparedness and Response (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.¹

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

Assessing and Addressing Supply-Side Vulnerabilities Is Essential to Reducing Drug Shortages

Vulnerabilities in supply chains manifest as shortages when supply is unable to meet demand, which may be due to demand spikes, supply disruptions, or both. Currently, there is little insight available into supply-side risk for medicines and the ingredients necessary to manufacture them that could help guide effective decision-making. 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. Before a crisis, companies and the government need a better understanding and mapping of their full supply chains to identify potential vulnerabilities.

Neither a single government agency nor any industry entity has a complete view of upstream supply. This lack of clarity contributes to a limited understanding of the risks affecting the U.S. medicines supply. This could lead to ineffective deployment of resources to reduce drug shortages and improve medicines supply chain resiliency by failing to account for the upstream root causes of many shortages.

The U.S. pharmaceutical supply chain will be more resilient and reliable for patients if Congress targets its efforts at drugs at long-term risk of shortage due to structural weaknesses in their upstream supply chains. The identification of upstream supply chain risks can enable regulator and industry action to reduce medicine supply disruptions by informing risk mitigation strategies, public and private investment, as well as policy reforms that build more resilience. A holistic approach to address medicines supply chain vulnerabilities – that encompasses both demand and supply-side indicators – can help inform medicines supply chain resiliency efforts to improve their design and effectiveness.

Recognizing the urgent public health need for better supply chain intelligence, USP has invested in the development and continuous improvement of a data intelligence platform, the *Medicine Supply Map* (www.usp.org/medicinesupplymap), to:

1. Help identify, characterize and quantify vulnerabilities in the upstream pharmaceutical supply chain;
2. Deliver insights that can guide risk mitigation strategies and investments; and
3. Help inform policy changes that advance supply chain resilience.

The *Medicine Supply Map* uses multiple sources of information to identify the worldwide sites of pharmaceutical ingredient and finished dose medicine manufacturing. More than 40 datasets from USP, 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 covers 92 percent of FDA-approved generic prescription drugs. Notably, 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 active pharmaceutical ingredient (API) manufacturing facilities.

Insights from USP's *Medicine Supply Map*: Risk Categories Driving Drug Shortages

Using the *Medicine Supply Map*, USP has identified, characterized, and quantified factors that contribute to the vulnerability of the U.S. medicines supply chain. USP identified over 200 potential drivers of drug shortages and quantified their contributions to drug shortages. Four risk categories were found 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, common in older drug products, have a higher risk of drug shortage.
2. **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.
3. **Geographic concentration:** Drugs with greater geographic concentration of 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 create manufacturing redundancies and may lead to underinvestment in quality management systems. To increase resiliency, it is important to account for these dynamics. We should incentivize geographic diversity of manufacturing, facility redundancies, and continuously improved quality management.

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." 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."² 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.

² FDA. 2019. Drug Shortages: Root Causes and Potential Solutions. Available at: <https://www.fda.gov/media/131130/download>.

USP *Medicine Supply Map* analysis shows low price is a significant risk factor for antimicrobial shortages, the impacts of which we very 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 U.S., 20 were in shortage (15.6 percent compared to 10.9 percent for all drug products).³

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. 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, 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.

Geographic concentration

USP's *Medicine Supply Map* data show that geographic concentration anywhere – including within the U.S. – 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 U.S. Within the generic drug market, 87 percent of FDA-registered

³ Supply chain vulnerabilities exist for antimicrobial medicines: USP Medicine Supply Map analysis | Quality Matters | U.S. Pharmacopeia Blog.

API facilities and 63 percent of FDA-registered FDF facilities were located outside of the U.S. While instructive, these figures do not account for the volume produced within these facilities.⁴

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%
- U.S.: 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 U.S. likewise contributed a lower percentage in 2021: 4 percent. China 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 U.S.

Understanding this 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.

⁴ 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>.

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.⁵ 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.

Using Data to Guide Policy Reforms and Investments

Leveraging a comprehensive set of data – including upstream and supply-side risk indicators and factors – to guide potential policy reforms and investments will reduce drug shortages and improve supply chain resiliency. Improved visibility into and analysis of the vulnerabilities of the upstream medicines supply chain can help target potential policy reforms and inform U.S. government investments to enhance resiliency.

Additional Data and Insights Are Needed to Guide Policy Reforms

Policymakers, manufacturers, wholesalers, and hospitals could benefit from intelligence to help size and scope geographic concentration and other types of risk, but some supply chain risk information is either not available or is considered confidential.

To address these challenges, USP proposes that the Committee consider the establishment of and investment in a public-private partnership to build an early warning system for the pharmaceutical supply chain. A “centers of excellence” model could be an appropriate construct for such a partnership, although other models could be effective as well. The USP *Medicine Supply Map* could be utilized in a variety of collaborative models that could include:

- Monitoring the pharmaceutical supply chain for disruptions, shortages and quality issues;
- Coordinating among the Department of Health and Human Services, Department of Commerce, Department of Defense, Department of Veterans Affairs, other federal and state agencies, allied trading partners, academic research institutions, non-profits and private sector entities to identify, assess and respond to supply chain challenges;
- Building predictive capabilities to inform stakeholders, including the U.S. Government, manufacturers, wholesalers and hospitals, of the risk of supply chain disruption with enough notice that mitigative action can be taken;
- Informing decisions made by the Strategic National Stockpile on medicines to include; and
- Periodically issuing public recommendations and reports on ways to prevent supply chain disruptions, shortages and quality issues.

Better Understanding of the Vulnerability of Key Starting Materials and Excipients Is Needed

There is very limited understanding today within the government or in the private sector about where many of the key ingredients used in the manufacturing of pharmaceuticals are made. Pharmaceutical supply chain data collection and analysis should be expanded to include key starting materials (KSM) and inactive ingredients known as excipients.

⁵ *Ibid.*

The U.S. needs better intelligence regarding which KSMs are commonly used in commercial synthesis; where KSMs are made and at what volume; and whether there are alternative KSMs and synthetic pathways. USP has initiated some methodologies to start this mapping, but more work is needed.

Additional visibility into the excipients supply chain is also needed, including where critical excipients are made and at what volume. Despite being called “inactive” ingredients, excipients play a critical role in drug development, delivery, effectiveness, and stability. Excipients comprise up to 90 percent of a medicine’s volume and serve important functions, including as binders, disintegrants, coatings, preservatives, colors and flavorings. As such, breakdowns of critical excipient supply chains can have significant downstream effects. For example, magnesium stearate is included in 32,060 drug products according to NIH DailyMed, including those to treat high cholesterol, high blood pressure, diabetes, and bacterial infections.⁶

Excipients are sourced from suppliers around the world and are used for more than just the manufacture of medicines. The reliance of the pharmaceutical industry on the global excipients supply chain presents challenges for supply chain resiliency as well as quality and regulatory oversight. Quality issues and shortages of excipients have contributed to supply chain disruptions. Critically, the impact of excipient quality failures extends beyond supply chain disruptions and drug recalls to include patient health impacts. A lack of awareness remains about how many and which drug shortages have been caused by shortages of or quality issues associated with excipients and which excipients are most vulnerable to quality issues and supply chain disruptions. Overall medicines supply chain vulnerabilities that apply to finished products, including geographic concentration, price, political and geopolitical considerations, sole/limited suppliers and climate vulnerabilities also apply to the excipients supply chain.

Incentives Are Needed to Promote Geographic Variation of Medicines Manufacturing

To minimize or prevent the occurrence of drug shortages due to disruptions, USP encourages diversifying the supply chain and building redundancies into the system. Similar to the way back-up systems work, perturbations in one part of the supply chain could be addressed or mitigated by scaling production in another, redundant part. The goal should be geographically diversified supply chains, as geographically concentration anywhere – even within the U.S. – is problematic and comprises a significant risk factor for drug shortages. For example, the recent Chapter 7 bankruptcy of a U.S.-based generic drug manufacturer had ripple effects on the production of certain medicines on the FDA Essential Medicines List, including levofloxacin oral/ IV (the company had 100 percent market share of ophthalmic form); adenosine injection (the company had 38 percent market share); and mycophenolate mofetil oral/ suspension (the company had 47 percent market of the injectable form).⁷

USP encourages policymakers to consider a range of reforms to foster geographic diversification of manufacturing facilities to reduce the risk of shortages that may occur from disruptions. These disruptions can occur globally, such as due to the COVID-19 pandemic, or locally, such as due to a natural disaster or political unrest. Policy reforms can include exploring economic or other incentive measures to support supply chain resiliency that will encourage geographic diversification of manufacturing facilities.

⁶ Wosinska, M. and R. Conti. Comments on the draft harmonized system code list of critical supply chains. November 7, 2022. Available at: <https://www.brookings.edu/opinions/comments-on-the-draft-harmonized-system-code-list-of-critical-supply-chains/>.

⁷ End Drug Shortages Alliance. 2023. “Supply chain disruption due to manufacturer closure: Akorn Pharmaceuticals ceases operations.” Available at: <https://www.enddrugshortages.com/files/Akorn-Pharmaceuticals-ceases-operations.pdf>.

U.S. government investment in domestic production of prioritized API is an important element of a comprehensive effort to enhance medicines supply chain resiliency. Economic incentives to help foster an environment conducive to more private sector medicine manufacturing in the U.S. should also be evaluated.

Stockpiling Decisions Should Factor in Medicines Supply Chain Vulnerability

The Strategic National Stockpile (SNS) is critical to the nation's response to public health threats to protect the American public. The composition of the products in national stockpiles should be continually reviewed and modified to address the most likely shortages of the included products. The list of pharmaceuticals to include in the stockpile should be informed by supply and demand side analysis, as described previously.

Additional Investments and Incentives Are Needed to Overcome Barriers to Adoption of Advanced Manufacturing Technologies (AMT)

Manufacturers have long produced pharmaceuticals using a method known as “batch manufacturing.” Advances in manufacturing technologies – collectively referred to as advanced manufacturing technologies (AMT) – could help to strengthen supply chain resilience, but significant hurdles must be addressed to foster broader adoption.

Traditional batch manufacturing will remain an essential pillar of global medicine manufacturing strength, and any discussion related to onshoring must consider existing capacity for batch manufacturing. Recent studies suggest up to 50 percent of manufacturing capacity in the U.S. is not utilized.⁸ Implementing market-based incentives that encourage utilization of this excess domestic capacity would enhance the resilience of the U.S. medicines supply chain.

At the same time, AMT, including pharmaceutical continuous manufacturing (PCM), can be phased into unutilized manufacturing sites in some cases. PCM can provide efficiencies for many medicines and their ingredients and could facilitate expansion of domestic manufacturing in the U.S., particularly for the manufacture of critical medicines.

PCM is highly automated and involves a continuous flow of materials in a single facility, from inputs to process outputs, such as an active pharmaceutical ingredient or finished drug product. It can enable flexibility and efficiency, lower production costs, cut the environmental footprint, accelerate production and scale-up in response to emergencies and reduce potential quality issues through real-time monitoring. In contrast, in traditional batch manufacturing, the raw materials that are eventually transformed into the final product (e.g., a tablet) are processed in different machines at different times and potentially in different locations. This process naturally requires many starts and stops in manufacturing.

Continuous manufacturing provides a set of technologies that can help 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 PCM. These obstacles can include knowledge about the areas where PCM use could be the most impactful and how to best implement it; workforce capacity challenges with an industry-wide shortage of PCM expertise; considerable capital and

⁸ Sardella, Anthony. Sep 2022. <https://wustl.app.box.com/s/32e1w52bqaip6pz22cf4vjoti78997uk>

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 PCM around the world.

USP is working with partners to address PCM knowledge gaps through educational programs; the creation of an online continuous manufacturing Knowledge Center in collaboration with the National Institute for Pharmaceutical Technology and Education (NIPTE) and funded by FDA; and the launch of a flow chemistry research and development (R&D) laboratory to investigate novel routes of synthesis for API using PCM and develop new analytical techniques to help ensure product quality. To build upon these efforts, USP supports the authorization of appropriations to fund workforce training on AMT.

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.

However, not all drug manufacturers have the financial resources necessary to invest in AMT; this is especially true for manufacturers of low-margin drug products. Addressing these economic and market factors will be fundamental to fostering broader uptake of these promising advanced manufacturing technologies for lower margin medicines.

Conclusion

USP thanks the Committee for this hearing and for the bipartisan, careful consideration of the underlying causes of drug shortages and needed policy reforms to improve medicines supply chain resilience. We look forward to working with the Committee and Congress to seek solutions that will ensure that the U.S. medicines supply chain will be more resilient and reliable for patients.