VIA ELECTRONIC SUBMISSION

July 7, 2023

The Honorable Cathy McMorris Rodgers
Chair House Energy and Commerce Committee
2188 Rayburn House Office Building
Washington, DC 20515

The Honorable Mike Crapo
Ranking Member, Senate Finance Committee
239 Dirksen Senate Office Building
Washington, DC 20510

Re: Request for Information on Drug Shortages

Dear Chairwoman McMorris Rodgers and Ranking Member Crapo:

The United States Pharmacopeia (USP) is pleased to provide a response to the bicameral Request for Information (RFI) on the increase in drug shortages. 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 that people rely on for their health are available when needed and meet quality standards as expected and required. 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]

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 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.

Drug shortages continue to pose a significant threat to our nation's public health. Mitigating and preventing drug shortages, and identifying vulnerabilities in the pharmaceutical supply chain, are essential to enhance our national security, including medical and public health preparedness and response, and to ensure patients have access to the critical and routine

[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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medical care they need. At the end of 2022, there were 295 active and ongoing drug shortages, the highest number since 2014.[2] The impact upon patients has been significant, causing delays in care or the use of less effective treatments, often with unfavorable outcomes.[2] With greater than 80% of active pharmaceutical ingredient (API)manufacturing facilities located outside of the United States, drug shortages can also pose a national security risk. Please see our below comments to specific questions from the RFI.

Question 1: How would you define the scope and impact of the recent and ongoing U.S. drug shortages?

Answer: The scope and impact of the recent and ongoing drug shortages have made clear that true patient harm can result from vulnerable medicines supply chains bending or breaking – regardless of whether medicines in shortage are currently considered to be "essential". As we have witnessed in the case of shortages of oncology drugs, treatment shortages can lead to delays in chemotherapy, changes in treatment regimens, missed treatments, adverse outcomes, and even patient death. Notably, shortages of one drug can cause a cascading effect and lead to shortages of alternative and/or second-line treatments.

Recent and ongoing drug shortages have also highlighted the need for stakeholders along the medicines supply chain – ranging from the U.S. Government to pharmaceutical companies to hospitals – to have a better understanding of medicines supply chains, to not only identify potential vulnerabilities, but to implement interventions or policy solutions to mitigate or prevent drug shortages.

To analyze current shortages of oncology drugs, USP used its *Medicine Supply Map*,[2] a data analytics tool that uses multiple sources of information to identify the worldwide sites of pharmaceutical ingredient and finished dose medicine manufacturing. USP analysis found that carboplatin and cisplatin volume sold during the first quarter of 2023 was higher than in previous years, even though they have had publicized shortages. This demand spike may have been caused by some hospitals' protective purchasing, which in turn, could be linked as a response to a 483 issued in January 2023 to a key manufacturer of cisplatin and carboplatin. 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/quota until actions could be taken to increase supply. In the case of methotrexate, its market has had signals of supply vulnerability for more than four years – long before the current 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. Furthermore, experts have flagged the ongoing shortages of capecitabine and fluorouracil as highly concerning. As such, immediate action to improve supply resilience may be warranted, including the identification of additional suppliers.

[2] 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.

USP underscores that leveraging data and insights can guide interventions and policy reforms to strengthen the resilience of the medicines supply chain and ultimately reduce or eliminate drug shortages. In the case of cancer drug shortages, such data and insights could have been acted upon by stakeholders to limit the impact of – or even potentially prevent – certain drug shortages. Analysis of cancer drug shortages represents only the latest indicator that an early warning system is critically needed 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 proactive and informed approach to preventing many more 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 specific vulnerabilities of specific medicines.

Question 2: What market and economic conditions undermine pharmaceutical supply chains or the availability of 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."[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.

USP *Medicine Supply Map* analysis shows low price is a significant risk factor for antimicrobial shortages, the impacts of which we very recently experienced. Manufacturers only receive pennies per dose for some of these drugs. 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).[4]

In addition, 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

[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.

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 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.[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 an estimate 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 these estimates of U.S. reliance on foreign API sources have 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.

Question 6: Given that supply chain issues can trigger manufacturing delays and disruptions that result in shortages, are further incentives necessary to address manufacturing issues?

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[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.

Answer: To minimize or prevent the occurrence of drug shortages due to supply chain 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.

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.

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.

Additional investments and incentives are needed to overcome barriers to adoption of advanced manufacturing technologies (AMT). AMT hold great promise to help 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.[6] 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.

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 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

[6] Sardella, Anthony. Sep 2022. https://wustl.app.box.com/s/32e1w52bgajp6pz22qf4vjotj78997uk

ensure product quality. To build upon these efforts, USP supports the authorization of appropriations to fund workforce training on AMT.

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 appreciates the opportunity to engage with the House Energy and Commerce Committee and the Senate Finance Committee to explore solutions to the challenges resulting from drug shortages. We look forward to working with you further on this critical problem. If you have any questions or would like additional follow up, please do not hesitate to reach out to Joseph M. Hill, Director, U.S. Government Affairs at Joe.Hill@USP.org or 202-239-4137.

Sincerely,

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