

VIA ELECTRONIC SUBMISSION

January 20, 2023

Dr. Arati Prabhakar
Director
Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, DC 20504

Re: Request for Information (RFI): National Biotechnology and Biomanufacturing Initiative

Dear Director Prabhakar:

On behalf of the United States Pharmacopeia (USP), I appreciate the opportunity to respond to the request for information (RFI) from the Office of Science and Technology Policy (OSTP) on the National Biotechnology and Biomanufacturing Initiative. USP is an independent, scientific, global non-profit organization founded in 1820 and dedicated to building trust where it matters most: in the world's medicines, dietary supplements, and foods through rigorous science and public quality standards.¹ A core pillar of USP's mission is to help strengthen the global supply chain so that the medicines, dietary supplements, and food 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 communities, as well as dozens of government agencies, who together comprise the USP Convention.²

USP supports the role of the National Biotechnology and Biomanufacturing Initiative (NBBi), as outlined in Executive Order 14081, "Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy," to advance biotechnology and biomanufacturing towards innovative solutions in health and supply chain resilience. USP appreciates the focus of OSTP to ensure that the U.S. has the right research ecosystem, workforce, data, and domestic biomanufacturing capacity to not only support a strong bioeconomy, but medicines supply chain resilience, medicines quality, and public health.

Please see our below comments to specific sections from the National Biotechnology and Biomanufacturing Initiative RFI (Data for the Bioeconomy, and Biotechnology and Biomanufacturing Workforce).

¹ USP standards are developed by Expert Bodies comprised of more than 750 scientific experts and in close collaboration with stakeholders and government agencies, including more than 100 staff from the U.S. Food and Drug Administration (FDA) who participate as Government Liaisons to USP's Expert Committees and Expert Panels. These experts collaborate to develop USP standards through an open, transparent process, offering the ability to adjust standards to confront public health emergencies, adapt to new industry practices, and keep up with evolving science and technology. USP's public quality standards are recognized in the Federal Food, Drug, and Cosmetic Act as official standards for medicines, dietary supplements, and food ingredients.

² USP's governing bodies in addition to the Council of the Convention include its Board of Trustees and Council of Experts.

Data for the Bioeconomy

There is a need for accurate data to guide the allocation and prioritization of resources to advance biotechnology and biomanufacturing towards innovative solutions to improve medicines supply chain resilience.

The global supply chain for medicines has numerous vulnerabilities that can be challenged by acute disruptions, for example, from natural disasters, public health emergencies, and quality-related disruptions in manufacturing. When such disruptions occur, the quality, safety, and adequate supply of medicines, particularly those used for critical treatments, become a national security issue, and can have unintended and dire consequences for public health infrastructure and the health of the American public. Unfortunately, the COVID-19 pandemic brought these impacts into sharp focus. USP urges OSTP to prioritize the identification of upstream supply chain risks in the medicines supply chain, which can enable regulator and industry action to reduce medicine supply disruptions while also providing evidence to inform public investment and policy reforms that build more resilience. Neither a single government agency nor any industry entity has a complete view of upstream supply. This lack of clarity leads to a poor understanding of the risks impacting the U.S. medicines supply, and misdirecting resources to support biotechnology and biomanufacturing from where they are needed most.

Since early 2020, USP has invested in the development and continuous improvement of an informatics tool, the *Medicine Supply Map* (www.usp.org/medicinesupplymap), to help identify, characterize and quantify vulnerabilities in the upstream pharmaceutical supply chain, deliver insights that can guide risk mitigation strategies and investments, and help inform policy changes that advance supply chain resilience. The *Medicine Supply Map* uses multiple sources of information to identify the worldwide sites of raw ingredient and medicine manufacturing. More than 20 datasets from USP, the U.S. Food & Drug Administration (FDA), the Centers for Medicare & Medicaid Services, European Medicines Agency, World Health Organization, and private sector sources are included in the *Medicine Supply Map*. These data are enriched with information about risk drivers such as price and ingredients and cover 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 nearly 22,000 finished drug product, active pharmaceutical ingredient (API), and excipient manufacturing sites in 150 countries.

For example, during the winter of 2022-2023, with multiple respiratory viruses circulating, drug shortages have been experienced among certain antibacterial drug products. Previously, in the summer of 2022, USP's *Medicine Supply Map* found that antibacterial drug products are 42% more likely to be in shortage than the average drug product. Out of the 128 antibacterial drug products, 20 are currently in shortage (15.6% compared to 10.9% for all drug products). Insights garnered from *Medicine Supply Map* data also showed that of the types of antibacterial drugs, Cephalosporins are at elevated risk for shortage: 31% (9 of 29) Drug Products and 40% (6 of 15) APIs used for Cephalosporins are currently in shortage. Characterizing and quantifying risk drivers in this manner is a foundational step to help stakeholders transparently share risk and improve patient access. USP *Medicine Supply Map* analysis indicates that the economics for specific antibiotics are not attractive and improving them could improve their consistent availability. For example, certain antibiotics require a dedicated facility, which would increase the cost to manufacture. At the same time, USP *Medicine Supply Map* analysis shows low price is a significant risk driver for antimicrobial shortages.



To help ensure that U.S. government investments in biomanufacturing and biotechnology are targeted to where they can be most effective in fortifying the medicines supply chain, USP recommends that the NBBI support efforts and tools, such as the *Medicine Supply Map*, to understand the root causes of supply chain risk and assess the resiliency of drugs and medical products, which can complement ongoing federal government initiatives.

Medicines quality needs to be included in the focus areas of research and investments addressing medicines supply chain resilience.

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, and increase the risk of substandard and falsified medicines. As a result, USP standards, solutions and initiatives serve as critical tools supporting global medicines supply chain resilience, enabling consistency and uniformity in the production of safe, quality medicines from raw materials through packaging, distribution and delivery, building trust in medicine. USP has recently performed and published research demonstrating that the availability of public quality standards helps increase the number of medicines, in particular generics, on the US market.³ This, in turn, leads to less vulnerability, for example by reducing the dependence on only one or a few manufacturers of critical medicines. We look forward to sharing more information with OSTP on the way medicines quality impacts supply chain resilience and the significance of quality standards in that context.

At this juncture, there is a need to include medicines quality in domestic medicines supply chain situational assessment research and investments addressing supply chain vulnerabilities. For example, USP is currently undertaking research to assess the perception of risk along the global medicines supply chain among global experts. We are learning that supply chain stakeholders consistently underestimate the amount and impact of risks associated with the medicines supply chain and there is little awareness or understanding of the nature of the risk drivers. The completed data set will be used to articulate supply chain vulnerabilities and potential regulatory and public policy reforms, investments, and standards to help address them. USP recommends that OSTP take this data into account as the NBBI pursues efforts and investments to advance biotechnology and biomanufacturing towards innovative solutions in medicines supply chain resilience. We look forward to providing additional data and insights to OSTP as the research is being completed.

Biotechnology and Biomanufacturing Workforce

A skilled workforce that supports and furthers the implementation of advanced manufacturing technologies (AMT) is necessary to meet the needs of the pharmaceutical industry today and in the future.

Pharmaceutical continuous manufacturing (PCM) is one of the most promising advanced manufacturing technologies (AMT) because it enables continuous use of a production line that can yield significantly more product output. This type of AMT has the potential to improve manufacturing efficiency, reduce production costs, and significantly reduce environmental footprints. 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

³ USP. 2019. New study recognizes that public quality standards support U.S. generics market. Available at: <https://www.usp.org/news/study-public-quality-standards-support-generics-market>.



times and potentially in different locations. This process naturally requires many starts and stops in manufacturing.

Substantial challenges stand in the way of broader adoption of PCM. Significantly, pharmaceutical manufacturers may not have access to staff trained with the technical knowledge of the processes, capabilities, and constraints of PCM to enable them to develop new process analytical technologies and statistical tools while also hiring or retraining their workforce. Reducing technical and training barriers to adoption of advanced manufacturing technologies like PCM will help strengthen resilience by allowing medicines to be made in more places. USP is working with partners and stakeholders to address PCM knowledge gaps through educational programs; create an online continuous manufacturing Knowledge Center in collaboration with The National Institute for Pharmaceutical Technology and Education (NIPTE) and funded by FDA; and launch 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 ensure product quality.

In addition, not all pharmaceutical manufacturers have access to the expertise, resources, or capacity to develop and qualify new in-line, at-line, and off-line analytical methods required for the new manufacturing processes. USP has developed analytical lab service offerings to help fill the gaps in expertise, and assist manufacturers to further drive innovation, contain production costs, and optimize efficiencies in staffing and resources while facilitating market access to quality medicines made with PCM. These analytical lab services aim to support the efforts of drug manufacturers seeking to adopt advanced manufacturing technologies including PCM as one way to help increase geographic diversity in pharmaceutical manufacturing and support medicines supply chain resilience. USP's analytical lab services leverage USP scientific expertise and state-of-the-art facilities at the USP Advanced Manufacturing Technology Lab in Richmond, Virginia, as well as the USP headquarters facility in Rockville, Maryland.

Adhering to quality standards helps with the implementation of new technologies in the pharmaceutical sector.

USP uses a comprehensive approach to improve medicines quality that focuses on the development of official standards as well as other materials such as reference chemicals, scientific papers, guidances, toolkits and more. To maximize their impact, we provide comprehensive stakeholder engagement, including user training, educational offerings, and workshops, to help implement quality manufacturing. We believe this strategy is also best suited to strengthen and expand the biotechnology and biomanufacturing workforce and result in success for the NBBI.

Recognizing the need for public quality standards and appropriate testing methods to help ensure the quality of medicines made utilizing innovative technologies, USP has convened its Expert Bodies, including volunteer experts and Government Liaisons, and developed analytical laboratory infrastructure staff expertise, as well as training for workforce development. For example, since the successful application of a platform technology, such as mRNA, is relatively new, there are limited regulatory guidelines and industry standards to guide non-proprietary aspects of mRNA quality during development and manufacturing. These include areas such as verifying the identity of the drug substance, controlling impurities, and measuring content for dosing. Without a common set of methods for assessing quality across these dimensions of product development, researchers and manufacturers of mRNA products must develop their own in-house methods and protocols, which diverts their attention and resources, and reduces



regulatory predictability. This can delay approval/authorization of an mRNA-based product, slowing patient access to it.

To help address this need, USP is developing a set of analytical methods for mRNA quality to support developers, laboratories, manufacturers, and regulatory agencies worldwide. The goal is to create scientifically-validated tools on mRNA quality attributes overall, which aim to help accelerate product development, guide successful scale-up of manufacturing, and fuel confidence that manufacturers are employing best practices and appropriate quality controls when using this new modality. Ultimately, this will yield faster patient access.

USP recognizes that there is limited experience with AMTs across regulators, and limited guidance for industry, which leads to uncertainty among manufacturers seeking regulatory approval for products manufactured with AMTs. As such, USP is exploring where there is a need and opportunity to develop new AMT guidelines, best practices, and quality standards, in order to support regulatory review efficiency.

USP appreciates the opportunity to engage with OSTP and applauds the effort to coordinate a whole-of-government approach to advance biotechnology and biomanufacturing towards innovative solutions in health and medicines supply chain resilience. Again, thank you for the opportunity to comment on the National Biotechnology and Biomanufacturing Initiative RFI. For more information, please contact Amy B. Cadwallader, Ph.D., Director, Regulatory and Public Policy Development and USP Quality Institute, at (301) 692-3567 or Amy.Cadwallader@usp.org.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Jaap Venema', written in a cursive style.

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