

Advancing Regulatory and Pharmacopeial Convergence, Harmonization, and Global Cooperation to Improve Medicines Supply Chain Resiliency

White Paper



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. 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.

Since 1992, USP has been the implementing partner for six USAID-funded programs, including the current Promoting the Quality of Medicines Plus (PQM+) program as well as several predecessor programs. PQM+ is a six-year cooperative agreement with a ceiling of \$160 million that improves access to quality-assured priority medical products in low- and middle-income countries through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps to create resilient and sustainable local health systems.

Under the sponsorship of U.S. FDA, USP is designated an Asia-Pacific Economic Cooperation (APEC) Center of Excellence in global medical product quality and pharmaceutical supply chain security. USP is a non-state actor in official relations with the World Health Organization (WHO) and the Pan American Health Organization (PAHO), advising and promoting WHO and PAHO policies and strategies to advance public health globally. USP has signed memorandums of understanding with regulatory authorities and industry representatives in 17 countries across the world. We maintain relationships with drug manufacturers in nearly every country.

Issue

Currently there are opportunities to address regulatory variation across countries to enable more efficient and effective responses to supply chain vulnerabilities or failures. Many of the drivers of drug shortages are global in nature and there is rising recognition that increased international coordination between governments, pharmacopoeias, stakeholders, and national regulatory authorities (NRAs) could help to support the shared goal of advancing the safety and accessibility of critical medicines and public health. The U.S. Pharmacopeia (USP) recognizes that global coordination, harmonization, and convergence efforts among governments and other stakeholders can facilitate and streamline responses and solutions to build medicines supply chain resiliency and reliability.

Background

Varying regulations of individual governments associated with components of the pharmaceutical supply chain have resulted in a patchwork system that can result in inefficiencies, increased cost, and quality risks. Globally, differences in risk tolerance, benefit-risk frameworks, and approval criteria used by regulators contribute to the diverse landscape of regulatory strength. Additionally, resources, capabilities, and skills vary widely across regulators. While there is recognition among stakeholders of the benefits of harmonization and convergence and the efforts on the part of U.S. and international regulators, ongoing work is needed to keep making meaningful progress toward alignment.

Convergence, harmonization, and reliance are distinct, yet interconnected concepts:

- **Regulatory convergence** is a “voluntary process whereby the regulatory requirements across economies become more aligned over time as authorities adopt internally recognized technical guidance, standards, and scientific principles and common or similar practices and procedures.”¹ This can improve the productivity of the regulatory processes, streamline processes to accelerate the availability of critical medical products, and aid in management of workload and prioritization of resources,

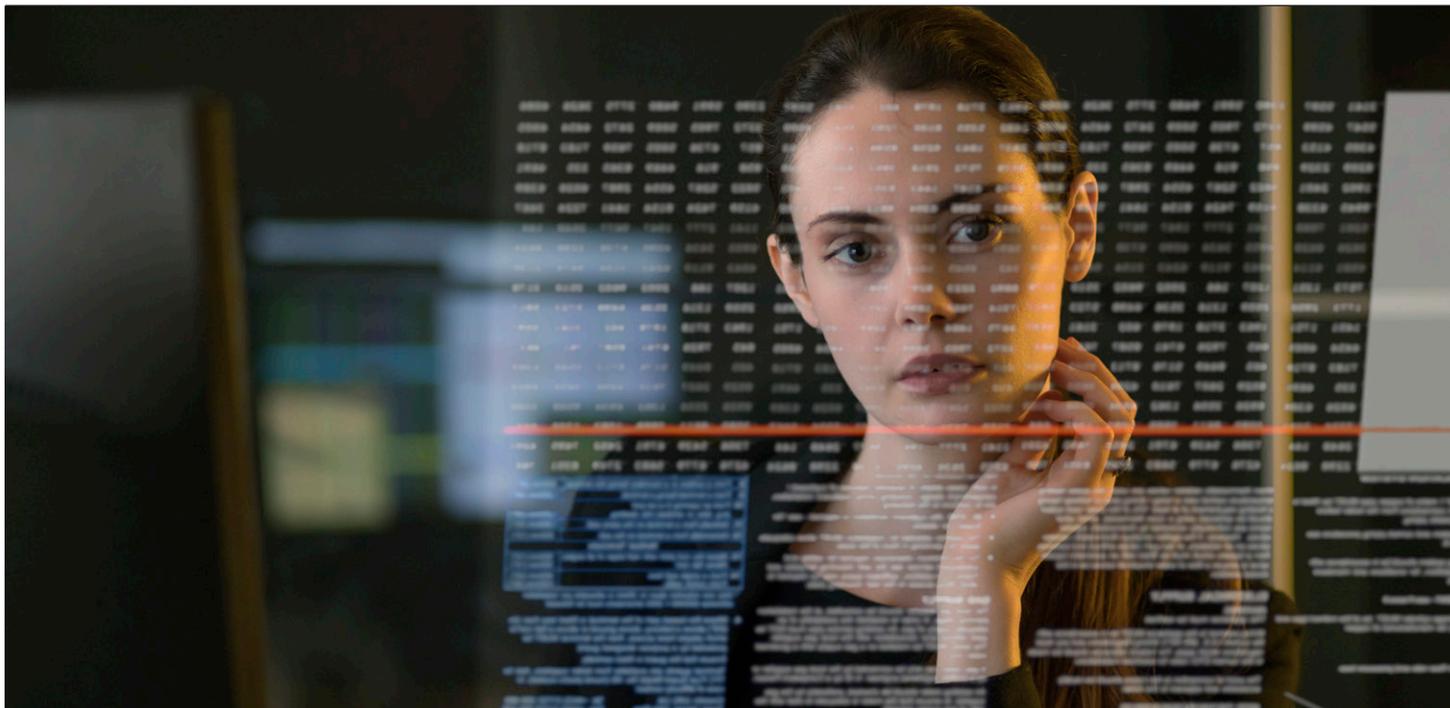
ultimately strengthening regulatory capacities across regulatory systems.

- **Regulatory reliance** is “the act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments (including inspections) performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible, and accountable regarding the decisions taken, even when it relied on the decisions and information of others.”² Reliance is generally supported by harmonized processes or standards but is not required.
- **Regulatory harmonization** is the process by which technical guidelines, processes, or standards are developed to be uniform across participating authorities; however, “the harmonization of laws and regulations is not a prerequisite for the alignment of technical requirements and greater regulatory cooperation.”³ Harmonization is often noted as the overarching goal of regulatory convergence, with harmonization efforts helping to create regulatory consistency and predictability but can be more challenging than convergence since harmonization agreements work within varying legal frameworks and health systems.

Benefits and Challenges of Convergence, Harmonization and Reliance Efforts

Convergence, harmonization, and reliance efforts can aid in the efficiency and predictability of the regulatory process, support equitable access to quality medicines, strengthen the capabilities of under-resourced or less experienced regulatory agencies, and help to establish best practices.^{4,5} Generally, alignment of priorities by NRAs and pharmacopoeias can help to foster a global regulatory landscape that supports agility and resilience of the supply chain by helping countries target resources, secure critical medicines, and help prevent the distribution of substandard or falsified products, this is especially crucial during public health emergencies or drug shortages.

In a 2019 report, the U.S. National Academies of Science, Engineering, and Medicine summarized the challenges



associated with an increasingly global medicines supply chain, the need for cooperation, and potential obstacles to achieving that mission:

“Rapid globalization of drug discovery, research and development, manufacturing, and delivery has significant implication for public health. The resources required to ensure comprehensive oversight of these activities is now an overwhelming task for even the well-resourced national medicines regulatory agencies...The ongoing evolution of the science and technology associated with drug discovery, research and development, manufacturing, and delivery (e.g., dramatic increases in more complex biological medicines and emerging use of cell and gene therapies) poses additional capacity challenges for regulatory agencies. These challenges underline the need for further cooperation and collaboration among agencies; however, achieving that cooperation is often challenging because individual agencies have different histories, legal frameworks, resources, and areas of expertise.”⁶

Additionally, variation between countries and regions in numerous areas of regulation exists and acts as an obstacle in manufacturers and other stakeholders’ ability to pivot

in response to supply chain vulnerabilities and failures, or to enable broader adoption of new technologies. For example, advanced manufacturing technologies such as pharmaceutical continuous manufacturing can facilitate efficiencies to help make more medicines in more places and reduce the over-reliance on sourcing from certain suppliers that can lead to supply chain disruptions. However, inconsistent, or non-existent regulatory pathways for the approval of these technologies may act as a deterrent for manufacturers to make investments in these technologies.

Use of Effective Tools and Approaches to Enhance Collaborative Efforts

In a global medicines supply chain and marketplace, collaboration, cooperation, and alignment are needed across governments and NRAs to help enable equitable access to safe, quality, essential medications, vaccines, and medical countermeasures. International collaboration and alignment of country- and region-level regulations should be ongoing, extend beyond the recent public health emergencies focus, and include building the necessary infrastructure have advocated for addressing these issues for several years.⁷

The trend toward regulatory convergence in the medical products sector has been building, and a number of programs and forums support regulatory convergence and

harmonization efforts, including the Asia-Pacific Economic Cooperation Life Science Innovation Forum (APEC-LSIF) Regulatory Harmonization Steering Committee (RHSC),^{vii} the International Council for Harmonisation (ICH),⁸ the International Pharmaceutical Regulators Programme (IPRP),⁹ and the Pan American Network for Drug Regulatory Harmonization (PANDRH),¹⁰ among others. The International Coalition of Medicines Regulatory Authorities (ICMRA) is comprised of health regulatory authorities from around the world and has called for continued cooperation among NRAs and supports regulatory reliance as a strategy - recognizing that each NRA will determine the degree to which reliance is suitable for their context and should follow overarching principles - to expediting access to quality medicines.¹¹ Aligning around strategic initiatives, ICMRA has developed resources on issues such as capacity building, pharmacovigilance, reliance, and supply chain integrity. Other groups, such as the Coalition for Epidemic Preparedness Innovations (CEPI), an international coalition of governments, academic, philanthropic, public, private, and intergovernmental institutions, recognize the need for coordination and participation of a vast array of international and intergovernmental stakeholders to successfully address vital public health needs. CEPI launched in 2017 with a primary focus on vaccine development, including rapid-response vaccine platforms and other biological countermeasures to support global pandemic readiness. Most recently, CEPI announced a partnership to support the development of monkeypox (mpox) vaccine candidates.¹²

These collaborative mechanisms to support movement toward convergence and harmonization play a critical role in strengthening regulatory systems globally. Capable regulatory health systems are critical for ensuring the safety and efficacy of medicines. In 2018, RHSC representatives proposed key performance indicators to measure the progress of regulatory convergence in the APEC region across four areas of best practice, allowing for a greater understanding of where progress has been made and where more efforts may be needed. APEC member countries were surveyed using the “Survey on APEC Regulatory Harmonization Key Performance Indicator” to collect this information; generally, the results showed a movement toward convergence in the region.¹³

Despite the potential value of convergence or harmonization efforts having been broadly recognized, interpretations and measurements of regulatory strengthening activities vary widely across the globe. The Global Benchmarking Tool (GBT) was introduced by the World Health Organization (WHO) to evaluate regulatory systems, bringing uniformity to the diverse landscape of regulatory strengthening.¹⁴ Rather than being subjected to myriad interpretations, the GBT provides regulatory bodies a common frame of reference. This ensures that every country, regardless of its internal perspectives, aligns with a global standard, ensuring consistent quality and safety measures worldwide. A standout feature of the GBT is its ability to measure incremental growth in regulatory capacities. By providing a consistent benchmark, it allows countries and regions to track their progress over time. This consistent measuring also promotes healthy competition, dialogue, and cooperation between countries to collectively move toward public health improvement.

Moreover, the experiences of the COVID-19 pandemic both highlighted the progress made toward convergence and the remaining and persistent gaps that hamper that ability of regulatory agencies and stakeholders to quickly adapt and adopt necessary changes in the interest of public health good. Although many countries were able to pivot and collaborate in the development, production, and distribution of vaccines, “a key challenge identified by the industry was the considerable heterogeneity of the global regulatory landscape and lack of convergence and harmonization in regulatory requirements with respect to evidence, review, and authorization processes.”¹⁵

As part of the global effort to quickly develop and distribute COVID-19 vaccines, the EMA launched a pilot initiative entitled OPEN to allow the participation of non-European Union (EU) regulators in the EMA assessment of COVID-19 vaccines and therapeutics under the terms of a confidentiality agreement. The OPEN initiative aimed to foster better understanding of regulatory outcomes, and these types of collaborative efforts bring additional scientific expertise and simplify expectations for manufacturers developing products. Key successes of the program include enhanced communication, facilitated assessment of similar

data by multiple authorities, reduction in duplication of work, accelerated COVID-19 medicines assessments outside the EU, and facilitated alignment and fewer labeling differences. While the OPEN pilot achieved its goal, potential improvements to the program include more explicit rules of engagement and enhanced communication and visibility of the OPEN framework.¹⁶

Proactively establishing agreements and approaches to enhance collaborative efforts, memorandums of understanding (MOUs), can help to facilitate an exchange of information and agreed upon actions to bolster convergence. Despite progress, variation between countries and regions in numerous regulatory areas exists and acts as an obstacle for the ability of manufacturers and other stakeholders to pivot in an efficient and effective manner in response to supply chain vulnerabilities and failures. USP urges the use of effective tools and approaches to enhance collaborative efforts among regulatory authorities, pharmacopoeias, and stakeholders and facilitate and streamline responses and solutions. Along with alignment of local and regional regulations with international standards, this can help to enhance medicines supply chain resilience and reliability.

Identification of Priority Areas for Health Authority Cooperation

Pharmacopoeial collaboration can support the resilience of the global supply chain by leveraging global expertise, underscoring the value of public standards, and facilitating global access to innovative technologies and products.¹⁷ However, broad harmonization across public standards-setting organizations is constrained by dependence on regulatory approvals and regulatory processes which vary across regulatory authorities. Various factors within the regulatory rules of individual countries, such as differences in the products approved, incongruent approval specifications, and the timing of regulatory or market approvals, can make harmonization across pharmacopoeias challenging.

The Pharmacopoeial Discussion Group (PDG) was formed by the USP along with the European Pharmacopoeia and the Japanese Pharmacopoeia in 1989 with the purpose of harmonizing select pharmacopoeia standards – monographs

and general chapters – in three major regions of the world. The World Health Organization has also participated in the PDG as an observer since 2001. PDG recently welcomed the Indian Pharmacopoeia Commission as a member in October 2023, facilitating the reach and enhancing impact of pharmacopoeial standards harmonization. In the context of PDG's work, "[a] pharmacopoeial general chapter or other pharmacopoeial document is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same result and the same accept/reject decision is reached." When full harmonization is not achievable, an approach referred to as "harmonization by attribute" in which some elements of a monograph or general chapter are harmonized but others are not, and a combination of approaches is needed.¹⁸ Implementation of harmonized standards vary depending on the legal and regulatory requirements in each of those regions, with a defined implementation period after the standard is published.

Related forums to advance convergence of standards through guidance, informal mechanisms, and bilateral agreements also function to support harmonization efforts. To that end, USP works with the European Pharmacopoeia through an informal mechanism on prospective harmonization on new active substance and medicinal product monographs for products still under patent and that have a strong impact on global public health. The initial program pilot resulted in four prospectively harmonized monographs for active substances, and later included 10 additional prospectively harmonized active substance monographs and 9 additional medicinal product monographs.¹⁹ USP also engages in close collaborations on a variety of technical topics with other global pharmacopoeias, including the Brazilian Pharmacopoeia, the British Pharmacopoeia, the Chinese Pharmacopoeia, the European Pharmacopoeia, the Indian Pharmacopoeia Commission, the Japanese Pharmacopoeia, and the Mexican Pharmacopoeia.

Furthermore, the WHO International Meetings of World Pharmacopoeias (IMWP) is a convening group for all national and regional pharmacopoeias that initially focused on providing high-level guidance on Good Pharmacopoeial Practices for the development of pharmacopoeial standards and has since produced outcomes such as the global



pharmacopeial alert system, which was activated during the COVID-19 pandemic and supported the development of an interactive dashboard listing mapping standards from various pharmacopeias for COVID-19 treatments.²⁰ These outcomes underscore the value of prioritizing efforts on standards that have a wide-ranging public health benefit and the need for alignment between pharmacopeias and regulatory bodies. For example, prioritizing harmonization on monographs on high-risk excipients commonly used in allergy, cold, and cough medicines where contaminants such as diethylene glycol (DEG) may appear could help to allow for a rapid response in the event of incidents of DEG contamination.

Continued attempts at regulatory harmonization and convergence in identified priority areas can ensure regulations and requirements are aligned and support the resilience of the medicines supply chain. USP recommends prioritizing key areas for alignment by health authorities and pharmacopeias. Such alignment will optimize impact, bolster preparedness, and address pressing public health concerns.

Broader International Cooperative Efforts are Needed to Strengthen Access to Medicines Globally

While general efforts continue by NRAs and pharmacopeias toward convergence and harmonization, there is currently no global agreement, infrastructure, or coordinating body to ensure that countries will work together to achieve

medicines supply chain resiliency, even in times of crises. When countries experience drug shortages resulting from supply chain breakdowns, they prioritize ensuring domestic medicines access. In situations where medicines supply chain disruptions impact multiple markets, like what was experienced during the height of the COVID-19 public health emergency, countries may compete with each other to secure alternative supply. In times of preparedness and recovery, there is no instrument to help identify countries with excess supply of certain medicines, including essential medicines, which could benefit countries experiencing shortfalls in supply.

During a special session convened in December of 2021, citing a “recognition of the catastrophic failure of the international community in showing solidarity and equity in response to the coronavirus disease (COVID-19) pandemic,” the World Health Assembly established an Intergovernmental Negotiating Body (INB) open to all Member States and Associate Members to draft and negotiate a WHO convention, agreement or other international instrument on pandemic prevention, preparedness and response. The “zero draft” of such agreement, considered by the INB and serving as the basis for negotiations at its fourth meeting in March 2023, calls for the establishment of the “WHO Global Pandemic Supply Chain and Logistics Network.” The draft WHO framework represents a significant effort with the aim of improving international medicines supply chain coordination. As this framework is considered, broad stakeholder engagement is needed to ensure that international



coordination in this space is not limited to pandemic-related products but includes building necessary infrastructure to strengthen the medicines supply chain and prevent and mitigate drug shortages globally.

Although progress has been made on convergence and harmonization with scientific principles, practices, and procedures becoming increasingly similar over time, industry stakeholders have identified that there is a need for more harmonization and convergence efforts to strengthen regulatory authorities, bolster regulatory capacity, and support the adoption of innovative products and technologies. These efforts should focus on the need for enhanced communication, information sharing, and

stakeholder engagement to help ensure there is common knowledge of gaps and challenges, and opportunities to improve existing paradigms. This will enable more efficient regulatory processes, improve the capacity of regulatory bodies, and bolster supply chain resilience around the world. As such, USP strongly urges for consistent and ongoing engagement between pharmacopoeias, regulators, specialized international health and economic agencies, and key public and private sector stakeholders. USP emphasizes the importance of periodic review and revision of regulations to align with internationally accepted standards, ensuring that the medicine supply chain remains adaptable to evolving global health challenges.

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