

USP Global Public Policy Position:

# Combating Substandard and Falsified Medicines

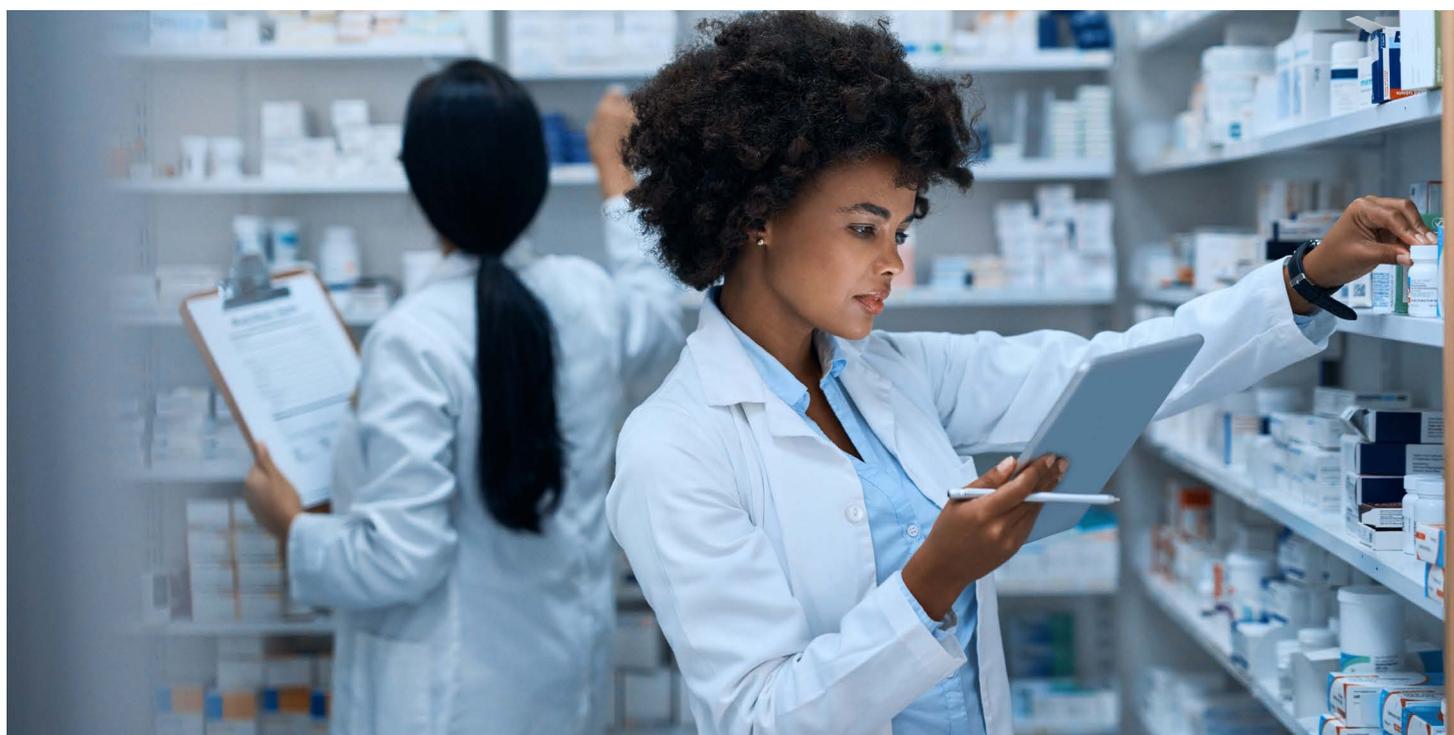


**ISSUE:** Substandard and falsified medicines pose a major threat to global health. Poor-quality medicines cause more than one million deaths per year,<sup>1</sup> reduce the effectiveness of authentic medical treatment, waste national resources, and contribute to antimicrobial resistance.<sup>2</sup> Global pandemics like COVID-19 can disrupt the supply of quality-assured medicines and lead to increased proliferation of substandard and falsified medicines.

USP supports comprehensive policies to combat substandard and falsified medicines, including the use of standards for medical product quality, building capabilities among global stakeholders to prevent and mitigate substandard and falsified medicines, and advocating for quality-assured medicines.

**USP supports policies and approaches that:**

- 1. Ensure medicines adhere to quality standards.** Public quality standards help ensure medicine identity, strength, quality, and purity, providing a benchmark against which to test medicines and assisting manufacturers in ensuring compliance with current good manufacturing practice (cGMP) requirements and applicable standards.
- 2. Build regulatory capability.** Regulators, manufacturers, and other stakeholders—especially in low-income countries—may benefit from additional resources as well as training, skills, and knowledge development to provide more stringent oversight for medical products, thereby securing a more resilient supply chain.
- 3. Strengthen surveillance systems and technologies.** Post-market surveillance provides information critical to detecting substandard and falsified medicines more efficiently. Innovations such as hand-held portable devices, blockchain, or track-and-trace systems can help link reporting in low- and middle-income countries (LMICs) to quality surveillance efforts.
- 4. Facilitate global cooperation.** Initiatives designed to build partnerships and increase transparency across national regulatory authorities and industry can be critical to securing global supply chains. Information sharing, work sharing, and mutual recognition agreements are essential tools that facilitate greater access to quality medicines.
- 5. Advance market incentives and investment.** Financial or other economic incentives for product innovation and quality, such as investing in quality manufacturing and advancing global procurement policies and practices, help ensure that everyone can access quality-assured medical products.



**6. Expand the existing evidence base.** Policymakers and regulators need more evidence on the scope, scale, and harm of substandard and falsified medicines.

Collaborating with academic and other research institutions can lead to evidence-based legislation, policies, and regulations that improve medical product quality assurance.

**7. Raise global awareness.** Global advocacy and outreach campaigns have the potential to inform and empower policymakers, healthcare practitioners, and patients about the risks of and effective responses to substandard and falsified medicines.

## I. What Are Substandard and Falsified Medical Products?

Substandard medical products are those that fail to meet quality standards or expectations—or both. By contrast, falsified medical products have been deliberately misrepresented in terms of their identity, composition, or source.<sup>3</sup> Whether substandard or falsified, poor-quality medical products can result from a variety of factors, including poor manufacturing practices as well as improper conditions during storage or distribution that result in degradation, and which can be either inadvertent or intentional. A substandard or falsified medical product may contain none of the active pharmaceutical ingredient (API), the wrong amount of it (too much or too little), or the wrong API. The product may contain incorrect, or incorrect amounts of, excipients (ingredients other than APIs found in a finished medicine), or unknown impurities.<sup>4</sup>

## II. Why Should We Be Concerned?

Access to quality medical products is critical for countries to meet their national public health goals. Substandard and falsified medical products may cause patient harm and fail to treat the diseases for which they were intended, leading to a loss of trust and confidence in medicines and healthcare systems.<sup>5</sup> Poor-quality medical products are found in every region of the world, affect all major therapeutic areas, and encompass a wide range of products such as medicines (including vaccines) and diagnostics.<sup>6</sup>

Substandard and falsified medicines can be less effective, or not effective at all, against the disease for which the patient is being treated. These products can also cause adverse effects that can lead to deaths and, in some cases, lead to the emergence and spread of antimicrobial resistance

(AMR).<sup>7,8</sup> Poor-quality medicines drive AMR primarily through subtherapeutic dosing. For example, when bacteria are exposed to sub-optimal levels of an API, weaker bacterial strains are eliminated but resistant ones are strengthened or give rise to new strains, potentially rendering the entire class of antibiotics ineffective.<sup>9</sup> Since AMR is not restrained by geographical boundaries, it can quickly become a problem across regions. For more information, read USP's global public policy position on [Combatting AMR](#).

Substandard and falsified medicines pose a threat to global health security and hinder the ability of strong and resilient public health systems to prevent, detect, and respond to infectious disease threats. Crises like the COVID-19 pandemic can expose supply chains to distorted market forces that subsequently result in product failure. E-commerce can also contribute to the spread of substandard and falsified medicines, as it makes it easier for patients to buy medical products from unauthorized sources.<sup>10</sup>

## Facts

### Scope and scale

- Nearly 1 in 10 medicines circulating in LMICs are substandard or falsified.<sup>11</sup>
- A systematic review and meta-analysis estimated that 12.4% of antibiotics and 19.1% of antimalarials in LMICs were substandard or falsified.<sup>12</sup>
- A study evaluating quality of cardiovascular drugs (e.g., anticoagulants, antihypertensives, and statins) in sub-Saharan Africa found that 16.3% of more than 1,500 samples randomly tested of cardiovascular failed the content analysis for APIs.<sup>13</sup>

### Health Impact

- Substandard and falsified medicines for tuberculosis and malaria contribute to 700,000 deaths per year globally.<sup>14</sup>
- In just one year, an estimated 122,000 children under the age of five from 39 sub-Saharan African countries lost their lives in association with consuming poor-quality antimalarials.<sup>15</sup>
- The U.S. Food and Drug Administration (U.S. FDA) has cited 81 deaths as a result of adulterated heparin—a blood thinner widely used to prevent clots—imported from China in 2007 and 2008.<sup>16</sup>
- In 2006, cough syrup distributed in Panama was found to contain diethylene glycol, an industrial solvent used in antifreeze; patients suffered from paralysis and other complications that led to 78 identified deaths.<sup>17</sup>



threatened by chronic vulnerabilities and acute disruptions. Vulnerabilities are the underlying weaknesses in the supply chain, which include but are not limited to geographically concentrated manufacturing and sourcing of materials, uneven regulatory environments, and constraints on regulatory enforcement or inspection capacity. Disruptions, meanwhile, can be event-based and include global health security concerns such as natural disasters, trade wars, and pandemics.

Global crises like COVID-19 create the possibility that some treatments will fail to reach patients due to unexpected surges in demand or limited supply caused by closed borders or restrictions on exports; these shortages also contribute to price increases. An unexpected and unmet rise in demand for medical products also can incentivize a market for substandard and falsified medicines.<sup>22</sup> Shortages of quality-assured medicines hinder treatment and create an environment where substandard and falsified medicines can flourish.<sup>23</sup>

Around the world, effective regulatory oversight remains uneven. While high-income countries tend to have stringent regulatory oversight, many LMICs still have under-resourced regulatory oversight, even as they face increasingly complex supply chains and procurement channels. As a consequence, these regulatory systems are not equipped adequately to provide quality assurance of medicines circulating in their countries. The World Health Organization (WHO) recently stated that fewer than one-third of the world's medicines regulatory authorities can perform the functions required to ensure that medicines, vaccines, and other medical products work as intended and do not harm patients.<sup>24</sup>

Furthermore, in the United States and around the world, patients and consumers have increasingly turned to online pharmacies which may offer reduced out-of-pocket costs or convenience, as well as increased access to medicines. According to some estimates, 96% of online prescription drug sellers are not in compliance with pharmacy laws and safety standards.<sup>25</sup> Lack of regulatory oversight over internet-based commerce puts consumers at risk of acquiring substandard or falsified medicines from unsecured supply chains.<sup>26</sup>

## IV. Solutions and Approaches

Around the world, governments, industry, and civil society, as well as USP and its stakeholders, are implementing programs to advance quality and combat substandard and falsified medicines. USP supports the following policies and

## Economics & Finance

- Substandard and falsified medicines cost LMICs approximately US \$30 billion a year.<sup>18</sup> For example, in Nigeria, substandard and falsified antimalarials accounted for nearly US\$30 million in direct costs annually, including close to US\$10 million in out-of-pocket costs to patients who sought care.<sup>19</sup>
- Falsified medicines have contributed to the loss of approximately 750,000 jobs in the United States and US\$200 billion in annual losses for U.S. companies.<sup>20</sup>

## III. The Situation

The complexity of the global pharmaceutical economy presents risks to the supply of quality-assured medical products and creates opportunities for substandard and falsified medicines to enter the market. More than 80% of medicines or their ingredients intended for the U.S. market come from outside of the country.<sup>21</sup> The globalization of the medicines supply chain has led to a fragmented web of ingredient suppliers, medicine manufacturers, packagers, and distributors.

While the global medicines supply chain enables broader patient access to medicines, the system is increasingly

approaches to combat substandard and falsified medicines.

## 1. Ensure medicines adhere to quality standards

Public quality standards set by pharmacopeias (USP and other pharmacopeias, including national, regional, and international ones), otherwise called pharmacopeial standards, should be applied across the entire supply chain. Pharmacopeial standards help ensure the quality of a medicine through its entire lifecycle, from manufacturing to transport, storage, distribution, and consumption. Public quality standards provide expectations and tests for identity, strength, quality, and purity of medicines, including:

- Quality of raw materials used to make the medicine
- Manufacture of the finished product
- General standards that ensure the proper dosage as well as control of impurities or toxins

Pharmacopeial standards serve as tools to help with compliance with certain cGMP and other regulatory requirements. Standards also help regulators and industry ensure continued access to quality medicines and monitor for substandard and falsified products. Many countries require manufacturers to comply with pharmacopeial standards to help protect patient safety and public health.

## 2. Build regulatory capability

Regulatory workforce training, national drug quality control laboratories, and industry compliance with international standards including cGMP can all help to build regulatory capabilities, especially in LMICs.

The WHO's "Prevent, Detect, and Respond" framework is the global cornerstone strategy to address substandard and falsified medical products.<sup>27</sup> Core elements include prevention (i.e., reducing manufacture of substandard and falsified products and improving supply chain integrity); detection (i.e., improving surveillance, effective investigation, and effective confirmation of suspect products); and response (i.e., increased notification, improved removal from the market, containment, and enforcement). This framework is flexible enough for countries to tailor actions based on their needs, capacity, and resources.

Additionally, the Promoting the Quality of Medicines Plus (PQM+) program, implemented by USP and funded by the U.S. Agency for International Development (USAID), works to improve country and regional regulatory systems to ensure the quality of medical products in the public and private



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sectors in LMICs. Strategies include improving sustainable systems for market authorization/registration, inspection, and licensing functions; supporting regional harmonization to strengthen medical product quality assurance regulatory capacity and networks; and supporting adoption of international data standards. The predecessor program to PQM+, or [PQM](#), launched many successful campaigns to help strengthen regulators' capacities. Some of those achievements included saving newborn lives through scaling up quality-assured chlorhexidine, implementing updated and internationally recognized standards for medicine testing in Bangladesh and Nigeria, and helping national quality control laboratories in Africa to strengthen their capacity for medicines quality testing.

Furthermore, USP collaborates with the U.S. FDA and the Asia-Pacific Economic Cooperation (APEC) Life Sciences Innovation Forum, a government and industry platform for 21 economies around the Pacific, to disseminate best practices, standards, and guidance for improving the quality and security of global pharmaceutical supply chains. The USP-APEC Center of Excellence has emphasized combining GMP and good distribution practices for all raw materials and finished drugs, as well as verifying materials, qualifying vendors, testing based on risk, and highlighting product quality as the responsibility of all players.<sup>28</sup>

Whenever possible, governments should continue to make investments to strengthen regulatory systems that can review applications for therapeutics and vaccines efficiently and enforce existing regulations that protect patient safety, or ramp up regulations where few exist, including adherence to quality standards. Regulators should strengthen these systems through investments in quality assurance via workforce training and national drug quality control laboratories.

### 3. Strengthen surveillance systems and technologies

Surveillance is a critical component of a strong quality assurance system and an essential component of the framework to prevent, detect, and respond to poor-quality medicines. In countries with stringent regulatory oversight, patients and consumers benefit from access to quality-assured medicines. However, many governments lack the resources or political will to monitor for substandard and falsified medicines.

In 2013, WHO launched the Global Surveillance and Monitoring System (GSMS) to encourage countries to report incidents of substandard and falsified medical products. The system provides technical support, links incidents between countries and regions, and issues product alerts. The GSMS also gathers evidence on the scope, scale, and harm caused by substandard and falsified medical products and identifies the vulnerabilities, weaknesses, and trends. It is critical to invest in efforts to strengthen surveillance, including risk-based market surveillance, product alerts, effective data sharing across systems, pharmacovigilance systems to track adverse events, tracking of the emergence of AMR, and good laboratories to test product quality.<sup>29</sup>

As part of its efforts to help build regulatory capabilities, the PQM+ program aims to sustainably strengthen medical product quality assurance systems and improve national and regional regulatory systems in LMICs. This includes strengthening sustainable post-marketing surveillance systems and medical product quality control laboratory capacity.

The global COVID-19 crisis has led many organizations to monitor and share information on substandard and falsified medical products. Most notably, WHO issues monthly [medical product alerts](#) on essential medicines and health products and has found falsified chloroquine circulating in several African countries.<sup>30</sup> The Infectious Diseases Data Observatory (IDDO) released a six-month [report](#) flagging growing medical product quality concerns around COVID-19.<sup>31</sup> The Center for Global Development also is engaged in [demand forecasting](#) for essential medical technologies at the clinic level.<sup>32</sup> Continued global monitoring of substandard and falsified medicines is needed to ensure that they do not fill the vacuum generated by the demand for essential products.

Investments in innovations for post-market surveillance, such as hand-held portable devices to monitor substandard and falsified medicines; blockchain technologies to make data more secure, transparent, and interoperable; or better

track-and-trace systems linking LMICs to quality surveillance efforts are needed to help prevent substandard and falsified medicines. Implementation of more transparent track-and-trace systems could enable manufacturers and regulators one day in the future to follow a dose from raw ingredients to finished medicine, to shipping container, to pharmacy shelf, and ultimately to the patient and then follow the clinical outcome of the medicine.

### 4. Facilitate global cooperation

Global cooperation is needed to prevent substandard and falsified medicines. Countries often are reluctant to share information on supply chain matters but doing so can be critical to ensuring the safety of their own supply chains. The WHO Member State Mechanism was established in 2012 for countries to convene, coordinate, decide, and organize actions to address substandard and falsified medical products.<sup>33</sup> Government regulators can work together and share resources to ensure that their citizens have timely access to safe, quality medicines. In 2020, the National Academies released a [report](#) with recommendations to promote information sharing among regulatory authorities to protect public health, ensuring faster access to critical medicines and encouraging innovation in medicine and technology.<sup>34</sup>

Countries can also enter into recognition or reliance arrangements, the process by which one agency relies upon another's work (e.g., inspection and scientific assessment reports) to inform its own regulatory decisions or recognizes the work of another regulator as equivalent to its own.<sup>35</sup>

**Regulatory authorities using recognition and reliance mechanisms have expedited the approval of essential vaccines and medicines, prevented the distribution of substandard and falsified medicines, and quickly mobilized resources during drug shortages and public health emergencies**

For example, in a mutual recognition agreement (MRA), one regulator may rely on and adopt another regulator's decisions about medical products—while retaining its decision-making responsibilities. Regulatory authorities using recognition and reliance mechanisms have expedited the approval of essential vaccines and medicines, prevented the distribution of substandard and falsified medicines, and quickly mobilized resources during drug shortages and public health emergencies.<sup>36</sup> Reliance mechanisms or regional regulatory systems can operate as networks to share information on quality, efficacy, and safety, thereby reinforcing regulatory oversight.

In the context of global health threats such as the COVID-19 pandemic, recognition and reliance mechanisms can help countries gain access to safe and effective treatments and vaccines. However, even with these agreements, regulators face barriers to detection of poor quality in the supply chain, as they may only be able to share heavily redacted reports with each other, and this reduces the utility and value of these information-sharing arrangements. Even with this information, regulators lack critical information from manufacturers, including adequate line-of-sight over raw materials and ingredients.<sup>37</sup>

## 5. Advance market incentives and investment

As countries improve their economic capacity, they may eventually receive little or no external funding and support from global medicines procurement programs. During this transition, these countries may struggle to maintain an adequate supply of quality-assured medicines as part of their own procurement processes. The WHO Prequalification (PQ) program helps Member States with assessing and assuring the safety, quality, and efficacy of medical products in some therapeutic areas.<sup>38</sup> Additionally, the WHO Model Quality Assurance System for Procurement Agencies (MQAS) guides Member States on the accreditation of suppliers and the purchasing, storage, distribution, and reassessment of pharmaceutical products.<sup>39</sup> Further, WHO's Regulatory Systems Strengthening (RSS) program helps Member States to identify strategies for regulatory reliance, convergence, harmonization, and work sharing to achieve long-term, sustainable oversight of medicines quality throughout the supply chain.

International donors have also come together to commit to accountability for the procurement of quality-assured medicine using public resources. To that end, USAID, the Gates Foundation, WHO, and several other United Nations agencies developed "Guiding Principles for Donors Regarding Quality Assurance of Essential Medicines and

Other Health Care Commodities."<sup>40</sup> This document outlines principles that donors should require of other countries, multi-laterals, and third-party procurers when they use donor funds to purchase essential medicines. These principles define "quality assurance," address gaps in current procurement channels, and can serve to inform both public and private procurers.

Governments and policymakers should also consider additional incentives to spur product innovation and quality, investment in continuous manufacturing, and facilitation of regulatory access to ensure the continued availability of quality medicines.

## 6. Expand the existing evidence base

Government policymakers and regulators need more data about the benefits of quality medicines to inform strategic decisions about where to allocate scarce public health resources and implement evidence-based quality assurance legislation, policies, and regulations. National regulatory authorities should take the lead in gathering this evidence, in collaboration with academic institutions as appropriate. The systematic and ongoing collection, analysis, and interpretation of data around substandard and falsified medicines, through post-market surveillance and other efforts, is critical.

Additional investment in global academic research can also add to the growing body of evidence on substandard and falsified medicines. For example, USP partners with leading academic institutions around the world through its [Quality Institute](#) to develop and disseminate research addressing evidence gaps around quality medicines. Other resources include a curated resource hub on substandard and falsified medicines launched by the advocacy campaign [Medicines We Can Trust](#)<sup>41</sup> and the [Medicine Quality Scientific Literature Surveyor](#), developed by The Infectious Diseases Data Observatory based at Oxford University, which provides summaries of published scientific reports on medicines quality.<sup>42</sup> In response to the urgent need for more transparency in the supply chain, USP created the USP Pharmaceutical Supply Chain Center. At the heart of it is the Medicine Supply Map,<sup>TM</sup> a data model that links across multiple data elements to derive insights on supply chain vulnerabilities for more than one million medicines.

Ongoing investment in data collection and interpretation at all levels—global, regional, and national—is needed to continue to support the evidence base on substandard and falsified medicines and empower national policymakers and regulators to use this evidence in their quality assurance and surveillance activities.

## 7. Raise global awareness

Over the past several years, the global health community has gained traction in advocacy and outreach on the issue of substandard and falsified medicines. Launched in 2018, the [Medicines We Can Trust](#) campaign is a global movement of more than 300 partners including civil society organizations, individual partners, government entities, and philanthropic foundations, working to raise awareness about the scope and impact of poor-quality medicines, inspire collective action, and mobilize policy change.<sup>43</sup>

In December 2019, more than 50 signatories representing diverse global health and research organizations released the Oxford Statement and call to action on global access to quality-assured medical products.<sup>44</sup> Signatories called for investment, policy change, and action to eliminate substandard and falsified medical products. Other efforts to build awareness include [Fight the Fakes](#), which encourages organizations and individuals around the world to help spread the word about the problem of counterfeit/falsified and substandard medicines.<sup>45</sup>

Continued advocacy in global health is needed to ensure that policymakers, regulators, clinicians, pharmacists, and patients are informed and empowered in the fight against substandard and falsified medicines.

## About USP

Founded in 1820, USP is an independent, nonprofit, science-based organization that safeguards the public's health globally by developing quality standards for medicines, dietary supplements, food ingredients, and healthcare quality. USP standards describe expectations and tests for identity, strength, quality, and purity; they assist industry in the development, manufacturing, and testing of medicines. USP standards have been used in more than 175 countries and are enforceable by the U.S. Food and Drug Administration (FDA) for medicines and their ingredients imported into or marketed in the United States. Standards in the USP compendia are developed by independent experts through a transparent and scientific process, with input from stakeholders and U.S. federal agencies such as FDA and the Centers for Disease Control and Prevention.

USP's Promoting the Quality of Medicines Plus (PQM+) program improves access to quality-assured priority medicines and addresses the proliferation of poor-quality medical products in low- and middle-income countries. PQM+ strengthens medical product quality assurance systems 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.

USP is implementing a comprehensive program to support the public health response to the COVID-19 pandemic. Our immediate work is focused on facilitating the supply of quality medicines across the global supply chain—especially for those medicines that treat symptoms associated with the virus—by working closely with regulators, manufacturers, and other stakeholders around the world. We are also engaging in middle- and long-term activities to assess vulnerabilities in the global supply chain for medicines, advocate for greater transparency and more diversity in the sources of medicines and their ingredients, and ultimately help build a more resilient supply chain.

**To learn more about USP's efforts to help prevent substandard and falsified medicines, please visit <https://www.usp.org/about/public-policy>.**



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