Statement of the U.S. Pharmacopeial Convention

Submitted to the House Committee on Energy and Commerce, Subcommittee on Health

For the Hearing on "Safeguarding Pharmaceutical Supply Chains in a Global Economy"

October 30, 2019

The United States Pharmacopeia (USP) is pleased to submit the following statement for the record on the hearing "Safeguarding Pharmaceutical Supply Chains in a Global Economy."

USP is an independent, non-profit organization founded in 1820 to help ensure the quality and consistency of medicines relied upon by Americans. USP's science-based quality standards are recognized in U.S. law as the official quality standards for medicines, dietary supplements, and food ingredients. Adherence to USP's quality standards for medicines is required for drugs marketed in the United States.

USP's mission is to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. With this in mind, we greatly appreciate the Committee's efforts to ensure that the medicines relied on by Americans are safe. To achieve our mission, USP convenes nearly 1000 scientific and healthcare experts who collaborate in a transparent process to develop publicly available, science-based standards that set the bar for the manufacturing and distribution of quality medicines. USP is governed by over 460 organizations from the scientific, healthcare practitioner, consumer, and industry communities along with dozens of government agencies, who together comprise the USP Convention. Our 1300 staff are based in the U.S. and around the world in locations where America's medicines and their ingredients are manufactured – including India and China. USP staff work with regulators, industry, health care practitioners, and other stakeholders to help ensure that our standards are utilized effectively to safeguard patients.

USP standards are not just used in the United States. In addition to having official status in the U.S., our standards are recognized in the laws of 40 other countries and are utilized in more than 140 countries.

Overview

Over the last decade, medicine manufacturing in the U.S. has become increasingly dependent on foreign sources for both finished drug products and their main ingredients, known as active pharmaceutical ingredients (APIs). According to the U.S. Food and Drug Administration (FDA), over 70 percent of all APIs are manufactured outside the United States, with almost a third of APIs manufactured in India or China. Over the past several years and more recently, numerous sources have identified concerns about the quality of APIs in medicines.

USP commends the Committee for its consideration of these concerns and the FDA for its commitment to addressing them. In this same spirit, USP is taking steps to ensure that the publicly available quality standards in the *United States*

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Pharmacopeia-National Formulary (*USP-NF*) – an official compendium of medicine quality standards – are accessible to industry and regulators. Furthermore, USP also works to ensure that stakeholders are fully trained to leverage the standards most effectively. While there are many components to the regulatory framework to safeguard medicine quality, publicly available quality standards and adherence to them remain foundational.

Over 5000 USP medicine quality standards to help keep patients safe

USP monographs for drugs and APIs are written documents that describe medicine quality requirements for the identity, strength, and purity of medicines. Manufacturers and regulators use USP's monographs when testing and monitoring the quality of APIs and finished drug products.

The key components of a monograph include identity tests, which help ensure that the drug or API is what it is supposed to be, as well as tests to measure potency, as reflected in FDA's approvals. For example, a monograph provides testing methods and acceptable ranges for the potency of a medicine, which indicates the amount of API present. Monographs also provide information about impurities that may be present in a medicine and the amounts of these substances that are permitted, along with testing methods to identify and measure them. This is important because levels that exceed these amounts may present patient safety concerns. Finally, monographs provide tests to predict and demonstrate how the medicine will be released as it enters the human body.

USP monographs are continually updated to reflect new drug approvals by FDA, advances in technology, and the latest safety data. *See* Attachment 1: An Overview of USP Monographs.

The *USP-NF* includes over 5,000 monographs for finished medicines (both chemical and biologic) as well as for APIs and excipients (the inactive ingredients in a medicine). Specifically, the *USP-NF* includes over 1500 API monographs, covering 50 therapeutic classes including oncology, cardiovascular, endocrine, infectious disease, and mental health drugs.

Education and training so industry and regulators can use standards optimally

To ensure that USP quality standards are effectively utilized by industry and by regulators, USP provides educational courses and trainings. The courses detail the use and application of quality standards. A wide range of technical topics are offered in classroom, laboratory, and online formats. More than 63,000 people worldwide have attended USP trainings since 2000, in courses provided in the U.S., India, China, Europe and other locations where medicines are manufactured. In addition, USP recently opened the *USP Education-Hyderabad Training Institute,* in Hyderabad, India to support manufacturers in building the capabilities necessary to manufacture quality medicines. Courses focus on quality control, quality assurance and research and development.

Working to ensure medicine quality across the global supply chain

While the focus of the Committee's hearing is on APIs, other vulnerabilities in the global medicine supply chain can also have a direct impact on patients in the U.S. To address this, the FDA, in collaboration with the 21 economies of the Asia Pacific Economic Cooperation (APEC), developed the APEC Supply Chain Security Toolkit,

which provides comprehensive guidance to help address these vulnerabilities. This toolkit contains recommended best practices and tools to prevent and detect substandard medical products before they reach the patient, and to respond and remove these products from the market.

USP was endorsed in 2017 by FDA and other regulators as an APEC Center of Excellence for "Medicine Quality Across the Supply Chain." In this role, USP disseminates the supply chain toolkit and provides education and training to manufacturers and regulators through the APEC Regulatory Harmonization Steering Committee, a government and industry platform for 21 economies around the Pacific. During the past 4 years, USP's APEC Center of Excellence has trained more than 600 regulator and industry participants across 4 continents and over 14 economies on best practices to secure the supply chain.

To expand use of USP quality standards: Announcing the *USP-NF Online* access initiative

Beginning in November 2019, USP will provide complimentary access to the new *USP-NF Online* platform for drug manufacturers that are not currently subscribed. In addition, we will be communicating with manufacturers who enroll in this program about USP training and education offerings that would expand their capabilities to ensure the quality of API and finished drug products.

Re-affirming our commitment to help address new medicine quality challenges

As we have done for 200 years, USP will continue to develop and train on adherence to standards, and to leverage our scientific expertise to help address new quality and patient safety challenges. For example, recent recalls have highlighted the presence of certain impurities in widely used medicines. Advancements in chemistry synthesis technologies makes it possible that a single drug's individual components can be synthesized using different methods, and a single drug can be manufactured using different processes. With each change to these methods and processes, impurities can change. Impurities tests and limits included in USP monographs represent those that are present in products when manufactured and held under the conditions reviewed, per FDA's approval. Changes to synthesis and manufacturing processes could introduce new impurities that monograph tests are not designed to detect. While USP monographs are not designed to detect the presence of all possible impurities, monographs can be updated to include new impurities in response to new methods and innovation.

In addition, in response to the recent recalls, USP is working on the development of long-term compendial solutions to address emerging challenges such as those represented by the nitrosamine impurities detected in some medications. To support regulators and industry, USP has initiated laboratory research to evaluate and develop testing methodologies for the analysis and monitoring for nitrosamine impurities broadly in the drug supply. Further, USP has initiated the development of Reference Standard (RS) materials for all six of the nitrosamine contaminants identified by FDA in angiotensin II receptor blockers (ARBs) and ranitidine. We are also working with partners to develop publicly available screening methods, tests, and materials suitable for industry and regulators to identify impurities of concern to help safeguard patient safety.

At the same time, USP is working to expand the adoption of advanced manufacturing technologies that will be critical for new medical product manufacturing technologies and improving drug quality for active pharmaceutic ingredients and finished drug products. USP is vigorously engaging with academic research centers, pharmaceutical manufactures, and regulators to drive the uptake of advanced manufacturing including pharmaceutical continuous manufacturing (PCM). To do this, USP is spearheading standardization efforts and the development of collaboration opportunities for many areas of PCM including ingredient characteristic standardization and control strategy standardization through the development of compendial documentary and physical reference standards.

Conclusion

We again thank the Committee for holding this hearing and drawing attention to these important patient safety and medicine quality concerns. USP looks forward to providing information and expertise and will work with Congress and stakeholders to advance our shared goal of helping to ensure the quality of the medicine supply for American patients.

Helping to Protect Patient Safety

An Overview of USP Monographs

The *United States Pharmacopeia–National Formulary (USP–NF)* includes over 5000 quality standards for medicines, both chemical and biologic; active pharmaceutical ingredients (APIs); and excipients (inactive ingredients). It is the most comprehensive source for medicine quality standards in the world. The standards in *USP–NF* are used to help ensure the quality of medicines and their ingredients, and to protect the safety of patients.

USP is an official quality standard for medicines marketed in the US. In addition, USP is utilized in over 140 countries worldwide and integrated into the laws of more than 40 countries.

USP–NF includes three types of quality standards for prescription medicines:

1. **Monographs** articulate the quality expectations for a medicine including its identity, strength, and purity. They also describe the tests to validate that a medicine and its ingredients meet these criteria.

2. **General Chapters** provide broadly applicable information to industry on accepted processes, tests and methods to support product development and manufacturing for innovative, generic, and biosimilar medicines.

3. **Material reference standards** are used in conjunction with monographs and general chapters to verify that a medicine and its ingredients can pass tests to ensure adherence to quality requirements.

The monograph development process

Development of a monograph generally begins a few years before an originator medicine loses patent protection. In most cases, the license holder for a medicine works collaboratively with the relevant USP Expert Committee to develop the monograph in a transparent process. The monograph may be revised as follow-on products (e.g., generics, biosimilars) are approved by FDA.

USP Expert Committees are comprised of scientific experts from academia, industry, and the healthcare practitioner community. Expert committee members are not compensated. They volunteer their time and work. FDA experts participate in each of the standard-setting expert committees as government liaisons.

Publication of a USP monograph

A USP monograph becomes publicly available after a medicine's patent protection expires and following completion of a transparent process that includes multiple opportunities for input from stakeholders.

Key components of a USP monograph

A monograph is a written document that reflects the quality attributes of medicines approved by the U.S. Food and Drug Administration (US FDA). **Some of these attributes include:**

Identity—Tests to identify that a particular substance is the medicine that it claims to be.

Strength—Testing methods and acceptable ranges for the potency of a medicine, as reflected in FDA's approvals. For example, this indicates the amount of API in a medicine.

Purity—Information on impurities that may be present in a medicine and the amounts of these that are permitted, along with testing methods to identify and measure them. An impurity is any component in the API or finished dosage form which is not the desired product or other formulation components. Levels that exceed may present patient safety concerns.

Performance—Laboratory tests to predict and demonstrate how a medicine will be released as it enters the human body.

Monographs articulate quality expectations. Compliance with a monograph does not demonstrate biosimilarity or interchangeability, nor is it a license to market a medicine. Approval, biosimilarity, and interchangeability are determined by the US FDA.

Revision of a USP monograph

USP monographs are continually updated to reflect the following:

- **New FDA approvals.** Monographs are updated when FDA approves medicines with new or different quality specifications than those expressed in an existing monograph.

  For example, if FDA approves a second generic or biosimilar version of a medicine with an impurity profile that differs from that of the first approved generic or biosimilar, the USP monograph would be revised to also integrate the quality specifications approved by FDA for the second generic or biosimilar. The same revision process would be undertaken for any additional FDA approvals of that medicine. In this way, monographs evolve as FDA approves new medicines. They are a publicly available articulation of the quality expectations of medicines approved by FDA.

  Through the USP Pending Monograph Program (PMP), monographs are updated rapidly prior to FDA approval. Through the PMP, USP works with the sponsor of a medicine under FDA review for approval, so that the monograph reflects the medicine's quality specifications as soon as it receives market approval from FDA. Monographs revised through the PMP process become publicly available as soon as FDA approves a medicine.

- **Changes requested by FDA or others based on safety data.** A monograph may be revised to reflect new data or science, subsequent to FDA product approval or monograph publication.

- **Advances in technology.** Monographs are revised to reflect new testing and manufacturing technologies.

Monograph revisions can be requested by any stakeholder including industry and FDA.

Monographs are utilized to help ensure patient safety

USP's publicly available monographs are used by regulators, public health authorities, and others to confirm that the medicines provided to patients meet quality expectations for safety and effectiveness.

Monographs help secure the global drug supply chain

USP's monographs are used by customs and border officials and public health and law enforcement authorities to confirm the quality of medicines and their ingredients from overseas sources. Medicine manufacturers use USP's monographs for APIs and excipients to test the quality of drug ingredients from suppliers, including ingredients produced overseas.

Monographs accelerate product development, competition, and patient access

Because USP's publicly available monographs articulate the regulatory expectations for quality, they accelerate product development and provide more regulatory predictability. As a result, monographs support competition, which generally reduces prices and expands patient access.

About USP

Founded in 1820, USP is an independent, scientific non-profit organization, committed to advancing public health and patient safety through standards and related programs that help to ensure the quality of medicines, dietary supplements and foods. USP standards are established by over 800 expert volunteers from academia, industry, and the healthcare practitioner community. We are governed by a Convention of over 460 organizations representing the healthcare community. Our staff of over 1000 scientists and dedicated professionals help to advance our mission for the people of the United States and from around the world.