

USP principles

for a robust and trusted
pharmacopeia



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Introduction and background

The United States Pharmacopeia (USP) has been an independent standards-setting organization serving public health needs since it was founded in 1820. Over the two centuries that followed, USP evolved to meet the changing priorities of public health while adapting to scientific and technological innovations and advances in healthcare. Today, USP and other robust pharmacopeias provide a multitude of scientifically rigorous, publicly available standards that secure public trust in the quality of medicines and medical products.

USP develops quality standards through *independent committees of scientific experts* who work with regulators, industry partners, and other stakeholders to establish scientifically rigorous, transparent, and publicly available *documentary standards* (general chapters and monographs) and *physical reference standards* (vials of pure drug ingredients). Taken together, documentary and physical standards articulate the quality expectations for medicine, along with analytical methods and physical specimens to help ensure that a product meets quality expectations. USP also works closely with other national pharmacopeias for global pharmacopeial *coordination* efforts. USP's unbiased, science-based approach to standards-setting is one of the key reasons USP is viewed as one of the most credible sources of public quality standards for medicines.

This paper will discuss the traditional and emerging roles of pharmacopeias and share USP's principles for building and maintaining a robust and trusted pharmacopeia.

Role and functions of a pharmacopeia

Safe and effective medicines, consistently manufactured according to established quality standards, are essential to preventing disease, treating illness, and saving lives.

Pharmacopeias institute public quality standards that provide benchmarks to ensure that specific medical products have the quality attributes required by regulatory agencies. USP and some other pharmacopeias also provide quality standards that guide quality assurance across multiple aspects of a medicine's lifecycle, including development, manufacturing, storage, distribution, preparation, administration, and use. Pharmacopeial quality standards include *documentary standards* such as monographs or general chapters, which articulate the parameters that indicate whether a finished dosage form or key process across the medicine's life cycle meet critical quality criteria; and *physical reference standards*, which usually consist of highly characterized substances against which manufacturers and others can test a product to ensure quality compliance. In addition to establishing documentary and physical reference standards, USP and some other pharmacopeias create tools and resources broadly applicable to multiple classes of medical products and seek innovative approaches to quality standards to support medicines' lifecycle beyond quality control.



pharmacopeia *noun*
or pharm•ma•co•pe•ia [fahr-muh-kuh-pee-uh]

One word, two meanings

The term "pharmacopeia" can represent both a **compendium of quality standards** for medicines and their ingredients, and **the organization and people** who establish those standards.

A compendium of quality standards: This official collection of information is publicly available, shared, and used by parties engaged in work that involves the quality of medicines. These parties include medicine manufacturers, analytical laboratories, raw material suppliers, policy makers, regulatory agencies, healthcare practitioners, and others. Traditionally, a pharmacopeial compendium was written as a printed volume. Today, many are available online, improving access and enhancing stakeholders' ability to benefit from the full range of standards, best practices, and guidance provided.

The organization and people: Experts in science, medicine, healthcare practice, law, and public policy collaborate to establish quality standards for medicines. The official *U.S. Pharmacopeia–National Formulary (USP–NF)* compendia could not exist without their expertise and participation.



Today's pharmacopeias describe the quality attributes of drug products and their ingredients. These descriptions, presented as monographs, help establish the medication's identity, strength, purity, performance, and other characteristics.

Protecting the global supply of quality medicines

Modern medicines are manufactured using ingredients and materials procured from global supply chains and distributed in global marketplaces. These commodities include active pharmaceutical ingredients (APIs), excipients,¹ raw materials, packaging materials, and finished dosage forms. As a result, before a medicine ever reaches a patient, manufacturers, suppliers, and distributors of all ingredients, materials, and their finished dosage forms may have made, stored, and handled these products in various locations around the world.

The globalization of the supply chain has improved access to ingredients, materials, and finished dosage forms. However, this increasingly complex and evolving network has also created challenges for regulators as they try to ensure that the ingredients and finished dosage forms are acceptable and consistent in quality. A significant challenge lies in the fact that supply chains for medicines are often fragmented, crossing numerous national borders where regulatory frameworks and resources may be uneven. Particularly in these circumstances, pharmacopeial quality standards have been essential to help ensure the supply of quality medicines.

Public quality standards provide benchmarks for drug identity, purity, potency, and consistency from the time that raw materials are procured through the manufacturing, packaging, storage, distribution and finally, administration of the medicine to a patient. For example, pharmacopeias provide resources for the industry for the development,

manufacturing, and analytical testing of quality medicines, thereby fostering fertile developmental environments and compliance with regulations. Some pharmacopeias, including USP, also provide standards to help ensure proper storage and handling of medicines by healthcare providers and patients.

Today's world features rapid progress in science and technology for medicines, new therapeutic modalities, and advanced healthcare practices, all of which increase the complexity of modern medicines. In this landscape, adherence to public quality standards is vital to building and maintaining trust in the quality of medicines.

A brief history: from *De Materia Medica* to the modern pharmacopeia

A pharmacopeia (also spelled *pharmacopoeia*, translated from Greek as "drug-making" or "to make a drug") is a collection of legally binding standards, in most cases prepared by a national or regional authority. An antecedent to current pharmacopeias, *De Materia Medica* (translated as "on medicinal materials" from Latin), included the names of and preparation methods for herbal remedies commonly used in ancient Greece and Rome.² Since that time, more than 40 pharmacopeias have been established worldwide.

The earliest pharmacopeias were essentially books of recipes for medicines in the form of tinctures, extracts, and other formulations that were often based on botanical ingredients. These recipes were gathered and published in a pharmacopeia to bring consistency to the methods used for preparing medicinal treatments. Today's pharmacopeias describe the quality attributes of drug products and their ingredients. These descriptions, presented as monographs, help establish the medication's identity, strength, purity, performance, and other characteristics.

National and regional pharmacopeias operate within their respective jurisdictions; however, pharmacopeial standards may acquire legal status beyond their jurisdictions for enforcement, depending on applicable national and regional statutes. In the U.S., enforcement of pharmacopeial standards is done by regulatory authorities at the federal and state level. Around the world, various approaches exist for the enforcement of pharmacopeial standards.

¹ Excipients serve many purposes, such as improving the absorption and bioavailability of the API. Excipients are not intended to have a therapeutic effect; however, they are not necessarily inactive. Worldwide, the regulation of excipients varies by country and region.

² International Meeting of World Pharmacopoeias. 2012. Review of World Pharmacopoeias. Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/resources/InternationalMeetingWorldPharmacopoeias_QAS13-512Rev1_25032013.pdf?ua=1

Seven Principles of a Robust and Trusted Pharmacopeia

USP embraces the following seven key principles for building and maintaining a robust and trusted pharmacopeia:

- 1. Scientific:** Makes scientific, evidence-based decisions
- 2. Dynamic:** Balances advancement with capacity and demand
- 3. Informative:** Educates and informs its users and stakeholders
- 4. Inclusive:** Seeks public input and stakeholder comments
- 5. Transparent:** Adheres to a clearly defined and open public process
- 6. Impartial:** Is free from bias and inappropriate influence
- 7. Responsive:** Anticipates and addresses stakeholder and public health needs

1. Scientific: Makes scientific, evidence based decisions

A fundamental function of pharmacopeia is to standardize scientific test methods and other requirements to safeguard the quality of medicines. Public quality standards and the processes for developing them should be grounded in rigorous, current scientific knowledge based on widely-accepted evidence and informed by experts with extensive subject matter expertise.

Pharmacopeias often rely on industry sharing or “donating” their analytical procedures; specifications for ingredients, excipients, and final dosage forms; and candidates for reference standards to accompany the documentary standards. Experts representing relevant scientific disciplines then evaluate the donated data and information and, along with stakeholder input and public comments, to establish documentary and physical reference standards. The best practice is for multiple independent laboratories to validate the results. During this process, the experts’ decisions are informed by science and public health priorities. In the absence of donated data and information, additional scientific experiments are conducted. This approach is also taken to help validate the donors’ methods and specifications as approved by regulatory agencies. Regardless of the approach, public quality standards must be scientifically tested, evidence-based and consistent with the best scientific knowledge available.

2. Dynamic: Balances advancement with capacity and demand

A dynamic pharmacopeia incorporates scientific and technological advancements while balancing the capacity and readiness of industry to broadly integrate technological advances in quality assurance.

Advances in science enhance and bolster our understanding of diseases and introduce innovative molecules and modalities to treat them. At the same time, digital connectivity can leverage scientific data to identify patient safety risks and rapidly incorporate new safety information into public quality standards. As more biomedical innovations are approved by regulators, new generations of pharmacopeial standards have emerged to embrace the increasingly diverse types of medical products. Likewise, evaluation methods have evolved from simple, qualitative descriptions of formulations to quantitative techniques that confirm a product’s identity and purity, determine the strength of the API(s), and evaluate product performance and other characteristics.

3. Informative: Educates and informs its users and stakeholders

A robust and trusted pharmacopeia provides industry, medical practitioners, and regulatory stakeholders with information and tools along with education and training opportunities. As standards are created and revised, it is important for a pharmacopeia to guide and support stakeholders’ adoption of those standards. Because positive public health impact comes from the actual application of the standards.

Interactive workshops and trainings allow the pharmacopeia to engage directly with stakeholders and foster scientific discussion to inform revisions of current standards or form new standards. Through these engagements, the stakeholders who use and refer to the pharmacopeia are better equipped to apply standards. The education and training materials evolve and expand continually with updates adapting content to cultural, geographic, and linguistic differences. By offering a wide range of education and training options on various platforms, the pharmacopeia provides critical information to all stakeholders who rely on public standards to protect public health.

4. Inclusive: Seeks public input and stakeholder comments

A robust pharmacopeia includes stakeholders in the process of developing its public quality standards. Inclusive and effective collaboration with all stakeholders is essential to ensure that the final, official standards will be relevant and up-to-date. The inclusive approach engenders trust in the pharmacopeia, which is critical to acceptance and use of the standards as well as future stakeholder engagement. The interactions with stakeholders can also lead to new areas of standard development, nurturing the development of new therapeutics and reaching beyond the traditional functions of public quality standards.

A robust and trusted pharmacopeia gathers public input through diverse and flexible communication channels such as meetings, workshops, and open forums. These channels also serve as opportunities for the pharmacopeia to communicate updates on standards-setting processes and decisions and engage the public for their input. After carefully collecting feedback and input from the public and stakeholders, these comments are discussed and considered by the pharmacopeia's body of scientific experts to update standards and relevant policies.

The practice of engaging experts and other stakeholders in standards development is crucial for preserving public trust in medicines. Developing standards together with key stakeholders, including academia, professional associations, regulatory bodies, and industry representatives, promotes alignment and identifies appropriate use of the standard.

5. Transparent: Adheres to a clearly defined and open public process

A transparent and well-defined public process for developing standards underlies the integrity and credibility of a pharmacopeia. This transparency applies to developing and revising the pharmacopeia's standards as well as the overall processes, principles, and rules for establishing these publicly available standards. Transparency is also important in how the pharmacopeia recruits and selects the scientific experts who develop the standards, and the recruiting policies and procedures should be publicly available. Finally, the pharmacopeia's commitment to transparency ensures that the public and stakeholders receive clear information on how the scientific experts and the pharmacopeia consider their inputs, regardless of whether their inputs are reflected in the final reports and published standards.³

6. Impartial: Is free from bias and inappropriate influence

A robust and trusted pharmacopeia maintains its impartiality at all times. Pharmacopeias often rely on donations of data and materials from industry partners, who are users of pharmacopeial quality standards themselves. Therefore, donations have the potential to create bias or the perception of bias in the standards-setting process. To overcome this, conflicts of interest must be managed, including having committee members that are reviewing standards must declare whether they have an interest (e.g., an employment or economic interest) in the manufacturer(s) of medicine for which a standard is being developed. Moreover, a review by multiple non-conflicted experts is critical to maintaining trust in each standard.

Under USP's Code of Ethics rules, 'Conflict of Interest' includes, but is not limited to, "any matter in which an expert has a direct or indirect financial interest or any other personal interest of any kind which would preclude or appear to preclude such individual from exercising impartial judgment or otherwise acting in the best interest of USP." The experts who disclose a conflict of interest are then required to recuse themselves from participation in voting on any matter in which they have a conflict of interest.

According to clear rules and policies, the members of USP expert committees participate independently as individual scientific experts rather than as agents or representatives of an organization or employer. This independence of the pharmacopeia's experts is critical in keeping the standards-setting process impartial and securing public trust in the pharmacopeia.

7. Responsive: Anticipates and addresses stakeholder and public health needs

When a pharmacopeia builds and maintains standards with the principles stated above, it is in a strong position to anticipate, identify, and address medicine quality issues that may arise suddenly or develop over time. In many cases, a robust and trusted pharmacopeia has worked with various stakeholders to respond to various public health crises. For example, a pharmacopeia may collaborate with regulators to detect mislabeled or substandard medicines and identify adulterated products that have caused patient harm (e.g., products contaminated with diethylene glycol). The pharmacopeia may collaborate with industry partners to address impurities such as nitrosamines in medical products.

It may also join forces with healthcare providers to respond to shortages of essential medicines and other medical products, such as hand sanitizers during the COVID-19 pandemic. Through its volunteer networks of scientific experts and stakeholders worldwide, USP stands as a robust pharmacopeia positioned to anticipate challenges and needs, thereby securing the supply of quality medicines and maintaining public trust.

Conclusion

The seven principles described above are the elements USP considers essential in building and maintaining a robust and trusted pharmacopeia. These principles provide a framework to govern a core function of pharmacopeias: establishing public quality standards to foster trust in medicines. Standards should be developed through scientifically vetted, unbiased, and transparent processes. Dynamic approaches in standards development enhance the responsiveness of the pharmacopeia to better address changes and challenges in the healthcare system. By working collaboratively and inclusively, robust and trusted pharmacopeias are able to develop standards and resources that are up to date and informative, and appropriate for meeting stakeholder needs. Following these principles, USP has evolved and adapted to

advances in science and medicine as well as the increasing complexity of the global supply chain. With these solid foundations and expertise, USP continues to serve as a steady partner to governments and industry, working across healthcare systems to help protect patients' well-being in the U.S. and around the world.

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 the industry in developing, manufacturing, and testing medicines. USP standards have been used in more than 175 countries, and they 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 the Food and Drug Administration and the Centers for Disease Control and Prevention.



³ USP has recognized opportunities to improve its efforts toward transparency regarding standards development and how public input is considered and implemented throughout the process. USP is continuously looking for new ways to define and foster the appropriate degree of public engagement before standards are published.