
Integrating Environmental Considerations Into
Quality Standards To Create A More Sustainable World

Executive Summary

U.S. Pharmacopeia (USP) standards help reduce the environmental impact of pharmaceutical manufacturing by supporting adoption of innovative analytical methods and technologies that rely on fewer resources and/or more eco-friendly alternatives for the quality testing of medicines.

Key achievements demonstrate significant progress: a 96% reduction in *United States Pharmacopeia–National Formulary (USP–NF)* (1) monographs using carbon tetrachloride (an ozone-depleting, hepatotoxic solvent) and an 83% reduction in monographs using benzene (a known carcinogen), along with decreased use of other hazardous substances including hydrogen sulfide, chloroform, fluorinated solvents, and mercuric acetate.

Moreover, USP continues to reduce reliance on animal testing by expanding animal-free testing methods to support biodiversity and minimize environmental impact. Through collaborations with other pharmacopeias, USP advances harmonized standards with environmental benefits worldwide. USP now offers resources to support advanced manufacturing technologies that can help reduce waste and resource usage in drug production. Moving forward, USP will continue collaborating with stakeholders to explore how standards and solutions can foster a healthier, more sustainable world. For a video overview, *click here*.

Introduction

USP has a longstanding commitment to social responsibility that is reflected in its mission to improve global health through quality standards. For over 200 years, USP standards have helped ensure availability of trusted, quality-assured medicines. Over the past 30 years, this commitment has expanded to include advancing standards and programs that support more environmentally sustainable quality testing practices and technologies throughout the drug product lifecycle, helping to mitigate climate change impacts and related health risks. Building on USP's progress in developing eco-friendly standards and programs, as outlined in this report, we recognize more work remains to be done.

An opportunity exists to utilize existing progress, further advancements, and innovation, and establish a more formal, structured, measurable approach to reduce environmental impact and promote sustainable practices throughout the drug product lifecycle. USP's call to action is for stakeholders across the healthcare landscape—including USP Expert Volunteers and Convention Members, manufacturers, governments, regulators, international pharmacopeias, academics, healthcare practitioners, patient group representatives and others—to engage and strengthen their collaboration in advancing quality standards and related practices that support environmental sustainability.

For over three decades, USP has worked with stakeholders across the healthcare ecosystem to advance sustainable quality testing and related industry practices that can help protect the environment. Such progress has been made possible in part through USP's development of standards—such as product-specific *USP–NF* monographs and *USP–NF* method-guidance general chapters—that can have a positive impact across the medicines supply chain when implemented and amplified through their use at thousands of facilities around the world.

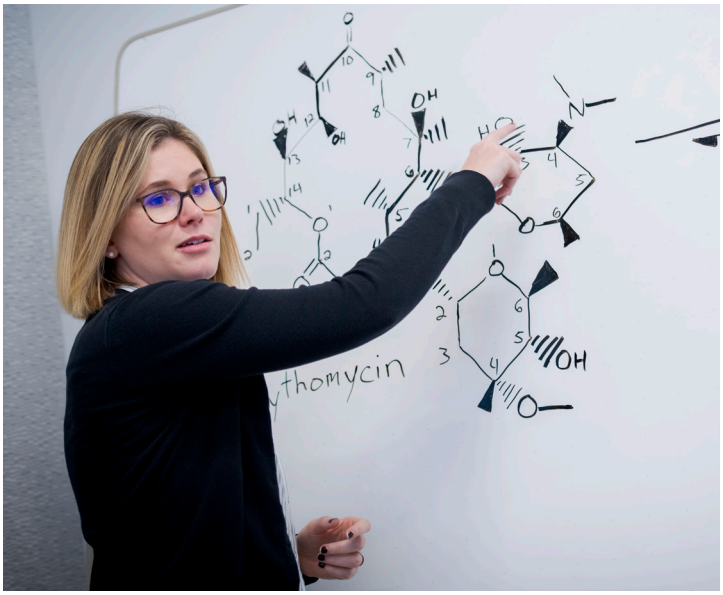
In fact, USP standards are used in 22,000+ locations in 150+ countries by global manufacturers, suppliers, distributors, pharmacies, healthcare providers and others, thus amplifying the environmental benefits of improved pharmacopeial standards. These improvements can help support environmental stewardship goals and address sustainability challenges of individual pharmaceutical companies. In aggregate, a 2019 study showed the environmental impact of drug makers to be higher than that of the automobile industry when measured in terms of CO^2 emissions relative to revenue (emissions intensity). (2)

Toxic and hazardous substances

Development of new and modernized USP standards has reduced the use of toxic and hazardous solvents, reagents, and other substances used in pharmaceutical production and quality testing, including carbon tetrachloride, benzene, hydrogen sulfide, chloroform, fluorinated solvents, mercuric acetate, and many others. By supporting alternative approaches to reduce or eliminate the use or generation of such hazardous substances in chemical processes—approaches sometimes referred to more broadly as green chemistry (3) or sustainable chemistry—USP has facilitated more eco-friendly production and/or quality testing of drugs and pharmaceutical excipients. These include the antibiotic amoxicillin, diabetes treatment metformin, decongestant phenylephrine, and blood pressure medicine metoprolol, as well as excipients like carbomers.

Key examples of specific USP actions and impacts over the last 30 years that have eliminated, reduced, and/or provided substitutes for hazardous and toxic substances used in pharmaceutical quality testing, production, and distribution—and/or supported resource conservation—include:

- **Carbon tetrachloride:** USP decreased by 96% the use of the ozone-depleting and hepatotoxic solvent in *USP–NF* monographs. The number of monographs using carbon tetrachloride was reduced from over 100 to just four. Reduced use was facilitated by General Chapter <467> *Residual Solvents/Organic Volatile Impurities*, which classified carbon tetrachloride as a Class 1 solvent to avoid in pharmaceutical production, setting a strict product concentration limit of four parts per million. The chapter also classifies other solvents by risk level, describing related control strategies, limits, and analytical methods.
- **Benzene:** USP reduced by 83% the use of the solvent—a known carcinogen—for quality testing in *USP–NF* monographs. General Chapter <467> classified the chemical as a Class 1 solvent to be avoided, setting a strict product concentration limit of two parts per million. Notably, it is anticipated that in 2026 all *USP–NF* monographs for excipient carbomers synthesized with benzene will be omitted from the compendium, keeping only monographs for carbomers prepared with alternative solvents.
- **Hydrogen sulfide:** USP curtailed by more than 50% utilization of the flammable, poisonous gas as a chemical reagent in *USP–NF* monographs. By 2018, a heavy metals testing requirement relying on hydrogen sulfide was eliminated from *USP–NF* monographs and related General Chapter <231> *Heavy Metals* was dropped from the *USP–NF* entirely with the advent of more modern quality testing methods.
- **Plastic packaging:** USP developed standards (e.g., *USP–NF* General Chapters <661>, <661.1>, <661.2>, <1663> and <1664>) as well as analytical reference materials that address the potential for substances to leach out of some plastic packaging products over time, including toxic and carcinogenic substances that can harm the environment, medicine quality, and human health. Meanwhile, USP is exploring how best to support expanded use of recycled plastic and biodegradable packaging materials. USP is also developing a standard for metal-based packaging materials to further support adoption of sustainable packaging alternatives.
- **Smaller sample sizes and fewer testing materials:** USP incorporated analytical procedures and additional volumetric apparatus, including micropipettes, into quality testing practices and standards to facilitate use of smaller sample sizes and fewer materials. For example, the new *USP–NF* General Chapter <1331> *Calibration and Verification of Volumetric Apparatus*, which is slated to become official in May 2025, includes information on the calibration of micropipettes. Meanwhile, *USP–NF* General Chapter <1220> *Analytical Procedure Lifecycle*, which became official in May 2022, introduced a methodology for evaluating potential improvements and updates to compendial analytical procedures that can help avoid unnecessary repetition of testing, reduce sample sizes, allow use of fewer testing materials, and cut waste.



- **Chromatography:** USP revised *USP–NF* General Chapter <621> *Chromatography* to introduce flexibility for the use of column packings with smaller particle sizes that can help cut analysis times and energy consumption during long chromatographic runs. Evolving chromatography methods and increased application of new column technologies supported by the standard also allow reduced use of toxic solvents and less waste. Meanwhile, gas chromatography—used in about 400 monographs—is generally seen as more eco-friendly than liquid chromatography since it requires less solvent use; this characteristic may play a role in deciding if more pharmacopeial methods using gas chromatography should be included in *USP–NF*. Separately, USP is researching supercritical fluid chromatography as a potential compendial method with possible efficiencies including shorter run times and reduced volumes of more environmentally friendly solvent compared with conventional liquid chromatography.
- **NMR & digital standards:** USP is advancing adoption of nuclear magnetic resonance (NMR) spectroscopy technology, which could enable the use of digital standards and other digital tools for quality assurance of medicines and has the potential to provide certain efficiencies such as reduced solvent volumes compared with traditional testing methods like chromatography. In March 2024, USP launched an automated NMR analysis software solution called *USP-ID*, which allows for the automatic identification and quantification of complex mixtures by applying a sophisticated algorithm to a database of high-quality chemical references.
- **Mass spectrometry:** USP has pursued evaluation of multi-attribute methods based on mass spectrometry, which have the potential to allow evaluation of multiple quality attributes within a single analytical approach to improve the efficiency of biopharmaceutical quality assessments versus conventional assays, thus reducing unnecessary waste. In September 2023, USP published in *Pharmacopeial Forum* the related proposed new General Chapter <1060> *Mass Spectrometry-Based Multi-Attribute Method for Therapeutic Proteins*.
- **Reduced volume dissolution testing:** USP has advanced assessment of reduced-volume dissolution systems, using particle image velocimetry technologies to evaluate the use of small dissolution vessels with the potential to require substantially less buffer—and allow less waste—than a standard apparatus for quality testing under possible future monograph standards.
- **Recyclable solvents:** USP documentary standards and related reference standards for evaluating the quality of solvents used in pharmaceutical production can also be used to ensure that recycled solvents are of suitable quality to allow reuse, cutting unnecessary waste.
- **Water efficiencies:** USP developed standards to help ensure the quality of high-purity water—widely used as an ingredient and solvent in making pharmaceutical products—through application of process analytical technologies (PAT) that can also help minimize energy and resource consumption, use of potentially hazardous chemicals, and unnecessary waste. For example, *USP–NF* General Chapter <1231> *Water for Pharmaceutical Purposes* supports energy-efficient water production and water system microbial control approaches, as well as reduced water waste and the use of eco-friendly alternatives to sanitizing chemicals, while also allowing the use of reclaimed/recycled water.
- **Antimicrobial waste:** USP has worked to facilitate stewardship of antimicrobial medicines and cut unnecessary waste, in part to mitigate the potential for antimicrobial resistance (AMR) that can stem from improper disposal and release of antimicrobials into the environment. Complementing USP standards that apply to antimicrobial medicines, the effort is driven primarily by USP's *policy advocacy* in concert with the collaborative, multisectoral "*One Health*" approach to AMR (and other health threats). Recommended by the World Health Organization and U.S. Centers for Disease Control and Prevention, One Health aims to achieve optimal health outcomes by recognizing the interconnection between people, animals, plants, and their shared environment.

Animal-based testing and biodiversity

Through modernization of standards and development of new ones, USP has also helped to decrease reliance on the use of animals for quality testing by incorporating expanded use of animal-free testing methods. This work helps support biodiversity and minimizes environmental impact. Key examples include USP's update of *USP-NF* General Chapter <121> *Insulin Assays* in 2020 to allow use of an *in vitro* cell-based assay in place of rabbit blood sugar assays for insulin quality testing that previously involved thousands of rabbits per year.

More recently in June 2024, USP published revisions to USP standards for *in vitro* and *in vivo* biological reactivity tests that allow animal-free alternatives to the use of guinea pigs and rabbits for such testing, as well as reduced use of mice, through increased reliance on *in vitro* technology. The changes are slated to become official in June 2026. USP is also evaluating the potential to further reduce the need for rabbits in quality testing through development of a new standard for monocyte activation testing as an alternative approach for the detection and quantification of pyrogens.

In addition, USP's Microbiology Expert Committee approved endotoxin testing using alternative, non-animal derived reagents under new *USP–NF* General Chapter <86> *Bacterial Endotoxins Test Using Recombinant Reagents* in July 2024, which could help preserve horseshoe crab populations impacted by traditional endotoxin test methods. USP published the proposed new standard in November 2023, and it is slated to become official in May 2025.

USP remains committed to continuing to support and advance quality testing methods and technologies using alternatives to conventional animal-based testing, in line with broadly adopted principles known as the "Three Rs" approach. This calls for *reducing* the number of animals needed to achieve research objectives, *refining* the nature of needed testing to minimize the impact on animals, and *replacing* research methods with non-animal-based alternatives wherever possible. (4,5)

Harmonization across borders

To help maximize the benefit of evolving medicines quality standards—including more efficient and environmentally friendly methods and practices—USP has collaborated with other pharmacopeias through the Pharmacopeial Discussion Group (PDG) to advance standards harmonization across borders. To date, a total of 48 excipient monographs and 31 general chapters have been harmonized across U.S., European and Japanese pharmacopeias, resulting in increased efficiencies and reduced waste. As an example, in the carboxymethylcellulose calcium monograph, harmonization has reduced the number of quality test requirements from 37 tests across the U.S., European and Japanese pharmacopeias that would have been required without global harmonization to 10 tests under the globally harmonized monograph. Notably, the PDG was expanded in 2023 to include the Indian Pharmacopoeia Commission, further broadening the reach of globally harmonized standards and related, potential efficiencies.

Through the PDG and USP's work with the International Meeting of World Pharmacopoeias (IMWP), USP also continues to pursue opportunities for standards convergence incorporating advances in eco-friendly quality testing. This work includes recent USP-led engagement with IMWP to develop shared principles for environmental considerations in pharmacopeial standards setting.

Advanced manufacturing technologies

USP is also working with stakeholders to address knowledge gaps and barriers to the adoption of *advanced manufacturing technologies* like pharmaceutical continuous manufacturing (PCM) and 3D printing, which have the potential to help cut waste and natural resource usage in medicine production. For PCM, such benefits are achieved in part through application of PAT, which can allow timely measurements of quality attributes throughout the pharmaceutical production process and reduce reliance on end-product testing.

USP's standards work has included development of several general chapters for analytical procedures with wide applicability in PAT. USP has also developed the on-line *Continuous Manufacturing Knowledge Center*, technical guides, workshops, educational programs, and related services to facilitate knowledge sharing and PCM adoption among stakeholders seeking to achieve potential efficiencies. Meanwhile, USP is using flow chemistry—a continuous manufacturing technique where chemical reactions occur in a continuously flowing stream that can be used to make active pharmaceutical ingredients and other substances—at its R&D lab in Hyderabad, India in pursuit of efficiencies including reduced waste.

What's next?

In May 2025, the USP Convention will weigh adoption of new Resolutions for the organization's 2025-2030 cycle that have been proposed by the USP Council of the Convention. One such proposal specifically calls for USP to help foster more environmental sustainability across the drug product lifecycle. The proposal represents a unique opportunity to reinforce and expand USP environmental sustainability efforts—including development of eco-friendly standards and related programs—that can influence the pharmaceutical industry. Stakeholder discussions will help inform USP's enduring resolve to build on its progress to date in advancing efficient, less wasteful processes and environmentally friendly technologies for the quality testing of medicines.

In preparation for the new cycle, USP launched its "call for candidates" in spring 2024, seeking to further expand its roster of hundreds of Expert Volunteers with diverse backgrounds from around the globe that help make USP's science and quality standards stronger. Qualified experts willing to share their scientific, professional, and real-world insights should consider applying to become a USP Expert Volunteer to help find solutions to current and emerging health challenges and advance modern and more eco-friendly quality standards. For more information, **click here**.

Looking forward, the efforts of USP staff and Expert Volunteers to advance more eco-friendly standards and programs will include convening and collaborating with diverse stakeholders to gather related insights and perspectives, identify existing challenges and opportunities, and prioritize initiatives to meet evolving industry needs. This will be achieved in part through in-person and virtual meetings, workshops, on-line communities, and other fora, with the ultimate goal of fostering a healthier, more sustainable world.

About USP

The U.S. Pharmacopeia (USP) is an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines, dietary supplements, and foods, through setting public quality standards in its various compendia.

Learn more about USP's commitment to sustainabilitiy considerations across its operations.

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