

Improving the Pharmaceutical Environmental Footprint: Exploring Options for USP Initiatives and Partnerships

A Roundtable Facilitated by USP

Waste from the manufacture of pharmaceutical products has increasingly become a topic of discussion worldwide. Hazardous or toxic waste in the ground, air, and water can harm people, animals and plants.¹ This waste can be the byproduct of a wide range of activities including those in labs and manufacturing. The global concern has spurred the exploration of the need to reduce the pharmaceutical environmental footprint so that harmful byproducts can be eliminated or significantly reduced.

For more than three decades, USP has been working with our stakeholders to improve the environmental footprint of pharmaceutical manufacturing and quality testing by decreasing the use of hazardous or toxic substances incorporated in our standards and employing new methods and technologies that are more efficient and less wasteful. In addition, the “Improving the Environmental Footprint” incubation project, a hands on, proof of principle study, was created with the goal of improving the environmental impact of pharmaceutical manufacturing and quality testing across the supply chain while ensuring quality medicines.

Given the interest shown by policy makers, industry and USP, and the urgent need for action, USP is inviting relevant stakeholders to participate in dialogue on how USP could further our efforts to reduce the environmental impact of pharmaceutical manufacturing and quality testing across the supply chain. The discussion will include an overview of current and prior work by USP and will focus on increasing the understanding of the barriers or challenges the industry is facing from a scientific perspective, and an exploration of potential future partnerships to expand USP’s work in this area. We anticipate an engaging and mutually beneficial discussion to further the efforts of all participants at the table.

Overview of USP’s work in reducing the environmental impact of pharmaceutical manufacturing and quality testing

USP is a nonprofit standard-setting organization with a mission to improve global public health through public standards and related programs. Our standards are used in 22,000 locations in 150 countries around the world.

USP has a long history of reducing the pharmaceutical environmental footprint through the use of standards. Over the past 30 years, USP has worked to decrease the use of hazardous or toxic substances in our standards and to employ new methods and technologies that are more efficient and less wasteful. Some specific examples of this work are described below.

Decreasing the use of hazardous or toxic substances

USP has reduced the use of hazardous or toxic substances in quality standards. For example, carbon tetrachloride is a manufactured chemical and an ozone-depleting substance. It is now primarily used as an intermediate in chemical manufacturing as consumer and fumigant uses have been discontinued. USP monographs had used carbon tetrachloride as a solvent. Since the mid-1980s, USP has decreased the use of carbon tetrachloride in two ways. First, *USP-NF* General Chapter <467> *Residual Solvents* classified carbon tetrachloride as a Class 1 solvent to avoid in pharmaceutical production and set a strict product concentration

limit of 4 ppm. Second, its overall use in the *USP-NF* has decreased by more than 96%. In 1985, over 100 monographs used carbon tetrachloride. As of 2021, just 4 monographs continue to use carbon tetrachloride.

Similarly, USP has also worked to decrease the use of hydrogen sulfide reagent for more than 30 years. Hydrogen sulfide is a flammable, poisonous gas used in the production of sulfuric acid and elemental sulfur; it can be used as a chemical reagent in the preparation of pharmaceuticals. Under General Chapter <231> *Heavy Metals*, hydrogen sulfide use was reduced “substantially”². In 2018, the heavy metals testing requirement using hydrogen sulfide was eliminated from monographs. So far, USP has cut the use of hydrogen sulfide in its monographs by more than 50% and continues modernization of tests and methods.

Incorporating new methods and technology that are more efficient and less wasteful

USP is also incorporating new analytical methods and technologies that are more efficient and less wasteful. For example, standards have included more efficient chromatography methods (within General Chapter <621> *Chromatography*) to reduce solvent (mobile phase) consumption. Gas chromatography use (in ~400 monographs in 2021) is generally viewed as a more eco-friendly method, in that it uses less solvents than liquid chromatography. Additionally, a combination of reverse phase liquid chromatography and new column technologies has led to less toxic solvents/mobile phase use, lower volume of waste and reduced run times. The modernization of these methods has resulted not only in a smaller environmental footprint, but also in improved time- and efficiency-savings for quality testing.

Other initiatives currently underway at USP explore emerging analytical technologies; these include:

- A Biologic Open Forum exploring **multi-attribute method (MAM)**, a mass-spectrometry-based technique that allows extraction of a large number of different quality parameters within a single analytical approach, increasing the efficiency of the biopharmaceutical development pipeline. We also have piloted MAM Exchange, an online community to increase and accelerate the early scientific knowledge exchange on various aspects of MAM, which has attracted more than 150 members since launching in October 2021 (<https://mam.usp.org/invites/rwS4ojeqvU>).
- Six summits on **quantitative nuclear magnetic resonance (qNMR) spectroscopy**, a relative primary measurement procedure for identifying and quantifying the main component, sensitivity, dissolvability and analysis of spectra for an organic compound. It promises rapid, SI-traceable purity assignment and uses significantly less solvent than HPLC.
- Modern Analytical Methods Joint Subcommittee work on **HPTLC, the high-performance version of thin-layer chromatography**, with significantly shorter developing times, lower solvent consumption and improved resolution.
- An advanced manufacturing program investigating **process analytical technology (PAT)**, a system for designing, analyzing, and controlling manufacturing by measuring the quality and performance data of raw and in-process materials to help ensure final product quality. (See next section in this document.)
- An incubation project on **small vessel dissolution apparatus**, which use ~80% less buffer than standard apparatus (100 mL compared to 500 mL or more).

Advancing continuous manufacturing methods and supply chain resiliency

Continuous manufacturing (CM) of pharmaceuticals is most prevalent amongst the advanced manufacturing technologies (AMT). CM is typically considered for solid oral dosages, small molecules and biologics, and is witnessing uptake in other dosage forms. It involves efficient handling and processing of smaller quantities of

materials at a time, with in-process analytical measurements and controls. By building efficiency in chemical processes, formulation and physical transformation while reducing wastage at every step, CM can have a significant positive impact on the environmental footprint of pharmaceutical manufacturing.

USP has taken several initiatives to support CM adoption and build better resilience and transparency in the supply chain. A strategic alliance between USP and the Phlow Corp. will result in a new cutting-edge laboratory to develop new analytical methods for essential medicine manufacturing. The methods developed through this work will be available for use by other manufacturers to reduce adoption risk for greener, efficient CM technologies. USP's expert committees on process analytical technologies (PAT) and materials characterization are working to identify opportunities for developing and updating CM-specific documentary standards.

Harmonization efforts to increase efficiencies in quality testing

In addition to the work described above, USP's work on harmonization through the Pharmacopeial Discussion Group (PDG) aims to improve alignment of quality standards across pharmacopeias. To date, a total of 46 excipient monographs and 28 general chapters have been harmonized across US, European and Japanese pharmacopeias, resulting in increased efficiencies. For example, in the Carboxymethylcellulose Calcium monograph, harmonization reduced the number of test requirements from 37 tests across the US, European and Japanese pharmacopeias to 10 tests in the harmonized monograph. Moving forward, USP is pursuing a vision of global convergence, with an increased focus on prospective harmonization.

Growing our impact together

Given USP's past and present work, as well as initiatives by industry to address barriers and unmet needs, discussion on moving forward with these initiatives should include best practices and areas where USP can serve as a critical resource for industry. This will help guide future USP efforts to ensure that our work best suits the needs of industry as we explore ways to reduce the environmental footprint of pharmaceutical manufacturing and quality testing. We also want to know more about the goals and initiatives of other scientific associations and stakeholders in this space. How can USP support your efforts? What problems can we help solve and what needs can we address together?

USP has developed the following thought starters on potential opportunities for partnership to improve the pharmaceutical environmental footprint. This is not meant to be a comprehensive or exhaustive list. These reflect our early thinking on where proposals of best practices could be developed and what other work could be undertaken. USP is seeking feedback on and discussion of these ideas as well as identification of other proposals.

- USP could incorporate green (analytical) chemistry principles when revising monograph methods and tests or developing new ones and could use tools and metrics to track the reduction of waste and demonstrate efficiencies.
- USP could potentially help promote usage of environmentally friendly, quality solvents. Aspects of this effort could include partnering with others to deploy and increase the adoption of solvent assessment and selection tools, assessing Chapter <467> Class 2 residual solvent limits, and/or providing greater guidance on QA in solvents, especially for recycling.
- USP could explore the role of standards in enabling solvent and other waste segregation and recycling rather than disposal, while demonstrating benefits.

- USP could explore how standards could encourage implementation of green cleaning techniques in the lab and manufacturing area while demonstrating benefit.
- USP could advance adoption of green chemistry by working with stakeholders to further develop green definitions, metrics and tools to quantify the complexities of overall environmental impact in the context of full product lifecycle. USP could then deploy and implement these resources to the USP-wide customer base (i.e., incorporate in standards, training and education).
- USP could explore the role of standards in enabling use of advanced pharmaceutical manufacturing technologies that can significantly reduce the environmental footprint of pharmaceutical manufacturing, such as utilizing continuous flow reactions when possible as well as PAT and real-time, in-process monitoring etc.
- Working with our global pharmacopeial partners, USP could work to improve the pharmaceutical environmental footprint in our international harmonization efforts by explicitly incorporating green/sustainable considerations into harmonization criteria, partnering with industry prospectively to build sustainability into quality standards, and in other ways.

USP looks forward to hearing more from you, as leaders in key pharmaceutical and environmental scientific associations, at our February 1st roundtable. We strive to grow our understanding of the actions that USP can take to improve the pharmaceutical environmental footprint, as well as ways we can best engage with you further and support your initiatives.

¹ Toxic waste, explained (June 2019). <https://www.nationalgeographic.com/environment/article/toxic-waste#:~:text=Toxic%20waste%20can%20harm%20people,eat%20fish%20or%20other%20prey.>

² USP (March 2000). Status of Progress on Resolutions Adopted by the 1995 United States Pharmacopeial Convention; USP 1995 Convention Resolution on “Environmental Concerns” indicated that: “The USP is encouraged to initiate a program to protect the environment by adopting standards and analytical methods for pharmaceuticals, containers, and other articles that reduce the amount of reagents and materials used in pharmaceutical tests and assays that have the potential to cause harm to human health and the environment.”