USP Pharmaceutical Environmental Footprint Roundtable Summary

February 1, 2022

Introduction

Global concern has been growing about the hazardous waste produced when pharmaceutical products are manufactured and tested. Efforts are underway to reduce the use of hazardous substances during these processes and thereby limit harm to the environment. The U.S. Pharmacopeia (USP) convened a small, informal roundtable on February 1, 2022, where invited stakeholders came together to discuss improving the environmental footprint 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. USP standards are used in 22,000 locations in 150 countries.

At the roundtable, USP engaged the participants in an open, productive conversation that encompassed the following topics:

- USP's efforts and impact to date
- Participants' current efforts and priorities
- Unmet needs, gaps, and barriers identified by participants
- Steps that USP could take to help address these needs, gaps, and barriers
- Suggestions for connecting with additional subject matter experts (SMEs) and Environmental, Social and Governance (ESG) movements in pharmaceuticals
- Potential future partnerships to explore

USP's efforts and impact to date

For the past 30 years, USP has worked with stakeholders to decrease the use of hazardous and toxic substances in the manufacture and quality testing of pharmaceutical products. However, there is more work to be done, with an urgent need for action on reducing the risk of harm to people, animals, and plants.

USP's previous work and current efforts were outlined in *Improving the Pharmaceutical Environmental Footprint: Exploring Options for USP Initiatives and Partnerships* and they include:

- Analytical methods that are 'greener' and more efficient have been incorporated into USP standards. Examples include incorporating gas chromatography to replace thin-layer chromatography (TLC) methods and reducing the use of hazardous solvents while increasing the method quality.
    - As of 2021, the number of USP monographs that use gas chromatography has increased to approximately 400.
    - Acknowledging the problem of hazardous and toxic solvents present in some drug products, USP created General Chapter <467> *Residual Solvents*, a guideline for industry that is enforceable by regulatory agencies. Carbon tetrachloride is one example of a Class 1 solvent that should be avoided in pharmaceutical drug products and dietary supplements; in 1985 it was used in 100 monographs, but in 2021 only 4 monographs call for its use.
    - USP's Analytical Development Lab works on method development and validation, with a focus on reducing the quantity of hazardous solvents while maintaining medicine quality.

- USP is also exploring emerging technologies for their potential advantages; these include multi-attribute method (MAM), qNMR, HPTLC, process analytical technology (PAT) as part of pharmaceutical continuous manufacturing (PCM), and small vessel dissolution apparatus.
    - USP has various PCM initiatives underway, including flow chemistry and continuous processing, which bring environmental benefits. Examples of initiatives include working towards facilitating adoption in industry and building flow chemistry capabilities.

- Harmonization of quality testing in monographs between pharmacopeias can be effective at improving efficiency and decreasing waste, thereby reducing the environmental footprint.
    - USP participates in the Pharmacopeial Discussion Group (PDG), where three pharmacopeias (USP, the Japanese Pharmacopoeia, and the European Pharmacopoeia) have harmonized 46 excipient monographs to reduce hazardous waste and improve efficiency.

Participants' current efforts and priorities

Roundtable participants gave a brief overview of their organizations' efforts to reduce the pharmaceutical environmental footprint.

- The American Association of Pharmaceutical Scientists (AAPS) represents about 7,000+ individual members across all pharmaceutical R&D spaces. From R&D through manufacturing/CMC, AAPS is covering a wide scientific waterfront. AAPS is not a trade

organization and does not lobby, but it provides scientific opinions on a variety of matters.

- The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) works toward advancing green and stable chemistry to reduce the environmental footprint. ACS GCIPR has focus teams in four strategic areas: Research, Tools for Innovation, Educate Leaders, and Collaborate Globally. In addition, ACS GCIPR has partnerships with the Green ChemisTree Foundation in India and PSCI, the Pharmaceutical Supply Chain Initiative. The ACS GCI is also a major sponsor and participant in the Annual Green Chemistry and Engineering Conference with 10 or 11 symposiums related to the implementation of green and sustainable chemistry in the pharmaceutical industry.
- The Association for Accessible Medicines (AAM) asked their members about their current efforts and activities, and many were listed. Specifically, some AAM members are focused on secondary and tertiary packaging and ways that they can reduce use of plastics. One member is looking at the distinctions between primary, secondary, and tertiary packaging.
- The Biotechnology Innovation Organization (BIO) is actively engaged with the National Academy of Medicine (NAM) on their Action Collaborative on Decarbonizing the U.S. Health Sector. Other interested organizations can join in as partners in this initiative: https://nam.edu/programs/climate-change-and-human-health/action-collaborative-on-decarbonizing-the-u-s-health-sector/climate-network-organizations/.
  In general, BIO is particularly interested in supply chains and sustainability.
- The Consumer Healthcare Products Association (CHPA) is a trade organization representing the OTC pharmaceutical industry, and also dietary supplements, and is active through lobbying and other efforts. One issue of concern to CHPA is the disposal of unused medicines and dietary supplements, a major problem with ramifications for safety, costs, and the environment. Another concern of CHPA is the disposal and recycling of plastic containers. Many large retailers want all their products to use recycled packaging, but U.S. Food and Drug Administration (FDA) guidance suggests using virgin plastics for primary packaging of drug products.

- The Enabling Technologies Consortium (ETC) of pharmaceutical and biotechnology companies has worked towards green and sustainable practices to reduce solvent waste in sample preparation and provide general gas chromatography methods for residual solvent analysis. Other initiatives and activities for green analytical chemistry and separations include supercritical fluid chromatography (SFC) and PAT projects for analysis of drug products and chemical synthesis in continuous manufacturing.

- The Green Chemistry Group has an annual conference on supercritical fluids, SFC, and related techniques including extraction (see https://greenchemistrygroup.org/) The Green Chemistry Group held a conference on green chemistry in 2016 in Rockville MD.
- At Virginia Commonwealth University, scientists are using the isolation of intermediates as a way of purging impurities from certain processes and crystallizing those intermediates. This approach is only partially amenable to flow chemistry, however, because some unit operations such as filtration and drying are more difficult to perform continuously. An analytical tool is needed to ensure a state of control in the processes. Using a manufacturing platform to accomplish feed-forward, feed-back information management and to control these processes in real time is a critical part of this whole analytical program. Interdisciplinary skills are going to be helpful for continuous platforms.

Unmet needs, gaps, and barriers identified by stakeholders

Connecting with regulators

- It is important to communicate effectively with regulators, but it can be difficult to connect with the right people at FDA.
- The U.S. Environmental Protection Agency (EPA) should also be involved; USP should invite them to participate in the discussions.
- Four states in the U.S. — California, Maine, New York, and Washington — are making strong efforts to protect the environment from waste due to pharmaceutical manufacturing and testing. USP could connect with some of these state legislators.
- The pharmaceutical industry is heavily regulated, and regulatory acceptance of a change is critical, particularly with long marketed and legacy products. Broad and early regulatory input is needed, so pharmaceutical companies are urged to engage early with regulators if they want to make a change towards greener manufacturing processes.

Need for metrics

- It would be very helpful to find some type of metric that would show that stakeholders have moved the needle on the impact of pharmaceuticals around the country and world.
    - The pharmaceutical industry has been using various metrics. For example, process mass intensity (PMI) calculations, introduced in 2008, have been used to estimate the amount of materials needed to produce 1 kg of isolated product, which is a proxy for reaction and work-up waste estimations.
    - There is also an expansion of PMI called iGAL (Innovation Green Aspiration Level), which is a benchmarked measure of PMI against industry. This could be

the latest tool that takes a more holistic view of pharmaceutical manufacturing processes.
    - A third metrics-driven tool is the Analytical Methods Greenness Score calculator, which evaluates the greenness of HPLC, UHPLC, SFC, and gas chromatography.

Potential benefits of alternatives to HPLC in manufacturing

- Most of these technologies are used upstream and in process chemistry and other types of chemistry in those areas, but they could have benefits if pushed out into the QC and manufacturing environment.
- The ACS GCIPR worked on replacing helium with hydrogen in gas chromatography and they have a grant coming up to look at higher-molecular-weight compounds. They will try to move away from HPLC by using higher-temperature gas chromatography and will explore what the scope is for that initiative.

Complexities of plastics recycling

- The recycling landscape is very complex, and it is important to recognize that not all virgin plastics are made the same way. Unfortunately, in a very good effort to reduce the use of virgin plastics, there may be some new technologies and innovations that are being unfairly penalized or labeled as toxic, even though they are not petroleum based.

Steps USP could take to help address these needs, gaps, and barriers

Flow chemistry

- USP could consider collaborating with the ACS GCIPR to influence the adoption of and training in flow chemistry, a relatively new method in the pharmaceutical industry.
- In flow chemistry / continuous manufacturing, the recycling or reuse of components as well as the cleaning, verification, and validation are very challenging. In the case of flow equipment, extractables and leachables also become an issue. All of these aspects also have regulatory considerations. Perhaps USP could play a role in bringing stakeholders together to discuss these challenges and come up with solutions.

Notification about which standards will be revised next

- USP could let stakeholders know in advance which specific standards might be under consideration for revision in the near future. This would be helpful.

Drug disposal

- USP might have opportunities to set guidelines for drug disposal, particularly for hospitals and pharmacies or at an industrial level.

- USP could potentially get involved in education around disposal of OTC medications and dietary supplements, i.e., any products that are self-administered. Education would be the main approach for reaching consumers. Working with retailers to provide means of disposal could also be effective.
- Medications that are considered hazardous, or that are administered in a hospital setting, would require a different approach. USP could work with the pharmacy associations on larger solutions, convening that part of the discussion.

Developing a new general chapter on supercritical fluid chromatography

- USP could develop a general chapter about the use of SFC, which is becoming a recognized technique. A lot of the companies that use SFC are not in late-stage analytics; instead, they do more upstream chemistry (or early-process chemistry), where speed and efficiency are most important. Could USP become involved in building further interest in the analytics, which have come a very long way?

Networking and partnering to grow impact

Participants discussed ways that USP and other stakeholders could strengthen their combined impact. Several opportunities were mentioned, including:

- The organization BIO holds meetings with the Environmental, Social, and Governance leads from their member companies. USP could link up with them to grow understanding of their goals and needs.
- USP and others could reach out to the contract manufacturing community.
- USP could connect at the international level, and early on, with regulatory agencies and industry groups through the Pharmacopeial Discussion Group (PDG).
- USP or others could reach out to both the innovators and the generics/biosimilars manufacturers, from small to large, in the US and internationally.
- ACS and USP could pursue and discuss mutual interest areas.

About next steps, one participant said they would welcome additional, in-depth review and engagement on the thought starters (see below) that USP provided in the pre-meeting materials.

Thought starters: additional ways USP could move the needle

- 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 benefits.
- 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 using continuous flow reactions when possible as well as PAT and real-time, in-process monitoring.
- With its global pharmacopeial partners, USP could work to improve the pharmaceutical environmental footprint via 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 welcomes further discussion and engagement with interested parties. USP also invites all stakeholders and others to send us your input on how to advance efforts to improve the pharmaceutical environmental footprint. Please send comments, questions, and requests for further engagement to Danielle Seiler, dxs@usp.org.