Sustainability in Pharmaceutical Manufacturing: A CDMO's Contribution

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Regulatory and consumer pressures to increase the sustainability of pharmaceutical manufacturing operations, combined with greater awareness of the economic benefits of reducing consumption and waste generation, have resulted in a growing movement to improve sustainability in pharmaceutical manufacturing. Consideration of sustainability early in process development, throughout the entire development cycle, and across the entire supply chain must also become common practice.

Multiple Sustainability Drivers

The global manufacturing community is experiencing a regulatory shift that has significant implications for operations and compliance. Driven by climate concerns and depletion of resources, regulatory bodies around the world and across industries are issuing new guidance to drive better tracking, reporting, and control of consumption and emissions.

The industrial sector, of which pharmaceutical manufacturing is part, accounts for about a quarter of greenhouse gas (GHG) emissions in the United States and is the third largest contributor to GHG.[1] While it can be argued that pharmaceutical manufacturing is a relatively minor component of the overall industrial sector, it is often regarded as one of the more inefficient and polluting in terms of the quantity of product produced.[2,3]

Despite its overweighted contribution to consumption and pollution per unit produced, the pharmaceutical industry has garnered little attention from the sustainability community over the years, and has only recently been under scrutiny for discrete issues, such as for levels of active pharmaceutical ingredients (APIs) found in the environment.[4] Relative to other industries, less has been published on the GHG emissions, consumption, and waste metrics of the pharmaceutical manufacturing industry.

Higher public consciousness[5,6] of the risks posed by climate change and unsustainable consumption is also generating pressure outside of government regulation on pharmaceutical manufacturers to adopt sustainable practices. Many companies see this as a matter of social governance.[7] Additionally, it is now widely accepted that a change toward more "green" practices is imperative to remaining competitive in the market. As such, there has been a growing movement to improve sustainability in pharmaceutical manufacturing.[8]

The COVID-19 pandemic has also had an impact. Lockdowns led to reduced manufacturing activity and vehicles on the roadways, leading to improved environmental conditions and even the return of wildlife to some areas. These changes raised awareness among the general population of our place in the environment. People now have a greater understanding of the connections among excessive consumption behavior, industrial manufacturing, and the environment.

This cross-pollination of experience and collaboration between the different centers is also encouraged by locating most of them near one another, in many cases on the same campus or within a short drive. Fostering an environment that facilitates cross-pollination of ideas while maintaining a focus on specific technology areas really helps spur innovation.

Green Chemistry and Pharmaceutical Manufacturing

Within the broader pharmaceutical manufacturing spectrum, the sustainability of operations surrounding API manufacturing is often framed by the term "green chemistry." There are 12 Principles of Green Chemistry that focus on safety, efficiency, and reduction of consumption: prevention, atom economy, less hazardous chemical synthesis, designing safer chemicals, safer solvents and auxiliaries, design for energy efficiency, use of renewable feedstocks, reduce derivatives, catalysis, design for degradation, real-time analysis for pollution prevention, and inherently safer chemistry for accident prevention.[9]

These principles support the "R's" of sustainability, with the three main activities being reduce, reuse, and recycle. Driven primarily by economics, efforts have largely focused on reducing waste at the source through process intensification. Metrics have been devised that focused narrowly on mass intensities, such as atom economy (AE), process mass intensity (PMI), and E-factor (EF).

There has been recent movement toward a more holistic, systems-level accounting that would consider the entire life cycle of a product, including sourcing, logistics, and end-of-life considerations, in an effort to move from "green" to "sustainable."[10] However, reasonable boundaries must be defined to parse the complex life cycle into segments that allow for meaningfully granular metrics and focused attention. PMI, E-Factor, and variants (sEF, cEF) remain a valuable method for assessing gate-to-gate sustainability of a chemical process and can be effectively used as a component of a larger systems and life cycle assessment (LCA) of sustainability.[11]

Application of emerging technologies is enabling process intensification and thus "greening" of pharmaceutical intermediate and API manufacturing. Continuous manufacturing and biocatalysis are perhaps most prominently reported in use in the industry.

Improving Sustainability with Flow Chemistry

Continuous flow was identified years ago by regulators as an emerging, potentially transformational technology with respect to both supply chain security and sustainability. One of the biggest benefits is reduced energy consumption, as heat and mass transfer are much more efficient. Another is the reduced manufacturing footprint. There are chemistry benefits as well. Operating in flow mode allows for control of highly reactive chemistries that cannot be safely performed in batch mode, opening the possibility to access novel structures and motifs. Furthermore, photochemistry and electrochemistry, which rely on greener energy sources, are much more practical as continuous processes owing to the removal of heat and flux limitations. Finally, from an engineering perspective, flow chemistry allows for efficient recycling of solvents and enables simpler workups that require less water and solvent and thus produce less waste.

It is important to note, however, that flow mode is not always applicable. API manufacturing is highly complex, and often reactions do not involve homogeneous solutions. Heterogeneous mixtures are not always amenable to flow processes. Long reaction times are common and are difficult to accommodate in flow. Purification and isolation steps can be highly involved and often generate the greatest amount of waste but are not always easy to implement in a continuous manner.

Need to Go Beyond Reduce and Replace to Include Recycle and Rethink

Continuous flow manufacturing and biocatalysis promote the concepts of "reduce" and "replace." The pharmaceutical industry has been pretty good about reducing energy and resource consumption. API manufacturers are also fairly effective at replacing toxic/hazardous reagents with more benign alternatives through process design. Recycling, however, is virtually ignored during product development.

Solvents account for 80–90% of the total mass of non-aqueous materials used, and consequently the majority of waste formed is solvent-related. In many cases, this waste is ultimately incinerated, adding to GHG emissions. In addition, recycling of solvents is virtually ignored during the discovery and clinical phases and only rarely incorporated into processes supporting new product launches. Only after a product is on the market for some time does recycling become a topic of investigation, driven primarily by economic considerations.

In many respects, the lack of attention to recycling at early development stages is understandable. Candidate attrition is high in early development and clinical phases of drug product development, and investing in research to support recycling efforts at that stage may be a poor use of capital. Process optimization often leads to suboptimal solvent choices from a recycling standpoint. Many different solvents may be used across a complete synthetic route to maximize the yield and quality of each step without consideration of recycling implications. The culmination of these factors is a process poorly designed for efficient recovery of the largest contributor to a process's E-Factor, postponing any attempts to a much later period of the product's life cycle.

However, there are arguments for considering recycling issues early in process development. Designing a process that minimizes the mixing of differing miscible solvents, or using solvents with no or poor azeotropes if mixed miscible solvent waste streams are unavoidable, will simplify the recovery process. Waste recovery and remediation can occupy as much as a third of the equipment dedicated to a process. More judicious choice of solvents can greatly simplify waste management costs and reduce impact to the environment, a win–win for business and sustainability. (The ACS Green Chemistry

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Institute (GCI) published a solvent selection guide that takes into account environmental factors when ranking the preferability of a solvent for use in pharmaceutical manufacturing.[12])

Indeed, API manufacturers are typically not sufficiently proactive about considering sustainability early on in the product development cycle. They should focus on "Rethinking" processes – one of the least well-known sustainability "Rs." The greatest emphasis is generally on quality and regulatory compliance, as well as optimizing each step in a synthetic route – all via a siloed approach. Once a process is solidified in the early stages of clinical development, it becomes increasingly difficult to make changes. As a result, processes are codified with little consideration of their sustainability, and changes to improve sustainability are postponed until there is an economic driver to catalyze such activities. In many cases, however, that cost driver is not sufficient to overcome the added costs of making process changes. A better approach is to factor in the cost upside of sustainability during early process development activities.

Considering Sustainability through the Development Cycle and Across the Supply Chain

In addition to incorporating sustainability considerations at the earliest possible development stage, it is equally important to continue to consider sustainability across the entire development life cycle as other aspects are treated. Quality, for instance, is considered to differing degrees depending on the development phase – coarse or rough early on during preclinical studies and increasingly refined as a pipeline candidate moves to phase I safety studies and ultimately to commercial launch.

Likewise, sustainability should be incrementally considered from the beginning of the development life cycle and advanced in a tiered manner, starting with simple assessments against sustainability principles and metrics early on and growing in detail and comprehensiveness as the product matures.[13] Establishing a sustainability culture and mindset among those involved in every phase of drug development will afford meaningful efficiencies in establishing a green process that will minimize the negative impacts to our environment and have positive business impacts without compromising the quality, effectiveness, or safety of the products we make.

Similarly, sustainability must be considered across the entire supply chain. An increasing fraction of pharmaceutical manufacturing is outsourced to contract development and manufacturing organizations (CDMOs), making them major players in sustainability efforts. In many cases, however, the corporate sustainability metrics and goals of pharmaceutical companies fail to include their supply chains, which mutes their sustainability efforts. The same is largely true about raw material suppliers, who also account for a large portion of the manufacturing and thus waste generation. It is important for pharma companies to partner with CDMOs and suppliers that share the same vision of a more sustainable industry.

Drug developers that want to truly claim to be carbon neutral must consider the sustainability of their supply chains. Sustainability should take into account the full life cycle of the product in question, from the raw material suppliers to outsourcing partners to end-of-life considerations – where it is going and how it is managed. Such life cycle assessments cannot really be made by suppliers but can be conducted by pharma developers that have control over the drug products they commercialize. CDMOs, meanwhile, should ensure the sustainability of their own operations and supply chains.

Sustainability without Compromising Quality

Sustainability efforts, of course, must be pursued without any compromise on quality. Patient safety is paramount. A holistic assessment of patient safety, however, should consider not only clinical factors but the effect that the drug product has on the environment.

For instance, the quality attributes of recycled solvents must be established and proven suitable for their intended use, accumulation of impurities understood and controlled, and recovery processes validated according to regulatory guidance. It is therefore important to plan early to run experiments designed to demonstrate that the quality attributes of recycled solvents and raw materials are suitable for use and pose no risk to operational safety and product quality.

As an added measure of risk mitigation, segregation of recycled solvents and their use in the same processes from which they are recovered can reduce chances of cross-contamination. With this approach, quality attributes of the recovered materials can be specific to the process and do not need to be the same as virgin material. Studies designed to demonstrate suitability of recycled solvents having quality specifications that differ from virgin stock will verify feasibility and possibly inform avenues for further sustainability studies. These data can be presented in regulatory applications, setting the stage for implementation after product launch, if not at launch.

Treating Sustainability in a Holistic Fashion

When treated holistically, sustainability takes into account business sustainability. In fact, sustainability must have a business case. Governments may try to skew the scales by imposing fines or requirements and offering carbon credits and thus in some ways artificially manipulate the business case. Such efforts reflect the recognition that increasing sustainability cannot simply be an expense; sustainability initiatives in some manner must enable profitability in order to be sustainable themselves.

Sometimes the business case is not immediately evident. For a company that has not yet implemented flow chemistry, there is an upfront investment that must be made in terms of capital, research, and engineering to install and get continuous manufacturing operations up and running. Fortunately, for flow chemistry and biocatalysis, there are now many practical examples that have demonstrated their economic benefits, which has made the theoretical calculus more straightforward.

Asymchem has enjoyed significant successes in the areas of flow chemistry and biocatalysis. We were presented the CMO Excellence in Green Chemistry Award from the ACS GCI in recognition of our efforts to promote the development and implementation of pharmaceutical green chemistry technologies.

The issue today is more of timing of implementation. When to implement flow chemistry and/or begin recycling solvents remains an open question. That can be attributed to the fact that such decisions must generally be made on a case-by-case basis, and any sustainability initiatives cannot compromise quality or jeopardize the business case. As more sustainability projects are successfully completed, the knowledge and understanding of how to achieve quality, safety, sustainability, and profitability will increase.

Asymchem's Sustainability Solutions

Despite the challenges, it is clear today that sustainability is increasingly essential to remaining competitive. Regulatory and consumer pressures will only increase further. On the regulatory side, the cost of waste disposal is rising. Energy costs are also climbing. Access to water in some areas of the world is increasingly restricted. Reducing consumption and waste and emissions generation positively impact the bottom line as well.

Asymchem has enjoyed significant successes in the areas of flow chemistry and biocatalysis. In collaboration with AbbVie, we recently implemented a photoredox trifluoromethylation in continuous flow at large scale that leverages a more sustainable trifluoromethylating reagent, very low catalyst demand, and a favorable energy source (light) to drive the reaction.[14] In collaboration with Amgen, another photochemical continuous flow process was developed[15] for which we were presented the CMO Excellence in Green Chemistry Award from the ACS GCI in recognition of our efforts to promote the development and implementation of pharmaceutical green chemistry technologies.[16] Likewise, we have reported on biocatalysis advances that have enabled the avoidance of more toxic catalysts/reagents and the potential reduction of organic solvent usage.[17,18] We have also combined biocatalysis with continuous flow to compound the advantages that each technology contributes to more sustainable processes.[19]

In general, flow chemistry is used if it is a good fit. That determination is made using a multifactor analysis that takes into consideration sustainability, cost, quality, and patient safety. Asymchem has an interim goal of transitioning at least one third of processes to flow. The issue cannot be forced, however. If batch mode offers the best solution, then a batch process will be implemented. Asymchem is working to develop continuous flow technologies – and particularly specially designed equipment – for post-reaction processing/purification, which is an area that has not received significant attention to date.

Biocatalysis has afforded Asymchem with measurable upsides. One key benefit has been elimination of a portion of the supply chain. That was achieved by investing in capabilities for enzyme development and production, not just performing biocatalytic reactions. In this manner, we have also achieved greater efficiency and sustainability and reduced costs, because there is often no need to isolate the enzymes; the resultant broth from the enzyme production step can be directly used in the biocatalytic process.

In addition, Asymchem works to develop new mutant strains that are more robust and efficient and continuously evaluate enzyme types that mediate transformations not prevalent in the biocatalysis space, such as oxidases, in order to broaden the scope of chemistries that can be realized using biocatalysis.

Asymchem also pursues recycling of solvents and reagents wherever possible. Most notably, we consider recycling opportunities early on in process development and build this information into our product development plans. In this manner, recycling plans can be included in early regulatory filings and therefore not constituted as changes, making it possible to implement them from the beginning of commercial manufacturing processes. We also seek to reduce water consumption and appropriately treat the waste that we do generate.

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Dr. McLaws obtained his Ph.D. from the University of Utah and has over 19 years of process chemistry experience in the pharmaceutical manufacturing industry. During his career, he has supported process development and manufacturing of clinical-phase and commercial small molecule APIs in a variety of therapeutic areas. At Asymchem, Dr. McLaws leads a team of technical experts to support CMC activities, with a particular focus on late-stage development, validation, and commercialization.

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