The Green Chemistry Approach to Pharma Manufacturing

By Michael Kopach at Eli Lilly & Co, David Leahy at Bristol-Myers Squibb and Julie Manley at the ACS Green Chemistry Institute

As sustainability rises to the top of many organisation's agenda, we see that 'being green' is more than just reducing waste. Using green metrics, tools and technologies is better for the environment, safer for employees and can have a positive impact on the company's bottom line.

Corporate sustainability is an emerging trend within the global economy and has been characterised as a 'key driver for innovation' (1). The pharmaceutical industry has embraced this movement, and most companies in the sector have made significant progress and set far-reaching sustainability goals for the future. One area of immense focus is the environmentally responsible manufacture of pharmaceutical products. It is here that green chemistry can make an enormous impact to a company's triple bottom line, as it is more cost-effective, safer for employees and better for the environment (2).

Green chemistry, formally defined as the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances, is arguably just good chemistry – highly efficient, safe and cost-effective (3). While gains can be made by applying green chemistry principles to an existing pharmaceutical manufacturing process, the far more effective strategy is to build in green chemistry design principles early in the development life cycle. This article outlines an integrated green chemistry approach to pharmaceutical manufacturing through the use of green technologies, performance metrics and tools for green chemistry.

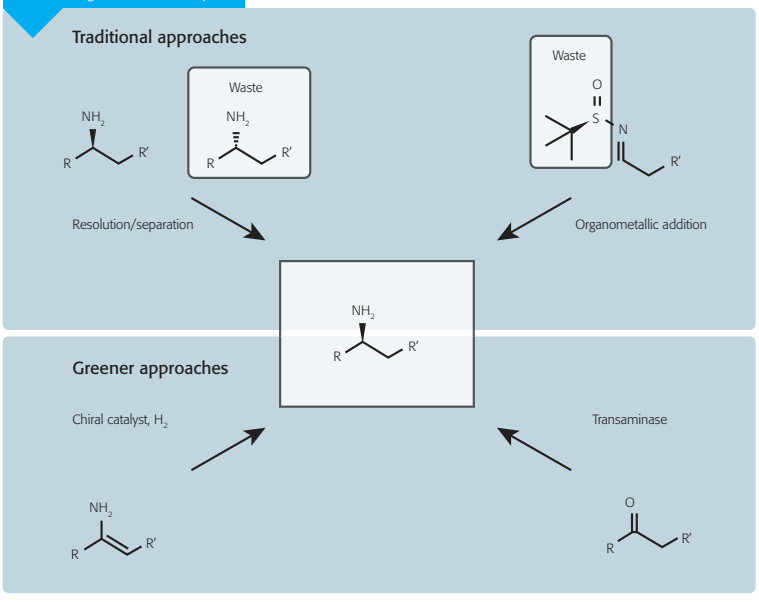
Keywords

Green technologies
Continuous processing
Solvent waste
Process mass intensity (PMI)
E-Factor

Greener Technologies

Fundamental to any green chemistry approach to active pharmaceutical ingredient (API) manufacture is an efficient synthetic route. Such a route should minimise the number of synthetic steps, while maximising atom economy. Each step should be as non-hazardous as possible and generate minimal waste. Green technologies – such as catalysis, biocatalysis, continuous processing and recycling – can all help achieve these goals. Catalytic transformations greatly extend the synthetic toolbox of process chemists, allowing for the direct and efficient formation of chemical bonds not achievable using traditional synthetic methods. Especially powerful examples are carbon-carbon and carbon-heteroatom coupling reactions where two complex intermediates can be efficiently coupled, thereby dramatically shortening the linear synthetic route, and often greatly improving the overall yield of API.

Figure 1: Greener synthesis maximising atom economy



In addition, traditionally problematic areas of single enantiomer synthesis can often be overcome using catalysis, thus circumventing the need for non-atom economical chiral auxiliaries or resolution/separation approaches where half of the product is wasted (see Figure 1). Likewise, biocatalytic approaches are often used for single enantiomer synthesis. Recent advances in the field allow for new genetically engineered enzymes to accomplish a wide range of transformations, with better enzyme productivity, in higher concentrations and shorter cycle times. As an added bonus, biocatalytic transformations most commonly occur in water, thereby reducing their environmental impact. As a result of the power of these green approaches, many companies have developed substantial in-house capacity for traditional catalysis and biocatalysis research and numerous US Presidential Green Chemistry Challenge awards have recognised achievements in these fields.

For many decades, traditional batch processing has been the *modus operandi* in the pharmaceutical industry, with the construction of large facilities with reactors sized up to 12,000 to 16,000 L to deliver high-volume products. However, operations at this large scale often greatly restrict the type of chemistries that can be performed due to process safety constraints. Over the past decade, pharma has began to focus on continuous processing which is inherently safer than batch processing and can be run with a substantially lower manufacturing footprint (often >100x scale reduction) with significantly lower material usage. In fact, many processes considered too hazardous to run by a conventional batch process can be operated safely and more efficiently in continuous mode. A common continuous process configuration is an integrated thermal tube reactor for a chemical reaction with mixed suspension-mixed product removals (MSPRs) in series for product crystallisation and isolation (see Figure 2). In fact, Pfizer uses a tube reactor-continuous stirred tank reactor (CSTR) series for the production of 400,000 kg/year of the arthritis medicine Celecoxib (4).

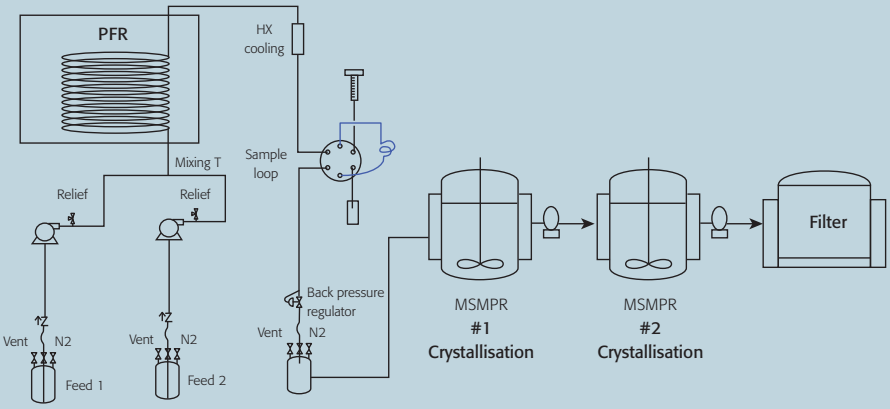


Figure 2: Integrated continuous process for intermediate and API production – thermal tube reactor and MSPRs in series

By far, solvents are the largest contributors to pharmaceutical process-related waste and emissions. A benchmarking study by the American Chemical Society's Green Chemistry Institute (ACS GCI) Pharmaceutical Roundtable revealed that organic solvent and water account for around 90 per cent of the total mass of material used in typical pharmaceutical manufacturing processes (see Figure 3) (5). In addition, a detailed analysis was recently performed on the benefits of recycling solvents in the pharmaceutical industry and, in each case, reducing fresh solvent or burning less solvent waste reduced total emissions for a process by more than 90 per cent (6). One of the main parameters that can lead to reduced emissions is careful solvent selection. Thoughtful selection of solvents that have favourable azeotropes, and low carbon footprints, can greatly reduce overall emissions and energy usage. In addition, simplifying

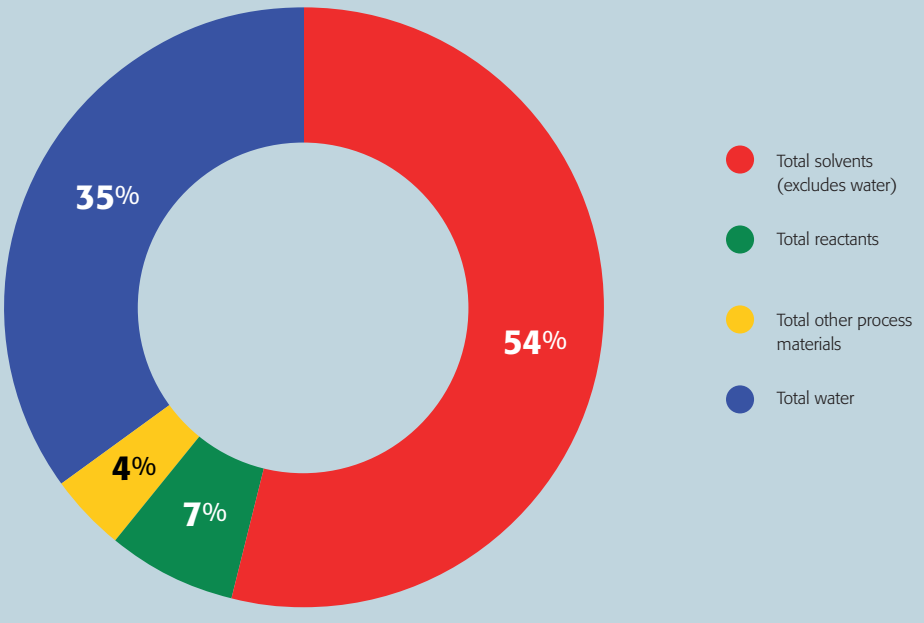


Figure 3: 2010 pharma PMI composition data (per cent)

processes to the minimum amount of required solvents also can have a large, positive impact on emissions reduction.

Green Metrics

The same benchmarking study that found that solvents are the primary contributor to the process mass intensity (PMI) of an API concluded that the mean PMI of the processes in the study was 120 kg/kg – meaning that 120 kg of raw materials were used to manufacture 1 kg of API. By focusing on the inputs to a process, one can influence changes as the processes and routes are being designed. There are a number of 'green' metrics to consider, but the two most common in the industry are PMI and E-Factor (mass of waste per mass of API). It has been argued that focusing on leading indicators such as PMI will maximise value and efficiency, with waste reduction a resulting benefit (5).

PMI is not a perfect metric as it does not include specific concerns regarding environment, health and safety of the materials involved or the waste produced. However, it is an essential intermediate step to estimate life cycle analysis (LCA). A full LCA requires considerable more information, time and resources. In an effort to quickly estimate LCA in a cost-effective manner, a new version of the PMI calculator is being developed to estimate LCA based on the solvents in the process (7).

The benefit of tracking metrics is to be able to drive improvements. Companies have now begun to set process development targets based on PMI. These targets are generally internal guidelines that help communicate progress and illustrate which processes need improvements before moving further into development. This practice further integrates green chemistry design principles early in the development process.

Tools for Green Chemistry

One of the largest environmental impacts that can be made early on in a drug's development life cycle is selection of as green a solvent system as possible from the outset of development. To encourage the greenest possible solvent selection, the Pharmaceutical Roundtable has developed a solvent selection guide that groups solvents into chemical classes and ranks their hazards with respect to safety, health and the environment (see Table 1) (8). The solvent selection guide helps a chemist make a more informed decision. Another important tool which the Pharmaceutical Roundtable has in development is a reagent guide that aims to identify the greenest possible reagents for the most used chemical transformations.

Over the past decade, most pharmaceutical companies have adopted electronic lab notebooks (ELNs) as a means for recording and sharing experimental data. This paradigm shift has created a unique opportunity to expose new scientists to green chemistry at the start of their professional careers. Key green chemistry metrics such as PMI, atom economy and E-Factor can be calculated and reported directly within the ELN without the need to do secondary calculations (9). In addition, an ELN is capable of linking to or launching a solvent selection guide. Thus, ELN technology has the unique

Table 1: Example of Pharma Roundtable solvent selection guide

Substance information			Scoring information				
Solvent class	Solvent name	CAS number	Safety	Health	Environment (air)	Environment (water)	Environment (waste)
Acid	Acetic acid	64-19-7	3	6	6	3	6
Acid	Acetic anhydride	108-24-7	3	6	6	2	7
Acid	Formic acid	64-18-6	2	6	5	4	7
Acid	Methane sulphonic acid	75-75-2			6	6	10
Acid	Propionic acid	79-09-4	2	5	6	4	6
Alcohol	1-butanol	71-36-3	3	5	5	5	3
Alcohol	1-propanol	71-23-8	4	4	6	2	6
Alcohol	2-butanol	78-92-2	4	5	6	3	5
Alcohol	2-methoxyethanol	109-86-4	4	9	5	3	7
Alcohol	Benzyl alcohol	100-51-6	4	3	4	2	4
Alcohol	Ethanol	64-17-5	4	3	5	1	6
Alcohol	Ethylene glycol	107-21-1	3	3	5	1	7
Alcohol	Isoamyl alcohol	123-51-3	3	4	5	3	4
Alcohol	Isobutanol	78-83-1	3	5	4	3	3
Alcohol	Isopropyl alcohol (IPA)	67-63-0	5	5	6	2	6
Alcohol	Methanol	67-56-1	3	5	6	3	6
Alcohol	T-butanol	75-65-0	3	5	7	2	6
Aromatic	Benzene	71-43-2	5	10	6	6	2
Aromatic	Toluene	108-88-3	5	7	6	6	2

ability to provide green chemistry metrics at scientists' fingertips within their primary workspace.

Green Chemistry Frontiers

Green chemistry is a drive for continuous improvement, and as such there continues to be opportunities for research, engagement and collaboration. Recognising that the fundamentals of green chemistry are non-proprietary in nature, the ACS GCI Pharmaceutical Roundtable was developed in 2005 as a partnership between the industry and the American Chemical Society's Green Chemistry Institute to collectively overcome challenges to green chemistry integration. Consisting of 15 global pharma-related corporations, the Roundtable catalyses the implementation of green chemistry and engineering into the business of drug discovery, development and production by informing and influencing the research agenda, developing tools like the PMI calculator and solvent guide, and educating current and future generations of scientists. More recently, the Innovative Medicines Initiative (IMI) has been developed and includes a green chemistry component. These organisations demonstrate that companies can have a greater impact collectively than any one corporation could individually.

While historically green chemistry efforts have focused on the development and manufacturing of small molecules, this view is ever evolving and expanding. Recent focus on drug discovery embeds green chemistry design principles even earlier in the process, while the application of green chemistry ideals into the biologics space is beginning to benefit this increasingly important class of pharmaceutical products. Regardless of the context, a holistic green chemistry approach to pharmaceutical manufacturing through the use of green technologies, metrics and tools will pay measurable and significant dividends to a company's sustainability efforts.

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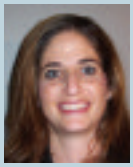

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