Applicability of Green Chemistry in Pharmaceutical Processes

Green chemistry has grown from a small idea into a new approach to the scientifically based environmental protection. Pharmaceutical companies can improve the environmental performance with utilizing green chemistry. This article reviews some of the challenges, new technologies and the exciting opportunities for more effective and less toxic, innovative chemistry research and application.

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For an industry that is focused on reducing the disease burden and improving the living standards of patients, it is ironical that pharmaceutical firms produce a higher ratio of waste per kilogram of product when compared to their peers, such as petrochemical, bulk, fine chemical, and polymer firms (See Table 1).

The chemical industry uses two measures to quantify the waste generated by a process:

1) E-factor, which is defined as the unit of waste generated per unit of product (API);
2) PMI, which is defined as unit of raw material used per unit of product. A lower value on both is desirable, and is the goal that the pharmaceutical industry is driving towards.

Green chemistry is a tool, which when implemented right, can help the industry achieve its environmental goals. Broadly defined as the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances, green chemistry allows companies to develop better products through sustainable processes. In this article, we will summarize the drivers towards successful green chemistry adoption, the technologies that enable execution, and finally, some of the challenges that need to be overcome.

Drivers for Green Chemistry Adoption

A survey across the industry shows that both, internal (commitment from senior management, demonstrable cost savings) and external (ability to meet regulatory requirements) drivers are keys towards successful adoption and implementation. We summarize the survey results and provide additional perspective on some of these elements (See Figure 1).

Management Buy in: A recent report on sustainability found that global CEOs believe that for green and sustainable processes to be successful, such initiatives must be fully integrated into the long term strategy and operations of the company. A further motivation for these leaders was the belief that "Brand, Trust and Reputation" be associated with the adoption of sustainable business processes (See Figure 2).

Cost Benefits: Based on the targeted disease area, it may cost between USD 500 million to USD 2 billion to take a New Chemical Entity (NCE) from lab to the market.[1] Of these total costs, approximately 25 per cent of the cost of developing a NCE is related to APIs, with manufacturing costs comprising 36 - 38 per cent of the total expense.[2]

It is estimated that green chemistry can save the industry an estimated USD 65.5 billion by 2020[3] primarily by reducing manufacturing costs. Green processes, when implemented right, can reduce waste, and decrease resource consumption. Such processes also likely result in reduced litigatory, regulatory, and social risks, and ultimately improve bottom line benefits.

Regulatory Fit: Regulatory initiatives have impacted the adoption of sustainable chemistry, both positively and negatively. In the US, the Environmental Protection Agency (EPA) has been actively involved in the policy making and implementation of legislation to promote adoption of green chemistry in the pharmaceutical industry. In the EU, the European Council and the European Parliament adopted a European Chemicals Legislation in 2007, REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), to ensure protection of human health and safeguard the environment. The REACH legislation holds companies accountable for the management of hazards and potential risks of substances that are manufactured or imported by them.

However, on the flip side, regulatory hurdles have also prevented quick adoption of otherwise strong green chemistry processes. For example, the existing regulatory landscape requires that every time a manufacturer changes the production process, it has to undergo a re-certification process with the

Industry	E-factor (Kg of waste/Kg of product)	Annual Production (Tonnes)
Oil Refining	0.1	10^6 - 10^8
Bulk Chemicals	<1 – 5	10^4 - 10^6
Fine Chemicals	5 – 50	10^2 - 10^4
Pharmaceuticals	**25 – 100**	**10 – 10^3**

Table 1: (Source: R. A. Sheldon, Chem. Ind., 1997, 12 – 15)

FDA. This process is both costly and time-consuming, and hence serves to dissuade firms that would otherwise invest in developing atom efficient chemistries that reduce waste.

Technologies that Enable Green Chemistry Execution

Catalysis: Traditional organic synthesis features stoichiometric quantities of reagents, leading to large quantities of by products, which add to the burden of wastage. The right catalyst technology enhances product value, while minimising waste streams, and improving cycle times. Significant advances in catalysis in recent years have paved the way for many valuable applications, notably in the synthesis of APIs and intermediates. There are two types of Catalyst technologies:

Chemocatalysis has developed sufficiently to be used extensively in manufacturing today.[4] It includes metal catalysis of various kinds, and organocatalysis, both of which have transformed the field of organic synthesis over the past few decades.

Biocatalysis offers many attractive features such as mild temperatures, less solvents, biodegradable nature of the enzyme catalyst, high selectivity and functional group compatibilities, all of which favour green chemistry. At Piramal, we have taken proactive steps to identify scalable biocatalytic routes to API synthesis at the process research stage itself. Utilizing our in-house biocatalysis expertise, we have been able to successfully develop processes that have fewer steps and less waste leading to significantly improved cost-effectiveness.

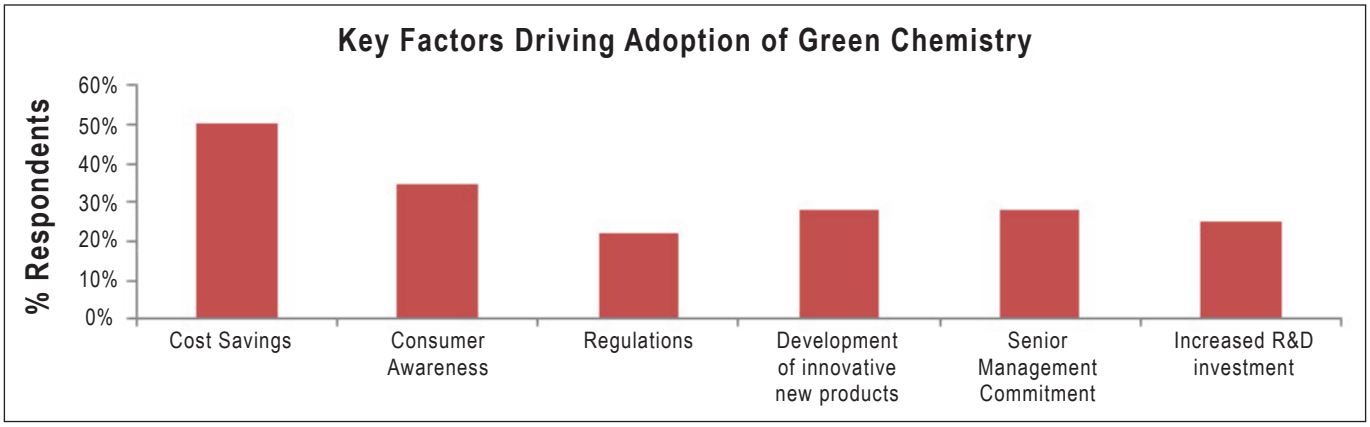

Figure 1: "Perceptions and Experiences of Green Chemistry Practitioners", Alcereco, 2014

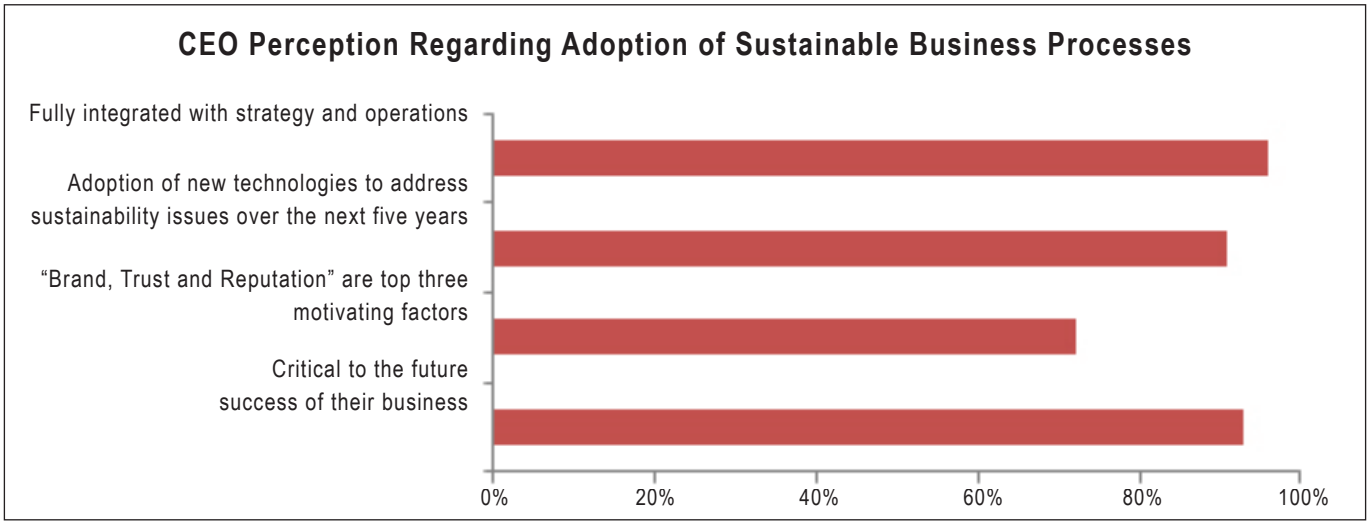

Figure 2: "A New Era of Sustainability", UN Global Compact-Accenture CEO Study 2010

There are a number of catalyst applications in the pharmaceutical industry that have helped firms develop cost-efficient process and reduce their environmental footprint. For example, Pfizer successfully developed and employed a new catalytic process for the manufacture of pregabalin (Lyrica). The new process was reported to decrease the reaction inputs by a factor of 5, and decreased the use of solvents by 90 per cent[5]. It is estimated that, this new biocatalytic method for pregabalin will cut down Pfizer's organic chemical waste production by 200,000 MT in the period from 2007-2020.[6] In another example, Merck successfully demonstrated the benefits of employing a biocatalytic process for its type 2 diabetes drug Januvia (sitagliptin) as a greener alternative to conventional chemical synthesis. The new biocatalytic route developed by Merck/Codexis improves productivity by 56 percent, while reducing overall waste generation by 19 per cent.[7]

Flow Chemistry: A sustainable production method, that is yet to demonstrate its full potential in the scale-up of APIs, is the incorporation of continuous manufacturing processes. Flow chemistry allows for superior reaction mechanics and better rates of heat and mass transfer over conventional batch reactors, leading to safe and economic processes. Further, a higher degree of customization with the rector design is possible with Flow Chemistry over Batch synthesis. All these factors contribute to increasing productivity, minimizing waste generation and much lower capital employment.

Parallel Screening: Molecules in the API business are typically NCEs or novel intermediates and reported procedures do not always work as expected[8]. As a consequence, existing conditions may have to be modified to make them practical. Reaction scouting to find new conditions may be necessary, requiring significant experimentation. Parallel reaction screening saves a substantial amount of time and enables timely activities during process research, provided it is planned and utilised well. With the aid of high throughput screening, and automation in activities such as weighing, quenching and analysis, it is possible to conduct hundreds of reactions in parallel for a given transformation during the feasibility stage of route scouting.

Challenges

The principal challenge for a pharmaceutical firm is identifying the right projects that lend themselves well for green initiatives. Unlike development processes in chemical firms, which have a high degree of commercialization certainty once the pre-defined goals have been achieved, pharmaceutical pipelines suffer from significant clinical attrition. Therefore, firms could balk at investing a significant amount of time or effort in identifying a green solution for the development pipeline. On commercialization, potential regulatory challenges (discussed earlier) may give firms a pause, when deciding on potentially attractive green processes. We submit that there are two potential spots for implementing green processes: (a) when the drug demonstrates efficacy, Ph IIb (b) Life Cycle Management (LCM), post commercialization, where the onset of generics brings external cost pressures. On (a), once the drug is deemed efficacious, the clinical risk is reduced enough to consider putting in R&D resources to develop an efficient process route. On LCM, the pharmaceutical firm is motivated to bring down its costs in the face of generic competition- therefore, atom efficient green routes that reduce the RM's used and waste, may be of high interest.

Conclusions

Green Chemistry is an important tool for the pharmaceutical industry to help achieve its environmental target while delivering economic benefits. Pharmaceutical companies and the Contract Research and Manufacturing Services (CRAMS) providers have now started employing the principles of green chemistry in developing atom efficient routes, which minimize excess solvents and waste, by utilizing technologies such as bio or chemo catalysis. For green chemistry to be successful, having that integrated into the larger business strategy is the key.

Implementing green chemistry solutions on the 'right' projects will be vital for its successful execution. We submit that development projects in phase II and Life Cycle Management projects are ones that firms may want to consider for this initiative. Once a set of projects are identified, additional filtering can be done by analysing the cost benefits and any regulatory impediments. Such a methodical approach manages expectations of key stakeholders, and prevents any surprises. A firm that practices green chemistry successfully can lever that as a differentiator and utilize that to build a brand for the longer term. ■

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