CLEAN-UP ACT

Green chemistry: A comprehensive tool to address environmental issues facing Indian API & fine chemicals industry

Adoption of the principles of green chemistry, involving the invention, design and application of products & processes that reduce or eliminate the use & generation of hazardous substances, is the only solution for the pharmaceuticals industry to overcome its environmental problems. There is a misconception that this approach to waste minimisation is an expensive one – not suitable for a time when cost pressures on the industry have risen and margins squeezed. On the contrary, green chemistry can cut costs, by eliminating or minimising the generation of wastes, reducing the amounts of reagents, solvents, energy and water used in the processing and by valorising by-products in a far more effective manner.

But for the industry to embrace the techniques of green chemistry and engineering effectively requires a paradigm shift in approach, a change in mind-set and the whole-hearted support of senior management that must look beyond short-term fixes.

These were some of the thoughts that emerged from a one-day conference on 'Green Chemistry & Engineering for the Pharmaceuticals Industry' organised by the Green Chemistree Foundation, a Mumbai-based foundation propagating the cause to the wider chemical industry, in Hyderabad on February 5, 2013.

Mr. Shiva Reddy, Senior Environment Engineer, APPCB lighting the lamp to inaugurate the conference

The event was attended by about 100 delegates, mainly from the local pharmaceuticals industry. An exhibition, showcasing green technologies from about a dozen companies, was also organised alongside the conference.

'All the more relevant when regulators implement laws in true spirit'

Speaking at the inaugural session, Mr. Shiva Reddy, Senior Environment Engineer, Andhra Pradesh Pollution Control Board (APPCB), noted that when regulators implement laws in true spirit, all of the benefits of green chemistry will become obvious. "The APPCB has created a separate cell to work with the pharmaceutical industry for promoting green chemistry," he added.

Mr. Arun Kumar, Chief Engineer, APPCB, highlighted the problems posed by indiscriminate usage and release of hazardous solvents in the manufacture of active pharmaceutical ingredients (APIs). "We would like to see solutions to tackle this huge and growing problem," he noted.

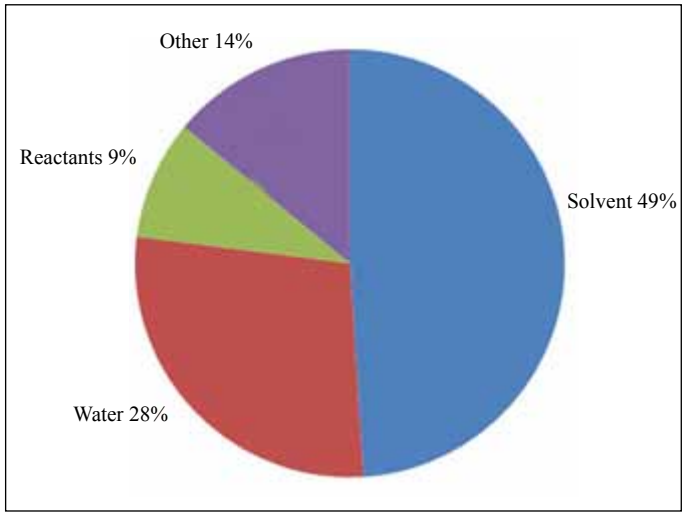
Mr. Madhusudan Rao, Member Secretary, APPCB, called for a clear commitment from the top management to implementing the principles of green chemistry. "It is vital to have clear waste accounting at each plant, and to deploy the right people to implement these new practices. Industry must see waste as a resource and be flexible to make process changes as and when required," he noted.

Dr. Vilas Dhanukar, Global Process R&D Head, Dr. Reddy's Laboratories, speaking at the inaugural session

'Huge scope to change processes to make them greener'

Dr. Vilas Dhanukar, Dr. Reddy's Laboratories (DRL), felt that there was huge scope to change processes to make them greener by focusing on innovation. In his view, the fundamental driving force for green chemistry is economics, but other important drivers are safety, compliance, efficiency and reliability. He noted that a lot of guidelines are now available in literature for route selection and optimisation. Likewise, a large body of work is available on the use of the right solvents for chemical conversions. "Use single solvents wherever possible, instead of solvents having diverse properties. Avoid halogenated and hazardous solvents, such as dichloromethane, acetone and acetonitrile; instead use green solvents such as methyltetrahydrofuran, which is expensive, but available even from renewable sources and can be recycled with the right techniques to bring down costs."

As an example of the work done in minimisation of solvent use he pointed to the developments in the manufacturing route for the active ingredient in *Viagra* (sildenafil citrate) wherein solvent usage was brought down from a whopping 1,300-litres/kg in the first medicinal chemistry route first proposed for its synthesis, to 7-litres/kg in the commercial route now practiced.



Solvent & water account for ~ 77% of PMI for APIs

Dr. Dhanukar also stressed the need to have the right matrices to measure and substantiate claims, and urged collaborative approaches between companies and between industry & academia to capitalise on the wealth of information available with different stakeholders.

Start wherever you can!

Mr. Nitesh Mehta, Green Chemistree Foundation, noted that the acid test of green chemistry is its ability to deliver the same level of efficiency as possible with the conventional process. As a strategy, he advised companies keen to implement green processes to carefully identify the right targets, based on a careful analysis of problem areas, capabilities, budgets, timelines available and management commitment. "It will be prudent to attack processes that have an high E-factor (the amount of waste generated per unit of the desired product) and/or high toxicity. Look at processes where there are cost pressures, as green processes can often result in significant savings. There are low hanging fruit that could be short-term game, with quick benefits. Start wherever you can, but start!" Mr. Mehta stressed. "Environmental challenges are opportunities to make profits."

Table 1
The Twelve Principles of Green Chemistry*

Principle	Description
Prevention	It is better to prevent waste than to treat or clean up waste after it has been created.
Atom economy	Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
Less hazardous chemical syntheses	Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
Designing safer chemicals	Chemical products should be designed to affect their desired function while minimizing their toxicity.
Safer solvents and auxiliaries	The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
Design for energy efficiency	Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
Use of renewable feedstocks	A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
Reduce derivatives	Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
Catalysis	Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
Design for degradation	Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
Real-time analysis for pollution prevention	Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control, prior to the formation of hazardous substances.
Inherently safer chemistry for accident prevention	Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

Source: American Chemical Society

'Go beyond synthetic routes developed by medicinal chemists'

Mr. Dhileep Krishnamurthy, Piramal Enterprises, pointed out that the fundamental issue with many of the processes employed in the industry is that medicinal chemists at innovator companies developed them. "The scale has manufacturing has gone up from a few grams to a few tonnes, but the processes have remained largely unchanged. This must change," he noted, while calling for a strong emphasis on process research.

Generic companies, in his view, have the luxury of time to focus on process development, but the challenge is to secure a strong non-infringing IP position due to the competition. "There is a large amount of prior art available from innovators and academic publications, which should be effectively leveraged," he added.

Solvent reduction efforts at LAZORR

Mr. Anil Kumar Jain, President (Operations), Aurobindo Pharma, dwelt on the success achieved at the collaborative network, LAZORR (for Lupin, Aurobindo, Zydus, Orchid, Dr. Reddy's and Ranbaxy – the participating companies in the consortium) in developing and sharing ideas for reduction in solvent and water use. "The focus has only been on sharing on non-classified information related to solvent, energy, waste, safety, water management and business continuity," he noted.

The solvent team, which started work in 2009 with a three-tier structure and nearly 60 personnel from the

Table 2
Matrices for determining how 'green' a process is

Matrix	Definition
E-factor	Quantity of waste generated [kg]/Quantity of desired product [kg].
Process Mass Intensity [PMI]	Quantity of raw materials input [kg]/Quantity of bulk API out [kg].
Carbon efficiency	Amount of carbon in product / total carbon present in reactants.
Atom economy	How much of the reactants remain in the final product.

Table 3
E-Factors across the chemical industry

Industry sector	Annual production (Tonnes)	E-factor	Waste produced (Tonnes)
Oil refining	10^6-10^8	Ca. 0.1	10^5-10^7
Bulk chemicals	10^4-10^6	<1-5	10^4-5×10^6
Fine chemicals	10^2-10^4	5-50	5×10^2-5×10^5
Pharmaceuticals	10-10^3	25-100	2.5×10^2-10^5

Source: Roger Sheldon

participating companies, has achieved significant results. "We have learnt from the best in the breed and have even started common vendor evaluations. We have also done low-cost, speed piloting of some new technologies, such as absorption of solvents going out through vents, distillation column automation and shifting to use of spiral condensers." By using pressure swing absorption for drying, the companies saved on the usage of more than 30-tonnes of solvents like ethyl acetate and isopropyl alcohol. "Overall, the LAZORR initiatives have resulted in savings of 1-mn gallons of solvents and 196-mn litres of water," Mr. Jain added.

Greener process for albendazole

Dr. Komal Maheshwari, Newreka Green Synth Tech. P. Ltd., provided a case study of the synthesis of albendazole, wherein the conventional four-stage route with an E-factor of 50, was replaced with a greener alternate with a 33% reduction in the amount of waste generated.

Process intensification through microreactors

Mr. Shailesh Dhume, Bayer Technology Services, highlighted the benefits of using micro-reactors for chemical transformations. These include lower development costs; lower risks when handling hazardous materials; and high flexibility and speed. "There are no scale-up issues as the characteristic dimensions remain unaltered," he noted.

Use of biocatalysts

Mr. Sandeep Bijamwar, Advanced Enzyme Technologies Ltd., a leading supplier of enzymes for bio-catalytic processes, dispelled some of the myths associated with using enzymes for chemical transformations: instability of enzymes; their ability to act only on natural substrates; high costs; and low productivity. "Hydrolases are an important category of enzymes, which play a major role in the pharmaceuticals industry," he added.

Mr. Bijamwar also pointed out that only less than 1% of the more than 3,000 known enzymes are used commercially in significant amounts. "The number of enzymatic processes is expected to increase for the preparation of optically pure fine chemicals and therapeutics, and for antibiotics," he added.