NATURE IS LIFE – WITH GREEN CHEMISTRY, YOU CAN CHOOSE LIFE

In this article, the Chief Scientist at the Indian Institute of Chemical Technology (IICT) discusses how green chemistry could be the key to reducing environmental footprint of chemical processes, in turn offering a sustainable business approach for the pharmaceutical industry.

Today, life sciences has a pressing imperative – providing effective and affordable medicine. Furthermore, the industry needs a sustainable business approach, since a majority of 'blockbuster' drugs are losing patent protection and returns on R&D spending are shrinking. Pharmaceutical companies invest, on an average, 12 to 15 years and incur a cost of US$2.5 billion to launch a new drug.

Big Pharma has explored several options to address their challenges – internal restructuring, substituting batch processes with flow chemistry, mergers and acquisitions, outsourcing of R&D and manufacturing, and acquisition of experimental drug candidates. Another widely explored option, open source drug discovery, while economically viable, involves issues such as IP rights of discovered molecules. Green chemistry, on the other hand, offers lasting value in terms of lean manufacturing; but it has not been widely adopted.

The pharmaceutical industry generates substantial waste during the synthesis and purification of active pharmaceutical ingredients (APIs) in preclinical and commercial processes. In industrial chemical manufacturing, the E-factor (kilogram waste per kilogram of product manufactured), is the highest in the pharmaceutical industry, ranging from 25 to over 100.

Green chemistry: The context

The pharmaceutical industry generates substantial waste during the synthesis and purification of active pharmaceutical ingredients (APIs) in preclinical and commercial processes. Roger Sheldon, Professor Emeritus of Biocatalysis and Organic Chemistry at the Delft University of Technology, Netherlands, developed the 'E-factor' (kilogram waste per kilogram of product manufactured), a metric to evaluate the environmental footprint of chemical processes. In industrial chemical manufacturing, he found E-factor to be the highest in the pharmaceutical industry, ranging from 25 to over 100. At the other end of the scale, E-factor of the oil refining industry is less than 0.1.

Green practices deliver value across the pharmaceutical value chain. Since chemistry is the lifeline of pharmaceuticals, green chemistry offers a sustainable business approach. The US Environmental Protection Agency (EPA) defines green or sustainable chemistry as, "the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances." In life sciences, green chemistry safeguards the interests of the environment and public health and safety, and furthers the research, discovery, development, and manufacture of medicines.

Safer chemical entities, an urgent need

The 2005 Nobel Prize in Chemistry awarded to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock provided an impetus for green chemistry. The breakthrough contributions of the scientists in metathesis simplify the synthesis of carbon compounds, which paves the way for more efficient manufacturing of medicines and pharmaceutical products.

The principles of green chemistry can be integrated in the formative phase of drug discovery. It ensures sustainability of products, while addressing public health and environment risks. Pharmaceutical companies and suppliers need to implement, monitor, and measure sustainable chemistry in the manufacture of medicine, whether in batch or continuous production. Regulations should mandate that companies avoid the use of toxic substances, explore the reuse of solvents, and replace hazardous solvents / reagents with biodegradable and energy-efficient alternatives.

Leading universities are sensitizing the life sciences workforce – chemists, biologists, chemical engineers, and drug researchers – about the environment. Harvard University's sustainability plan adopts green chemistry. It proposes to identify hazardous chemicals and eliminate their use on campus. "In our research, and our careers, we must endeavor for a toxicological understanding of the compounds we create and assume the responsibility for determining their ecological fate," says Allen Aloise, FAS Science Director of Graduate Studies at Harvard University. According to Professor Wei Zhang, the Director of the Center for Green Chemistry at the University of Massachusetts, Boston, "Green chemistry is not an independent field but a philosophy that will be a non-separable part of chemistry."

Cleaner solvents, a must

Aqueous effluents and stoichiometric oxidants and reductants, such as KMnO4, MnO2, LiAlH4, and Zn are the major sources of waste in pharmaceutical processes. Stoichiometric oxidants can be substituted with catalysts to increase process efficiency. Biocatalysis and heterogeneous catalysis production processes ensure higher conversion and yield in reactions. In addition, they realize sustainability through 'lean' manufacturing - optimizing resource consumption, minimizing waste generation, decreasing greenhouse gas emissions, and improving product quality.

Solvents used in organic synthesis play a critical role in making a reaction homogeneous and in allowing molecular interactions to be more efficient. However, the environmental impact of several solvents is a cause of concern. Ionic liquids are an alternative, but the preparation of ionic liquids is tedious. Moreover, the jury is still out on the environmental safety of ionic bonds.

The Indian Institute of Chemical Technology has undertaken extensive research to identify liquid polymers and low melting polymers to replace hazardous solvents such as benzene (carcinogen) and chlorinated solvents (ozone depleting agents). The Institute has identified eco-friendly solvents, including supercritical carbon dioxide and Polyethylene Glycol (PEG) for industrial application. PEG, which has a low molecular weight (2,000 or lower), is an efficient reaction medium for Pd-catalyzed C-C bond formation. Organic transformation with PEG is rapid and high-yielding. It is superior to conventional solvents and ionic liquid media since reactions take place easily with electron-deficient and electron-rich olefins, and high region and stereo-selectivities.

The green movement

Green chemistry helps Big Pharma improve process efficiency. Janssen, the pharma arm of Johnson & Johnson, anticipates tangible value from green practices. It can reduce raw material requirement by 67%, water consumption by 75%, and hazardous waste generation by 87%, according to Philip Dahlin, Director of Sustainability at Janssen, in the FT Health Report June 2014.

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Pfizer is at the forefront of green pharma. The Pfizer solvent guide helps researchers and chemists select solvents for medicinal chemistry based on diverse sustainability criteria. The company's green chemistry and biotechnology program guides the creation of a portfolio of green compounds as well as the adoption of green practices in production processes.

Pfizer, Merck & Co., and Bristol-Myers Squibb have been recognized with the annual US EPA Presidential Green Chemistry Award for implementing environment-friendly drug development and manufacturing processes. GlaxoSmithKline uses an eco-design toolkit for sustainable operations. The toolkit has five modules to help chemists, researchers, and process engineers adopt green chemistry, select sustainable solvents and reagents, and also gain a better understanding of hazardous substances.

The American Chemical Society Green Chemistry Institute (ACS GCI) Pharmaceutical Roundtable seeks to promote green chemistry and engineering among companies involved in R&D and manufacture of APIs and medicinal products. Participating members include industry leaders like – Eli Lilly and Company, AstraZeneca, Merck, F. Hoffmann-La Roche Ltd., Johnson & Johnson, Dr. Reddy's Laboratories, and Pfizer.

Software for sustainability

Cross-disciplinary collaboration is a prerequisite for process and product innovation in the life sciences. Scientists, product specialists, process engineers, and sustainability officers need visibility across the enterprise – research initiatives, procurement and production processes, and packaging.

Software tools integrate green chemistry with pharmaceutical applications, while enabling real-time sharing of information between stakeholders, including suppliers, contract manufacturers, and research organizations. IT systems boost productivity of the research organization and rationalize the cost of drug discovery by eliminating errors and superfluous research / processes.

Research scientists at Pfizer Global Research and Development use a web solution developed by Infosys on the Microsoft .NET Framework 3.0 and Windows Presentation Foundation to store and share knowledge. The application allows researchers to present research findings in 3-D images and graphs, and search databases containing millions of records for specific details such as results of an experiment or the chemical name of compounds.

Interactive dashboards with visualization tools help identify areas where adequate research has not been undertaken. Collaboration tools and unified repositories enable biologists, chemists, and discovery scientists working in diverse therapeutic areas to build hypotheses in real-time, analyze results, eliminate ineffective drug candidates in early stages, and discover hidden connections between

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different experiments across time spans. A multidisciplinary approach vastly improves research outcomes and facilitates repurposing of existing drugs. A stellar example is the use of anti-inflammatory drug, aspirin, to manage cardiac disease.

Molecular modeling and in silico screening accelerate drug discovery. Continuous monitoring of ambient temperature and pressure increases energy efficiency of chemical reactions. Significantly, in-process monitoring minimizes the formation of byproducts. Pharma companies should use tools to assess the environment, health, and safety footprint of their ecosystem.

Sustainable life sciences requires more than environment-conscious pharmaceutical engineers and technologists. We need to encourage green chemistry across the supply chain and practice sustainability at a molecular level.

About the Author

Dr. Srivari Chandrasekhar

Chief Scientist and Head – Division of Natural Products Chemistry, Indian Institute of Chemical Technology (IICT)

Dr. Srivari Chandrasekhar received his B.Sc. (1982), M.Sc. (1985), and Ph.D. (1991) degrees from Osmania University, and pursued post-doctoral research at the UT Southwestern Medical Center, Dallas, USA, with Prof. J. R. Falck. As a Humboldt Fellow at the University of Göttingen, he worked on the synthesis of hybrid natural products with Prof. L. F. Tietze.

Dr. Chandrasekhar was instrumental in setting up the state-of-the-art Molbank facility at the IICT for the storage and retrieval of chemical samples for HT screening.

He has over 240 publications in national and international journals. He won the Infosys Prize 2014 in Physical Sciences for his diverse and notable contributions in synthetic organic chemistry with special focus on the synthesis of complex molecules from natural sources. He has devised innovative, practical approaches to pharmaceuticals of current interest to industry.

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