# Pharmaceutical industry to benefit greatly from implementation of green technologies

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The Green Chemistree Foundation (www.greenchemistree.co.in) organised a two-day conference on 'Advancing Implementation of Green Chemistry & Engineering in Indian Pharma Industry' at Hyderabad, on September 27-28, 2018. The conference was conducted in association with American Chemical Society's Green Chemistry Institute (ACS-GCI) – Pharmaceutical Roundtable and Telangana State Pollution Control Board.

Four separate seminars were conducted in parallel over two days:

- 'Pharma Leadership Summit' and 'Workshop on Bio-Catalysis in Pharmaceutical Industry' were conducted on the first day;
- Seminar on 'Ready To Implement Tools, Technologies and Solutions in Green Chemistry/Engineering for Pharma Industry', and the 'ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) Workshop on Essential Tools and Technologies for driving Green Chemistry in the Pharmaceutical Industry', were conducted on the second.

More than 300 delegates from the pharmaceutical industry and academia, from India and abroad, attended the events.

In his welcome address, Mr. Nitesh Mehta, Co-founder & Director, Green Chemistree Foundation, and Conference Convener, reviewed the progress of the Green Chemistree Foundation, since its inception in 2009, and the growth of Pharma Roundtable, which now has 21 companies as members.

Bristol-Myers Squibb, Hikal, GVK Bio, Laurus Labs, Natco and Pfizer were the Industry Partners for the event, while Pharmexcil, Bulk Drugs' Manufacturers Association (BDMA) and Pharmaceutical Supply Chain Initiative (PSCI) were the Associate Partners. The Research and Innovation Circle of Hyderabad (RICH) were Knowledge Partners., while *Chemical Weekly* and *Express Pharma* were Media Partners.

A small exhibition was also held alongside the conference in which several organisations exhibited their products and services, especially related to implementation of green technologies. Participants included the ACS-GCI – Pharmaceutical Roundtable, Advanced Enzymes, Equinox, Geocycle, Johnson Matthey, Mettler Toledo, Newreka, PerkinElmer and Sugam Paryavaran Vikalp.


**Inauguration by dignitaries (L to R): Dr. Juan Colberg; Dr. David Constable; Mr. R.K. Agarwal, Managing Director, Nakoda Chemicals; Prof. S. Dayanand, Dept. of Animal Sciences, School of Life Sciences, University of Hyderabad; Dr. Guy Humphrey; and Mr. Nitesh Mehta**

PHARMA LEADERSHIP SUMMIT

# Strategic decisions and actions needed for sustainable growth of Indian pharmaceuticals industry

The objective of 'Pharma Leadership Summit' was to deliberate on strategic decisions and actions needed to be taken by the Indian pharmaceuticals industry to grow sustainably; and learn from global MNCs about strategies and tools for implementing Green Chemistry & Engineering (GC&E) to reduce costs and environmental footprint.

## Future of pharma and value addition through GC&E

Dr. David Constable, Science Director, ACS-GCI, offered a global perspective on how GC&E can add greater business value for a more sustainable pharmaceutical supply chain. While there is now more than 25-years' history of green and sustainable chemistry efforts in the US, for a majority of chemicals in common use, GC&E is not broadly implemented throughout the typical chemical or pharmaceutical supply chains.

Dr. Constable's presentation provided an overview of green and sustainable chemistry efforts in USA that have helped spur chemistry innovations. "A review of the depth, breadth and variety of these innovations gives one hope that chemists and chemical engineers will make many significant advances in the next 20 years, which will move society towards a more sustainable lifestyle. Such green chemistry innovations hold the key to solving most of environmental problems," Dr. Constable added.

He opined that the global chemistry enterprise, as is currently operated, is unsustainable. The sustainability risks include diminishing resources, stressed environment, etc. Supply of critical elements, such as rhodium, for example,

**Dr. David Constable**

is not sustainable, as the metal is not abundantly available in nature. Likewise, indium has many applications in electronics, but its recycle is a major challenge. "Socio-economic costs of mining valuable platinum group metals, is high. Phosphorus, though cheap, will not be available forever. Production of most precious and speciality metals are coupled to that of major metals. Also, supply of many 'technology metals' is price inelastic."

Dr. Constable presented an overview of the pharmaceutical supply chain, wherein outsourcing is today a common trend, driven by the need to costs, for flexibility, etc. He enumerated various sustainability risks in these supply chains – waste production and its recycle, pollution, etc. Generally, the steps of disposal, treatment, control and source reduction are followed for pollution prevention, in this order.

Dr. Constable stressed the need for systems-level thinking, and for more use-inspired fundamental research. "Green is not synonymous with sustainable," he cautioned, adding that the major challenges for attaining sustainability, include some traditional sticking points, such as infrastructure. He also highlighted the need for integrating sustainability principles into the design of products and processes. Dr. Constable pointed out that in a random selection of 100 chemistries in a review of named reactions, it was found that many chemists still use old chemistries, and chemical technology has not changed much over several decades.

## Importance of sustainability in Indian pharmaceutical industry

Mr. Sai Sethuram, Head – Product and Portfolio Development, Pfizer Essential Health, Pfizer Healthcare Pvt. Ltd., offered an Indian perspective on sustainability. He shared his company's experiences in reducing waste generation in a pharmaceutical production process through reduction of solvent and water consumption, as well as their recovery, which led to increased yields and significantly higher profit margins.

Mr. Sethuram opined that in the current scenario of cheaper renewable energy, increasing investor focus on sustainability and progress towards a 'circular economy', the Indian pharmaceutical industry has immense opportunities. The industry here, he pointed out, has several advantages: it is seeing rapid growth, and is expected to reach a size of US$30-bn to US$50-bn by 2020. "India is the third-largest supplier of drugs by volume in the world; the country has become a destination of choice for large multinationals with many of them establishing R&D and innovation hubs here."

However, he cautioned that the industry is also facing headwinds, including quality concerns, environmental issues, etc. "The Indian pharmaceutical industry must address these issues head-on for success."

Mr. Sai Sethuram

According to Mr. Sethuraman, sustainability – economic, social and natural (resources) – is key for continued growth of the industry. "Sustainability is the right thing to do as it enhances organisational reputation, trust and confidence; ensures better employee engagement; and has positive impact on communities. Reduction in waste increases efficiency, reduces costs and increases productivity," he noted.

Mr. Sethuram discussed some of the sustainability initiatives of Pfizer India and the global targets for 2020 – greenhouse gases reduction by 20%, all waste reduction by 15% and water withdrawal by 5% – from their 2012 levels. The sustainability initiatives at the R&D and manufacturing sites of Pfizer include: increasing solar and wind power generation; zero liquid discharge; energy conservation; improved air handling efficiency; right disposal of wastes; rainwater harvesting, etc.

## Business case for green and sustainable chemistry development

Dr. Guy Humphrey, Distinguished Senior Investigator, MSD (Merck), USA, pointed out that GC has been a fundamental part of Merck's culture for many years, as is a conviction that sustainability is critical to achieving the 'triple bottom line' of economic, environmental and social benefits. Merck, according to Dr. Humphrey, is a recognised industry leader in sustainable process design.

The importance of GC to the pharmaceutical industry is amply illustrated by the fact that the industry produces more than 100 million kg of APIs annually and the Process Mass Intensity (PMI) – the ratio of total mass of all raw materials to the total mass of all isolated products – is 150 (implying a high generation of wastes).

To reduce this waste generation, the industry needs manufacturing routes that are easy to operate, have low costs, give high yields of desired products and are efficient. In addition, the routes should have ease of supply of raw materials, be safe, reproducible, robust and sustainable.

According to Dr. Humphrey, the benefits of sustainable chemistry for a new product need to be realised throughout the product lifecycle, and innovation plays an important role. Tools enabling innovation and optimisation include structural elucidation and phase characterization, high throughput experiments, predictive sciences, in-line analysis and kinetic profiling, chemo-catalysis, etc.

GC teams, he pointed out are cross-functional – consisting of synthetic chemists, analytical chemists, engineers, bioprocess chemists, etc. He emphasised development of a GC mindset through education, awareness & recognition and investment in green technology (catalysis, flow, etc.). "There are several barriers to implementation of green chemistry within the industry – lack of harmonisation among available metrics, government regulations, lengthy regulatory reviews for post-approval changes, etc.," he added.

Dr. Humphrey also discussed the limitations of the PMI metric, especially the fact that it does not include environmental and safety concerns of the materials involved.

He discussed several innovations at Merck including in the synthesis of greener routes for MK-7264 (a chronic cough treatment), in which the process has poor yield, large PMI, poor impurity control and consists of four steps to install three carbons in the product molecule. "The green chemistry mindset resulted in development of one-step or two-step processes," he noted.

Likewise, a new green process for another life-saving drug, *Zerbaxa Gen-2*, approved by the US and EU, has improved PMI to 200 (from 800), overall yield to 75% (from 40%), etc.

Dr. Humphrey expressed the need for pharmaceutical, agrochemical and animal healthcare industries, as well as Contract Research Organisations to inculcate the GC mind-set even among the manufacturers of intermediates.

## Application of GC principles in early phase chemical development

Dr. Rajappa Vaidyanathan, Group Director and Head, Chemical Development and API Supply, Bristol-Myers Squibb (BMS) India, pointed out that while PMI is a useful metric to track 'greenness' of a process, a more comprehensive and quantitative assessment that takes into consideration the inherent safety aspects of a reaction has been developed at BMS.

Dr. Rajappa commented that the complexity of synthetic processes – from making drugs to iPhones – has increased over time, and this offers a lot of scope for improvement. Strychnine, an alkaloid, was first synthesized in 1954 in a 29-steps process, but thanks to innovation this was brought down to just six steps in 2011.

Dr. Vaidyanathan described the BMS Greenness Scorecard – a mass-based metric to assess the greenness of a chemical process. It is designed

to comprehensively assess the environmental health and safety impacts of chemical processes, and complements mass-based metrics such as PMI. The scorecard collects and evaluates several parameters such as class of solvents used, number of unique solvents used, solvent recovery, etc. Greenness scores and PMI calculations are generated for each step, as well as the cumulative synthesis process. The BMS Greenness Scorecard has been implemented for all BMS small molecule projects.

## Hikal's journey towards greener pastures – from identification to implementation

Dr. Sudhir Nambiar, President – R&T, Hikal Ltd., noted that the company's tryst with green processes is not new; Hikal accessed technology for the production of a nitrile through ammoxidation about two decades ago. The obvious advantages of this technology include the avoidance of handling cyanide, as well as reduction of effluent.

A significant portion of the transition towards greener pastures has involved the identification of greener routes for both established products and those under development that result in higher atom efficiency, reduction in waste and hazards. Similarly, the company has benefited by the active adoption of biocatalysis as a part of its manufacturing strategy. The adoption of solar and more fuel-efficient utilities has also helped the company on its sustainability journey.

Dr. Nambiar enumerated various challenges currently facing chemistry and the chemical industry. "Biology is rapidly replacing chemistry in various processes and there is a need to recognise this shift. Due to pollution crackdown in China, several pharmaceutical raw materials are not available and they need to be produced here through backward integration. There is rapid commoditisation of several APIs. Many talented people are opting for information technology, away from chemistry, making it difficult for chemical companies to attract new talent," he observed.

Hikal's sustainability initiatives encompass carbon & water footprint reductions and waste reduction. He opined that in future, water footprint reduction will need more attention.

Hikal, he added, has started looking at GC options at the early stages of product development. After the target molecule is finalised the focus is on scale-up, process innovation and technology development, though it is difficult to change the process routes after the product is established in the market, due to regulatory issues.

He discussed several process improvements carried out at Hikal, especially in the area of continuous processes. These included the use of continuous liquid-liquid extraction with a feed rate of 2,500-kg/hr; conversion of a large batch reactor (16 cu.m.) for highly energetic diazo compounds, to a small continuous process reactor (0.7 cu.m.); use of a pinched tube reactor for continuous bromination; and continuous production on pilot scale using Agitated Thin Film Dryers.

## Gaps & opportunities in implementation of GC for pharmaceutical industry

Dr. Vilas H. Dahanukar, R&D Director, Bioxera Research Pharma LLP, dwelt on the challenges facing the Indian generics industry. The regulatory landscape, he noted, has changed due to Generic Drug User Fee Amendments (GDUFA) requirements, need for more transparency in supply chains, etc.

The typical reaction flow for API syntheses includes route selection, reagents & solvents selection, work-up, unit operations, optimisation of reaction parameters & unit operations, and isolation of products with high purity. "The GC&E principles provide a strong framework towards addressing the key issues in API synthesis processes," he noted.

Dr. Dahanukar discussed the development of green processes for several molecules through three case studies:

- Telescoping of five reactions for the synthesis of Dasantafil, a drug for treating erectile dysfunction, by a one-pot process with more than 90% conversion in each step using phase transfer catalyst.
- Synthesis of Ramipril by biocatalysis using a lipase, replacing the earlier synthesis scheme using pig liver esterase (of animal origin). Optimisation of the enzymatic system, to establish optimum process conditions with 8-10% of immobilised enzyme loading, gave product yields of 85-90%. The immobilized enzyme can be recovered and reused for about ten cycles.
- In the synthesis of Suvorexant, a drug, direct activation of C-H bond and coupling, using copper, has improved the greenness of the process.

Dr. Dahanukar stressed the need to develop a mind-set for greener and simpler processes for the manufacture of APIs. "Chemistry and technology are both changing rapidly and there is a need to try newer approaches to solve process problems using novel chemical transformations," he noted.

## GC and manufacturing technology at Pfizer: Innovation for a sustainable future

Dr. Juan Colberg, Senior Director, Pfizer Inc., USA, observed that GC&E is a different way of thinking about how chemistry and chemical engineering can be done in the chemical and pharmaceutical industry.

Over the past 15 years, Pfizer's GC Programme has focussed on different ways to design, develop and implement chemical processes to deliver life-saving drugs to patients. The programme has come a long way since it was started in 2001, and uses creative and innovative ways to reduce waste, conserve energy and water, while delivering cost-effective processes. The company has also prepared GC guides, e.g. for solvents, acids and bases, etc. that are used for training.

The business case for GC implementation include benefits such as:

- Faster access to market – from new drug discovery to commercialization;
- API supply chain de-risking;
- Potential for reducing manufacturing costs;
- Addressing regulatory and social risks;
- Brand enhancement and protection, etc.

Pfizer also has an environmental sustainability programme with public goals – e.g. greenhouse gases reduction targets – as well as sustainability expectations and principles that guide the company's supplier relationships.

Dr. Colberg discussed the green process development for the drug Sertraline (*Zoloft*), used to treat depression. The US FDA approved the drug in 1986 and over 300-tonnes were produced annually in the USA at peak sales. "The process efficiency (atom and energy) have major impact at this level of production, and therefore was the focus of process development."

He described the discovery route to sertraline and the history of various commercial routes for the drug, with details of solvents used, the consumption of raw materials, as well as costs of waste treatment. The development of a new route by Pfizer led to construction of a new plant due to use of different solvents, etc.

The company has also done considerable work in developing processes based on non-ferrous metal catalysts, especially for cross-couplings. Data on various metal catalysts based on Pd, Ni, Cu, Fe have been collected and analysed covering parameters such as cost per mole, annual production, oral exposure limits, natural abundance, supply risk, carbon footprint, etc. Based on this data, the most suitable metals have been selected for various processes.

Dr. Colberg also discussed the use of Flow Chemistry and continuous API production, with the example of commercial process development for the drug, Pregabalin (*Lyrica*). Continuous manufacturing, he added, can impact cost and sustainability through reduced solvent usage, reduced cycle times, etc. He also offered details of several other processes including: diastereo-selective approach to a chiral lactam (improved reaction speed); and Suzuki coupling with continuous process (better product quality), with improvement in yield from 56% (batch) to 80% (kilo-lab level continuous).