POLLUTION PREVENTION

Green chemistry & engineering: Key to sustainable pharmaceuticals manufacturing

A two-day conference and exhibition on 'Green Chemistry and Engineering: Enabling greater business value for an environmentally responsible pharma supply chain,' was held in Visakhapatnam on February 20-21, 2017. The event, organised by the Green ChemisTree Foundation, in partnership with the ACS-Green Chemistry Institute, Pharmaceutical Roundtable and the Pharmaceutical Supply Chain Initiative (PSCI), highlighted the challenging regulatory environment facing the Indian pharmaceuticals industry, including suppliers of active pharmaceutical ingredients (APIs).

Green Chemistry (GC) and sustainable science is the strategic design, development, and implementation of chemical products and processes that reduce or eliminate the use & generation of hazardous substances and waste, are inherently safe, and increase efficiency while minimizing environmental footprint and impact. Good science is the key to sustainability, GC, and low-cost manufacturing.

GC can have an enormous impact on the company's triple bottom line: it is cost effective, safer for employees and better for the environment.

Reducing the environmental impact of the supply chain

Speaking at the inaugural session, Mr. Nitesh Mehta, Co-Founder & Director, Newreka Green Synth Technologies Pvt. Ltd., pointed out that GC is still at a nascent stage in India. "Expertise is lacking, and successful case studies are few, but there is a rise in demand for tools and technologies that aim to reduce the environmental footprint of the supply chain," he noted.

Inauguration of conference

Green Chemistry and Engineering (GCE), he added, gives several advantages to industry including:

- Freedom, in terms of expansions, as the methodology strongly emphasises pollution prevention at source;
- Opportunity to enhance profitability; and
- Opportunities for the pharma industry to integrate backward, to production of intermediates, wherein dependence on China is currently overwhelming.

Ensuring safety of drugs

Dr. A. Ravishankar, Andhra Pradesh Drug Regulatory Authority, noted that regulators have a long way to go to catch up with technological developments in the industry. "The 13th rule of Green Chemistry should be to update regulators," he quipped.

In his view, costs of GCE initiatives are an issue for SMEs, and adoption & integration of these technologies into their production processes are challenging. "As a result, India lags behind in sustainable production of chemicals and related products." He added that inter-ministerial coordination is also lacking for promoting sustainable development.

Dr. Ravishankar called for an effective 'track and trace' system for the pharmaceutical supply chain to tackle the menace of spurious drugs. "Mechanisms are needed to ensure safe drug delivery to the customer."

'Great role in pollution prevention'

Mr. Bhaskar Rao, Zonal Officer, Andhra Pradesh Pollution Control Board (APPCB), observed that the

Mr. Nitesh Mehta, Co-Founder & Director, Newreka Green Synth Technologies Pvt. Ltd

focus of regulators has shifted to prevent pollution, rather than end-of-pipe treatment. "Of late, this emphasis has yielded good results," he noted.

The APPCB, on its part, have been organising several clinics for industries and providing forums for interactions to tackle the problems of pollution.

Pointing to the pharma industry in Visakhapatnam, where about 80 units operate, he noted that the experience with Common Effluent Treatment Plant (CETP) has not been successful due mixing of various types of effluents. "Source level treatment is always better and segregation of problematic effluents enables better operations of the CETP."

In the Pharma City, near Visakhapatnam, the treated effluent is now stored in 'guard ponds' for about a week and discharge into the sea is permitted only after compliance to norms is verified. "All stakeholders have accepted this," Mr. Rao added.

Co-processing as an option

As part of another initiative, the Cleaner Production Cell in the APPCB has worked with the pharma industry to develop co-processing of organic wastes in the cement industry. The waste-to-energy concept, developed in partnership with the Confederation of Indian Industry, is still in the early stages, but a beginning has been made.

"On-land discharge of pharma industry effluents are a problem and sea-discharge can work well. Green Channel Consent has now been introduced on a self-declaration basis as pro-active measure. Online systems have been put in place for clearance within 21 days. But there will be no compromise as far as pollution is concerned," Mr. Rao added.

In another initiative, distilleries, which faced problems when discharging effluents into water bodies, have been encouraged to opt for anaerobic digestion, which has not only ameliorated the waste disposal problem, but also made it possible to generate up to 3-tph (tonnes per hour) of steam from boilers running in bio-methane produced in the digesters. In addition, solid wastes find use as bio-fertiliser.

Sustainable growth path needed

Dr. David Constable, Director, ACS-Green Chemistry Institute, highlighted the fact that the global chemistry enterprise, as currently operated, is unsustainable – be it in the raw materials or the processes it uses. It treats the environment as an infinite sink, which is clearly not sustainable. "Green Chemistry is about innovation and holds the key to solving most of the environmental and health issues we face today," he noted.

He pointed to the critical and unsustainable position with respect to supply of critical elements. As an example, he observed that reserves of rhodium (Rh) – present at a level of 0.0002-ppm, and found mainly in South Africa and Russia – are likely to last anywhere between 5-50 years. The element is used extensively in catalytic conversions, but the socio-economic costs of mining, especially in underdeveloped countries like Burkina Faso – wherein small families own the mines and children are often used as labourers – are significant. The primitive production processes employed to extract the metal use toxic chemicals such as mercury, with significant socio-economic costs.

"Demand for rhodium and several other elements are rising sharply and recycling is challenging as very small quantities are used per unit, but are distributed in several units. A lot of mass and energy will be needed to get the metal back – thermodynamics is against us here," he observed.

Dr. Constable also observed that production of most precious and speciality metals are coupled with that of major metals, and increased demand for the former can only be met by ramping up production of the latter. Restricted availability of even more common elements – such as tin – could have adverse implications for the pharma

Panel discussion in progress

industry considering nearly half of all pharma catalysts use tin. "Phosphorus won't be available forever. Morocco and China – the two largest suppliers – have about limited supply, and little or no phosphorus is recycled."

New ways of doing chemistry needed

Dr. Constable also spoke about the challenges of getting chemists to do chemical transformations in new ways. "Chemists still use old chemistries – 54% of named chemical reactions were discovered before the First World War and 74% before the Second. Many of these are pretty bad from green and sustainability perspectives," he noted.

He traced the usage of primitive forms of the batch reactor – the preferred choice for producing most APIs – to the Bronze Age. Likewise, primitive forms of distillation can be traced to the 18th century, and crystallisation also back to the Bronze Age.

"The industry needs to embrace flow technologies more," he added.

Dr. Constable also stressed that sustainability concerns should be designed into products and processes. "Early design that incorporates sustainable and GCE principles is imperative to achieve the most cost-effective gains. If we want to make the biggest impacts to products, services and costs, we have to start from the ground up. If we want to build sustainability into the design of products and services we have to think differently about R&D."

In his estimate, the market for GC is expanding, and will surpass earlier estimates that the market will grow from $2.8-bn in 2011 to $98.5-bn in 2020. "There are many examples of success, despite negative perceptions associated with sustainable and green chemistry. Implementing more sustainable practices requires patience and persistence."

'Inculcate culture of GC and sustainability at innovation stage'

Dr. Juan Colberg, Sr. Director Technology & Green Chemistry Leader, Pfizer Inc., also stressed the need to inculcate the culture of GC and sustainability at the innovation stage itself. "Pfizer has GC teams at all research centres and has integrated GC into all development activities," he noted.

In his view, there are seven important elements of a GC programme:

1. Empowered GC teams with management support;
2. Metrics and targets;
3. Resources and tools;
4. Education;
5. Investment in green technology;
6. Awareness and recognition; and
7. External collaboration.

Strategic priorities

Pfizer, he added, started out on the GC journey in 2001 and in 2005 teamed up with Merck and Eli Lilly to put together the Pharma Roundtable, in a bid to catalyse innovative approaches to improving process efficiency and product quality through GCE. "By working together, the Roundtable provides leadership and influence throughout the industry and supply chain."

Pfizer also put together several strategic priorities and in 2007 identified a series of reactions for which greener solutions were needed. They included current reactions such as amide formation, OH activation, amide reduction, greener Mitsunobu reactions, oxidations and epoxidations; as well as more aspirational ones such as C-H bond activation, chiral amine synthesis, and asymmetric hydrogenation. Key ideas outside the reaction theme included solvent-less reactor cleaning and greener alternatives to polar aprotic solvents.

Research grants were given to academia to support several initiatives including greener biologics processing, continuous flow, iron catalysis, amide reduction, non-precious metal catalysis, Grignard in greener solvents, etc. The Pharma Roundtable funded nearly $2-mn to academics for these projects. These academics have been able to leverage additional funds to the extent of about $1.3-mn from US government agencies.

Right solvent selection

The Pharma Roundtable has also worked to define and deliver tools in areas such as solvent selection, reagent guides and process mass intensity (PMI). "Many pharma companies, including Pfizer, have developed their own tools, and collaborations have enabled savings on these efforts and costs. Ten reagent guides are now available; solvent selection is one of the most important decisions and having a simple tool available all the way to discovery is extremely useful," Dr. Colberg observed.

The impact of solvents in the process 'greenness' within the API industry can be gauged from the fact that solvents and water contribute to >80% of the PMI; 60-70% of waste streams; ~75% of the energy usage; 70% of the photochemical ozone creation potential; 50% of greenhouse gases; and 10-40% of costs. In addition, 30-40% of VOC solvent use in a pharmaceutical plant is in cleaning. A 4-kl reactor uses about 5-kl of solvent in a traditional cleaning process. "Small decisions made in this area at the beginning of the process route can make a big difference later on," Dr. Colberg added.

Metrics developed

Metrics are important to measure progress and identify opportunities. They help identify baseline performance and set targets for future improvements. The Pharma Roundtable has created standardised metrics to measure chemical process greenness. These include:

- Chemistry – yield, selectivity, atom economy, reaction mass efficiency; and
- Process – E-factor, PMI and Life Cycle Analysis (LCA).

While PMI and E-factor are common GC metrics, LCA provides a more holistic view and includes an assessment of raw material production, manufacture, distribution, use and disposal, including transportation.

The PMI calculator tool is a publicly available spreadsheet with embedded calculations and users only need to fill in the amounts of reagents, solvents and water. The spreadsheet calculates step and overall PMI for linear sequences, and also calculates separate PMI for solvents, water and reagents.

A recently introduced tool, Green Aspirational Level (GAL), serves as a novel process performance metric that quantifies the environmental impact of producing a specific pharmaceutical agent while taking into account the complexity of the ideal synthetic process for producing the target molecule. Application of the GAL metric will make possible for the first time an assessment of relative greenness of a process, in terms of waste, versus industry standards for the production process of any pharmaceutical. The recommendations also include a simple methodology for defining process starting points, which is an important aspect of standardizing measurement to ensure that Relative Process Greenness (RPG) comparisons are meaningful.

'Need to integrate GC throughout the lifecycle of a drug research, development and manufacture'

Dr. Ingrid Mergelsberg, Director, Process Chemistry, MSD, stressed the need to integrate GC throughout the lifecycle of drug research, development and manufacture. "Early awareness can delver large paybacks later," she noted. Barriers to GC in the pharmaceutical industry include short development cycles, limited patent life, product quality, regulatory requirements, lack of unified metrics, high cost of development and high project attrition.

Implementing an effective GC program needs empowered GC teams – that are usually grassroots, multi-disciplinary and empowered to change the culture of companies. Management support is critical for sustained progress. "The teams have different functions – education, resources & tools, awareness, development of metrics & targets etc. MSD has different GC teams with a steering committee that ensures there are clear objectives and deliverables."

RESPONSIBLE SUPPLY CHAINS

Pharmaceutical Supply Chain Initiative – joining forces for sustainability

The Pharmaceutical Supply Chain Initiative (PSCI) is a group of pharmaceutical and healthcare companies who share a vision of better, social, environmental and economic outcomes in the communities where they buy. Consisting presently of 24 companies, PSCI aims to promote responsible supply chain management and better business conditions across the industry.

This is not the first initiative addressing responsible buying; similar initiatives are operational in industries as diverse as automotive, electronics, fast moving consumer goods and chemicals, to name a few. PSCI addresses five areas of responsible business practices and the relevant standards any business is expected to uphold: Ethics, labour practices, health & safety, environment and management systems.

The initiative has made significant

View of the audience

progress. It has developed and deployed tools to assess the supply chain against the principles. These tools include the PSCI Self-Assessment Questionnaire and Audit Protocol. It also assists in capability building through a resource library on the PSCI website, training programmes, etc.

The vision is that, through the application of the PSCI Principles, better environmental, social and governance outcomes will result for all those involved in the pharmaceutical supply chain.

The Principles are complimented by Implemented Guidance, which provides a framework for implementation, and gives examples of how to meet PSCI guidelines.

According to Mr. Steven Meszaros, Senior Director of Business Resilience and Business Development, Pfizer Inc., stakeholder expectations are changing in the pharmaceuticals industry. "The extent to which we manage our supply chains responsibly is becoming a key measure of Corporate Social Responsibility competence. Customers increasingly expect to buy from companies who purchase responsibly, respecting the rights of citizens in the local community."

"We believe that by sharing knowledge and expertise, PSCI can drive complex, global change more effectively than one organization alone," he added.

Benefits of following the PSCI Principles include:

1. Utilizing a common standards across the supply chain;
2. Benchmarking and sharing of best practices with other pharma companies, and other sectors;
3. Being recognized as a supporter and advocate of Responsible Supply Chain Management;
4. Suppliers gain a more in-depth understanding of customers' expectations for responsible business practices and raise their profile as a high-performing and sustainable supplier for current customers and future prospects;
5. Suppliers have the opportunity to collaborate with customers to build the sustainability capabilities of their facilities;
6. Both the Self-Assessment Questionnaire and Audit allow suppliers to cut down on duplication of effort in supporting multiple assessment requests from customers.

According to Ms. Shelly Shope, CIH, HSE Advisor – Elanco Animal Health, an Eli Lilly & Company,

Table 1
Pharmaceutical Industry Principles for Responsible Supply Chain Management

Ethics	Labour	Health and safety	Environment	Management systems
Business integrity and fair competition	Freely chosen employment	Worker protection	Environmental authorizations	Commitment and accountability
Identification of concerns	Child labour and young workers	Process safety	Waste and emissions	Legal and customer requirements
Animal welfare	Non-discrimination	Emergency preparedness & response	Spills and releases	Risk management
Privacy	Fair treatment	Hazard information		Documentation
	Wages, benefits and working hours			Training and competency
	Freedom of association			Continual improvement

Source: PSCI website

PSCI requires compliance with the law, suppliers to follow PSCI principles and the right to conduct audits through on-site assessments to verify adherence.

"By 2025, India's pharmaceuticals industry will reach a size of about $45-bn from $15-bn now; it is not possible to reach this level with a business-as-usual approach," Mr. Meszaros noted. PSCI is planning to start Associate Membership – at a different price structure – and several companies from India have reached out.

WATER POLLUTION

'Action plan with emissions reduction targets needed now'

The API industry in India, especially the ones in and around Hyderabad, has come under considerable scrutiny for waste generation from manufacturing operations. At the same time, global companies are being subject to increased scrutiny by NGOs, investors and the media in relation to their supply footprint, and in particular their environmental impact.

As far back as 2007, a study by Larsson indicated high levels of pharmaceuticals in the effluent from the Patancheru wastewater treatment plant near Hyderabad, which serves approximately 90 API manufacturers. The study called for "an increased focus on the potential release of APIs from production facilities."

Potential impacts of antibiotics

Other research papers and studies have also looked at the potential impacts of antibiotics on the environment – including papers commissioned and published in the EU and India.

More recently, Nordea Asset Management, which manages Norway's sovereign fund, produced a video (2015) and report (2016) on the impacts of pharmaceutical pollution on communities and the environment in India, with a focus on the Hyderabad region.

Earlier, in 2015, SumOfUS, an NGO, produced a report on the potential impacts of the pharmaceutical industry on the rise of antibiotic resistance, with a focus on China and India.

Mr. Sasja Beslik, Head of Sustainable Finance, Nordea Wealth Management

And in the following year, the European Public Health Alliance published a report calling for the UK NHS to stop sourcing from pharmaceutical companies contributing to the spread of antimicrobial resistance (AMR).

An investigation carried out in the summer of 2016 by Changing Markets found antibiotic-resistant bacteria at manufacturing sites in Hyderabad, Visakhapatnam, Chennai and New Delhi. Companies involved included Aurobindo, Orchid Chemicals, Asiatic Drugs & Pharmaceuticals and Hetero Drugs.

In response, the International Federation of Pharmaceutical Manufacturers and Associations framed an 'Industry Roadmap and Combating Antimicrobial Resistance,' which had the support of 13 companies. In 2016, the UN General Assembly reaffirmed a commitment to develop national action plans on AMR based on a 'Global Action Plan on Antimicrobial Resistance.'

Among other initiatives the roadmap focuses on review of manufacturing and supply chains to assess good practices in controlling releases of antibiotics; work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations of antibiotics and good practice methods to reduce environmental impact of manufacturing discharges by 2020; and ensure antibiotics are only used in patients who need them.

Major business risk

According to Mr. Sasja Beslik, Head of Sustainable Finance, Nordea Wealth Management, pharmaceuticals production is one of the most heavily polluting industries in the neighbourhoods of Hyderabad and Visakhapatnam. "Pollution from antibiotics production is particularly problematic because it fuels the spread of antimicrobial resistance."

"Pharma pollution is a major business risk. Manufacturers risk jeopardising supply contracts with companies and procurement bodies in Europe, US and other regulated markets."

Nordea's expectation is that the leading Indian companies commit to contribute to the protection of water resources, by creating an action plan addressing the issue, with emissions reduction targets for suppliers at relevant production sites. "It needs to be a process, but needs to be initiated now. India can lead on how this can be addressed by working together and with the regulators," Mr. Beslil noted.