Mother's little helper

An Indian company is pioneering some key green chemistry concepts. We caught up with **Newreka Green Synth** at Chemspec India 2008

Although the company stand was located right at the back of the hall at Chemspec India 2008, it was swarming throughout. Founder director Nitesh Mehta said: "It has been so amazing. There has been no beating about the bush, it is all real business." Clearly Newreka Green Synth Technologies had identified something that the Indian chemicals industry wanted.

Although the firm has been active for six years, 2008 may prove to be its breakthrough year. In January, alongside SMS Pharmaceuticals, Newreka won the Indo-US Green Chemistry Network Centre (GCNC) Award for the successful commercialisation of green chemistry-based technologies at the Indo-US Science & Technology Forum Workshop on Green Chemistry.

The GCNC itself is an umbrella organisation that grew out of the India Green Chemistry Chapter of the American Chemistry Society Green Chemistry Institute (ACS GCI) and now encompasses several centres, institutions and industries. It organises various symposia, workshops and training courses to further the concept of green chemistry.

The event in Delhi last January, the third in the series, attracted some 200 delegates from industry and academe. It was addressed by Professor John Warner of the Warner Babcock Institute for Green Chemistry, who is widely regarded as one of the fathers of green chemistry.

The ideas behind Newreka actually go back to conversation in a hostel room at IIT Bombay, where Mehta was studying under Bhadresh K. Padia, in 1998. The basic idea, Padia says, was that the chemicals industry sees pollution as something that needs to be controlled when it should rather look at the issue in terms of 'prevention by recycle at source'.

"The industry always sees effluents and their end of the pipe treatment as a cost centre, when it is possible to transform it into a profit centre through the 'prevention by recycle at source' approach. For example, when you lose selectivity, you lose materials in side reactions and it ends up as an effluent, leaving no chance of recycling the mother liquor" says Padia.

"Even if in the laboratory you get 100% selectivity, it is important to ensure proper scale-up through appropriate mixing, reactor design and engineering to have uniformity over large-volume operation. This is where green engineering plays a critical role in 'prevention by recycle at source' at industrial scale."

The key, he adds is 'prevention, not control'. If the industry avoids the need for purification steps and does not produce effluent because it achieves a complete recycle at the end of the process, this is not only 'green' but economically sound and competitive. Padia and Mehta believe that most chemical processes can actually be reviewed and reinvented in an entirely green way.

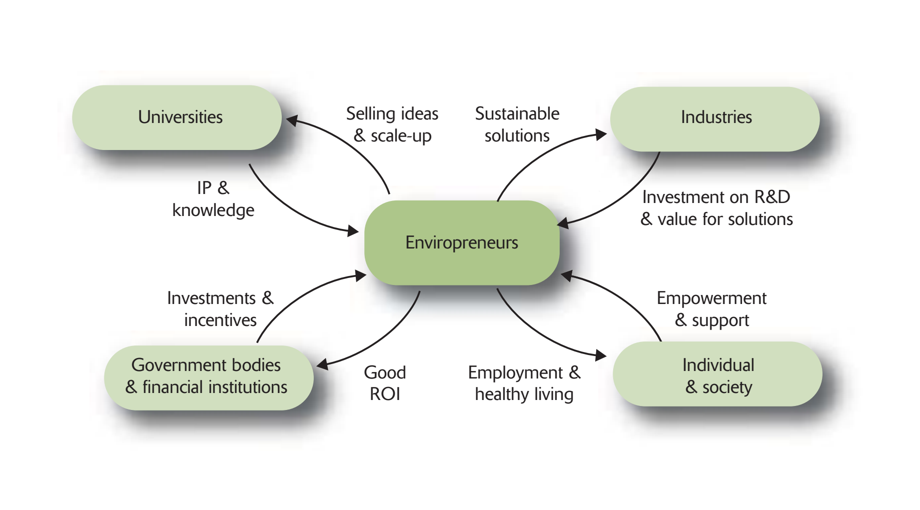

Figure 1 - Green partnerships based on enviropreneurs

Padia himself is an expert in iron oxide catalysis, process intensification, scale-up, unit processes like reduction, nitration and diazotization-hydrolysis, and unit operations like crystallisation, extraction, filtration and isolation. He founded Newreka along with Mehta, the public face of the company, whose interests are in similar areas, and Vineet Shroff, whose main areas of competence are engineering and industrial mixing. The company name is a combination **N**ature's **E**nthusiastic **W**orld and 'Eu**reka**', Archimedes' joyous cry of scientific discovery.

Over the past ten years, Newreka has grown to about 100 chemists and engineers, who have carried out some 20,000 experiments in unit processes, with a focus on recyle. Growth was an uphill challenge, however, because it is very difficult for knowledge-based start-ups, unlike software start-ups, to generate seed capital.

"Knowledge doesn't show up on a balance sheet and venture capitalists and banks are not interested in things with a six-to-seven-year turnaround period. Government bodies have their limitations, due to their bureaucratic set-up and their limited ability to deal with high risk-oriented knowledge platforms. and hence they have shown limited interest," Mehta admits.

Normally, the investment needed to create new knowledge far exceeds the business returns in the initial stages creating financial challenges to sustaining such knowledge platforms. In the future, Mehta believes, there is a need for finances customised to knowledge-based start-ups in the fields of environment and energy.

Originally, Newreka acted as a consultancy but this did not work. Between 2002 and 2005, it visited every Chemspec, Informex and CPhI show across the world and found that potential customers wanted more product-based services. Now it has its own facility in Dombivli in the suburbs of Mumbai.

For the first couple of years, a focus on unit process of reduction was the company's key marketing strategy. This was based on the Newreka Reduction Technology (NRT), in which proprietary catalytic formulations are used in reduction. More recently it has expanded to offer systems for other reactions, including nitration, diazotisation-hydrolysis, isolation, oxidation, sulphonation, acetylation and Friedel-Crafts.

Thus, Newreka has slowly achieved recognition, culminating in the award at the GCNC symposium. This was based on case studies of its work in two specific areas - the recycle of mother liquor from chemical process streams and the use of its proprietary catalysts to replace harsh with mild conditions - plus its concept of the 'enviropreneur'.

Mother liquor typically contains raw materials, finished product and both organic and inorganic impurities. Depending on the reaction medium, it can be acidic (when sulphuric acid is used in nitration, diazotisation, methylation, precipitation, etc.), neutral (when water is used in reduction) or alkaline (when sodium hydroxide is used in fusion, hydrolysis, crystallisation, etc.).

The company claims that its Newreka Recycle Solution (NRS), which covers all of these areas, has several important advantages in addition to the green chemistry principles it is based on, notably: high selectivity leading to high quality, no need for purification, the ability to customise catalyst formulation, close to theoretical yield and recovery, low capital investments, savings on cost and legislative compliance, thus freeing up room for expansion, and better access to markets in the developed world.

The first case study of the implementation of the NRS showcased at the GCNC symposium concerned the intermediate for an anti-AIDS drug made by Matrix Laboratories in India. Conventionally, this is produced by reduction using catalytic hydrogenation with a pyrophoric Raney Nickel catalyst.

The reaction is carried out to convert R-NO_2 to R-NH_2 in a high pressure autoclave is hydrogen gas at high pressure, Raney Nickel and methanol as solven. The spent nickel is filtered and the filtrate undergoes two stages of distillation, isolation and filtration, the second of which need another solvent. The end result is two lots of light and dark brown amine and some spent solvent effluent, as well as a poor yield.

Using the NRS, the reaction is carried out to convert R-NO_2 to R-NH_2 in a simple vessel at atmospheric conditions, using water as a solvent and proprietary catalytic formulations like the Newreka Reduction Catalyst (NRC) and the Newreka Green Catalyst (NGC). After the reaction, the spent NRC is filtered out. After crystallisation and centrifuging, off-white amine is produced, along with mother liquor that can be stored and recycled back into the process 25 times.

The main advantages of this are that water can be used as the reaction medium instead of solvent, no hazardous materials are used, the reaction takes place at atmospheric pressure, neutral pH and below 100˚C and that the mother liquor can be recycled 25 times at plant scales and 50 times in laboratory trials, rather than being treated at the end of the pipe.

The yield is up from 85% to 95% of theoretical and the whole process is much less energy-intensive, leading to substantial savings - thus establishing, in Mehta's view, that 'prevention by recycle at source' is a huge profit centre.

Another factor is the soaring costs of nickel and other noble metals in India, like everywhere else in the world; prices have increased four- to five-fold in the past five years. In addition, Indian pharmaceuticals companies face much the same pressures as their Western counterparts to reduce both costs and pollution.

Mehta believes that there is huge potential for iron-based catalysts to replace not just nickel but platinum and other platinum group metals in catalysis. Iron, he observes, is not just cheaper and less hazardous than these metals, but has proved its safety to living creatures by the way it is widely used in natural chemistry, where nickel and other noble metals are not.

Since it is also ubiquitous and well-nigh inexhaustible, the price of iron remains stable by comparison with noble metals. Newreka is now working intensively on developing new formulations based on nano-iron catalysts using green chemistry principles.

The second case study concerned 3-hydroxy acetophenone, the intermediate for the decongestant phenylephrine hydrocholoride. This drug is increasingly replacing pseudo-ephedrine in the US market and its production is growing very fast, but the conventional process for its manufacture is highly polluting.

In the conventional process, 3-amino acetophenone is diazotised with $NaNO_2$ using sulphuric acid as the reaction medium. After the diazotisation-hydrolysis reaction is complete, ethyl acetate is used as a solvent to extract the product, an aqueous layer

Professor John Warner spoke at the workshop in Delhi

containing sulphuric acid is separated and the ethyl acetate layer is taken for distillation to recover the product, 3-hydroxy acetophenone.

The process needs additional raw materials like $CuSO_4$ and acetic acid, which never take part in the reaction. It generates brown-coloured product and huge quantities of sulphuric acid effluent, achieving 65-70% of theoretical yield.

Using the NRS in a patent-pending process, 3-amino acetophenone is diazotised with $NaNO_2$ using sulphuric acid mother liquor as the reaction and extraction medium. Ethyl acetate solvent is not required.

After the diazotization-hydrolysis reaction is complete, the product is extracted using acidic mother liquor. Following the recovery of product, the entire acidic mother liquor is recycled back in the process after reacting it with RCat, Newreka's proprietary recycle formulation.

This process, the company claims, led to a 75-times recycle of the reaction medium instead of producing a highly acidic effluent. Because of the improved chemoselectivity and the elimination of side-reactions, sulphuric acid was recycled up to 50 times at plant scale and there was no need to use $CuSO_4$ or acetic acid. Yield rose from 75% to 90% of theoretical. As with the neutral mother liquor, water can replace solvent as the extraction medium and the process is more energy-efficient.

Padia notes that no modification was needed to the plant in either of these cases and that this applies to most of Newreka's work. Only the mixing systems in the reactors were modified to ensure uniform mixing in every corner of the reactor, thus leading to high chemoselectivity.

Crucial to the success of all this is that Newreka chemists and chemical engineers are required to work together in harmony. "They should be like husband and wife," Padia says.

(Some cynical Westerners might say that chemists and chemical engineers in most firms are very much like husband and wife already. They have totally different points of view on every subject, they never listen to each other and they invariably blame each other for anything that goes wrong. But that's another story...)

The term 'enviropreneur', which Newreka also showcased in Delhi, is a fusion of '**enviro**nment' and 'entre**preneur**'. The idea is to combine the passion of an environmentalist with the spirit of adventure of an entrepreneur to create wealth from waste and produce benefits for the environment. The word refers to the firm's individual workers, who are reqiured to do more than slot into the role of chemist or chemical engineer, and to the company itself.

Universities, industry, government bodies and NGOs, individuals and society as a whole are all divided from each other, Mehta says. The former, for instance, are a source of new ideas but lack the ability to scale them up or commercialise them; industry has the resources but is impelled by the rush to market to stick to existing processes. The 'enviropreneur' can be a bridge between them, forming mutually beneficial, green partnerships with all of them (Figure 1).

Implementing Newreka technology at a customer's site is of necessity a slow process, involving R&D and plant operatives and others, as well as senior management. "The challenge we face is to show them that green chemistry is actually a profit centre rather than a cost centre," Mehta says. "In our experience, green chemistry is always cheaper."

The process begins with a confidentiality agreement, finding out what the customer's expectations are, then submitting a detailed proposal and signing a commercial agreement. The R&D process then begins, followed by a demonstration of the NRS by a lab demo team, then at plant scale by a separate team. RCat formulations are then put into action, supported by ongoing optimisation, process intensification and troubleshooting services.

Much, of course, can go wrong at any stage in a country notoriously reluctant to pay for knowledge. Newreka and its customers work on a 50-50 risk basis. Customers give an initial commitment amount to Newreka to start the work on all aspects of converting the conventional process(es) to its technologies.

Typically, a project takes from six to 12 months to implement and six to nine to break even. If the project is unsuccessful, customers are offered a choice of a 50% refund of their initial commitment amount or the chance to replace the old project with a new one.

To date, Newreka has not done much business outside India, though it has fielded many enquiries from the Paracetamol industries in Iran, Bangladesh, Turkey, Pakistan, Egypt and South Africa. Mehta and his technology implementation team recently spent a month in Iran demonstrating how NRS could be used to convert para-nitro phenol to para-amino phenol, a key intermediate in Paracetamol, using a water-based process with more than 100 recycles of mother liquor and producing off-white and stable para-amino phenol.

This, Padia adds, could ultimately lead to "a complete green solution for Paracetamol". It also serves as an example of where, according to Mehta, the well-known 80/20 rule also applies.

"In all industries, 20% of the products create 80% of the pollution," he says. Converting this 20% to green chemistry will be more profitable, advance the technology and will go furthest to reducing pollution, significantly impacting the environment specifically water bodies.

For this reason, Newreka is not running small-scale projects but is prioritising the 20 products in every market by bulk. It has, in many cases, worked on them already, generally to develop a green route for every step of a four- to ten-step synthesis.

Examples in pharmaceuticals other than those cited already include caffeine, citalopram, triclosan, and, perhaps most interestingly of all, sildenafil citrate, the API in Viagra. Rakshit Drugs, India's largest producer of sildenafil citrate, has implemented the NRT in one of the steps in place of catalytic hydrogenation by hydrogen gas and Raney Nickel, achieving among other things a 30% reduction in batch time and improved intermediate quality.

In agrochemicals, dicholoro and tricholoro aniline have been the subjects of projects. Newreka has also been working with Shree Hari Chemical Exports on H-acid, a very large volume intermediate for brown and black dyes. In pigments, it has been working with Pidilite Industries, the main producer of Pigment Violet 23

The unit processes of H-acid, Violet 23 and Paracetamol, plus DASDA, Phenylephrine and Pigment CPC, all consume sulphuric acid. It is used in vast quantities in both the general chemicals industry of Gujarat and Mahrashtra and in the pharemceuticals industry around Hyderabad and Bangalore. Therefore, sulphuric acid is a big target of investment for Newreka.

In addition, Newreka is working on next generation nanocatalysts. Nano-iron compounds and biomimicry has huge potential according to Padia. The former are very common in nature right from amoeba to whales; they are, for example, the natural magnets behind homing pigeons, Padia observes. Biomimicry - observing Nature's own innovation to develop products and processes - he sees as essential to achieving a sustainable environmental footprint for the future need of mankind.

"We are always looking at gaps from the economic and the environmental point of view. The only issue, as Professor Warner said in Delhi, is that the toolbox is not yet full. We have not yet, for example, worked on chlorination or bromination but we will do so and we think that in ten years' time there will be a green chemistry solution for every problem," says Mehta.

Newreka sees itself as a global company in the long term and the Western world is obviously the next target. Mehta notes that, where India is more focused on intermediates, the European and US markets are more focused on custom synthesis and manufacturing and there are close relationships between them and Big Pharma companies.

"The pharmaceuticals industry, creates huge amounts of waste, around 50-100 kg per kg of product. It is normally difficult to get involved in this area once DMFs have been filed and the process is hard to change. However, when patents have expired or are about to, there could be more interest in our technology," he concludes. "I have not come across anyone else doing what we do, so I believe that our business model is unique."

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