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MAKE IN INDIA

An analysis of Atmanirbhar Bharat initiative's impact on the manufacturing sector.

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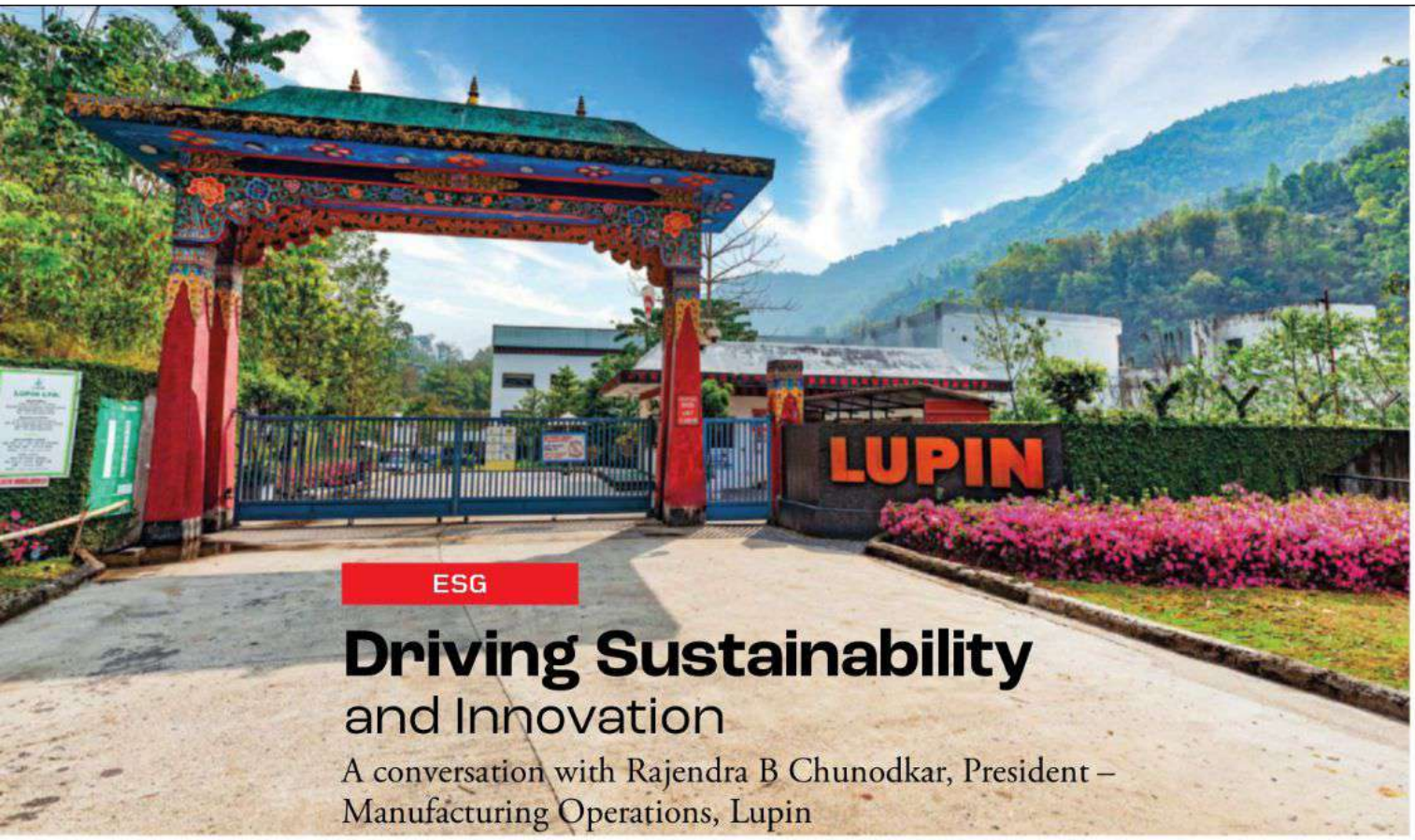

ESG

Driving Sustainability and Innovation

A conversation with Rajendra B Chunodkar, President – Manufacturing Operations, Lupin

Lupin, a global leader in pharmaceuticals, is setting benchmarks in sustainable manufacturing with its unwavering commitment to Green Chemistry. At the forefront of this transformative approach is Rajendra B Chunodkar, President – Manufacturing Operations, whose leadership has spearheaded initiatives to minimise waste, reduce hazardous substances, and embrace cutting-edge technologies. Through a combination of innovation and adherence to global sustainability standards, Lupin has significantly enhanced its operational efficiency and eco-footprint, achieving impressive reductions in waste, water, and solvent usage.

In this exclusive interview, Chunodkar delves into the strategies and measurable impacts of Green Chemistry, including the application of telescoping processes, biocatalytic routes, and statistical tools to optimise manufacturing.

He also discusses the challenges of implementing these practices at scale and how digitalisation, AI, and automation are streamlining Lupin's operations.

The conversation extends to Lupin's expertise in complex generics, highlighting how the company balances regulatory compliance, sustainability, and innovation to meet global demand. This insightful dialogue offers a blueprint for integrating sustainability with operational excellence in modern manufacturing.

What strategies has the company adopted to minimise waste and hazards?

Lupin is advancing the adoption of green chemistry to minimise hazardous substance generation by leveraging metrics like atom economy and e-factor. Our objectives align with the 12 principles of green chemistry, and we regularly train process development scientists to embed these principles in their work. This proactive approach focuses on eliminating hazardous materials at the source rather than addressing waste streams post-production.

Notable transformations include the use of telescoping principles and lean processes for 17 flagship API molecules, eliminating isolations at intermediate steps. Optimising water and solvent usage has reduced both aqueous effluents and the mix of organic solvents. Additionally, statistical tools like Design of Experiments (DoE) have helped explore innovative design spaces, significantly cutting cycle

▲ **Lupin exemplifies how** the pharmaceutical industry can align growth with environmental responsibility.

times and energy consumption. Lupin is committed to scaling these practices across all processes, reinforcing its focus on sustainability and environmentally responsible manufacturing.

How has Green Chemistry adoption advanced Lupin's sustainability and operational impact?
Optimising water and solvent usage in manufacturing and prioritising yield maximisation have significantly reduced aqueous effluents and organic solvent streams, cutting waste and byproducts. Notable achievements include a 30% average reduction in waste, 45% lower water consumption, and 60% reduction in solvent/reagent usage.

A high-volume API batch process was successfully transformed into a continuous process at a commercial scale, delivering shorter processing times, enhanced safety and efficiency, and a reduced environmental footprint. This shift also minimised manual intervention and overhead costs.

Adopting biotechnological routes and enzymatic catalysis has allowed us to catalyse numerous chemical reactions, offering a sustainable alternative to traditional chemical synthesis methods.

The metrics used to benchmark against the current include (a) Enhancement in atom economy, (b) Reduction of E-factor (<100, which is pharma benchmarking), and (c) Minimization of process mass intensity (PMI). Together, these serve as key indicators for the active pharmaceutical ingredient (API) process.

The introduction of technology with flow chemistry and biochemical conversion requires capex to create the facility and then manufacturing expertise to meet the business requirements.

What are the key challenges in implementing Green Chemistry in large-scale pharmaceutical manufacturing, and how is Lupin addressing these challenges?
The dynamic regulatory landscape and time required for the implementation of technology across all geographies pose a bottleneck. The introduction of Noble metal catalysts for selective reactions at large-scale pharmaceutical manufacturing is a challenge and can be overcome by the use of skilled and trained staff with established safety practices and modern facilities. The introduction of technology with flow chemistry and biochemical conversion requires capex to create the facility and then manufacturing expertise to meet the business requirements, ROIs, and approval time across all geographies, which is quite complex and time-sensitive.

Could you share examples of specific technologies that have improved operational efficiencies in your manufacturing plants?
Telescoping Process for API: We optimised API manufacturing by enhancing key reactions and adopting telescopic steps, reducing hazardous reagents, solvents, and solid waste. This improved process shortened production steps from four to three, increasing yield by 19% and overall API quality. Quality control efficiency was boosted by reducing batch testing

samples from 19 to 12. Solvent usage dropped by 44%, water consumption by 75%, and waste generation by 83%. These improvements translate into significant cost savings through reduced raw material usage and shorter production cycles. Additionally, the process lowers energy consumption and waste output, delivering substantial environmental benefits. This innovative synthetic route advances pharmaceutical manufacturing by combining efficiency, sustainability, and economic viability, offering a superior alternative to conventional methods.

Safe and operation-friendly process: The earlier process for manufacturing a specific API involved multiple reagents and high-pressure hydrogenation. It has now been replaced with a simpler chemical deprotection using an alkaline alcoholic solution at atmospheric pressure, resulting in a 15% yield improvement, better solvent recovery, and reduced waste and water usage. This streamlined workflow has enhanced the process's viability and improved Lupin's market competitiveness. For another API, the original three-step process delivered low yields. Through extensive research, our team developed a single-stage process, eliminating high-pressure hydrogenation, reducing reagents from five to one, solvents from six to one, and improving Atom economy from 35 to 80 and E-factor from 89 to 10. This greener, cost-effective method also enhanced product quality and operator safety.

Biocatalyst route: For a particular product, the industrial commercial processes involve a 5-step racemic resolution, delivering a very low yield. We improved the process through asymmetric reduction by an enzymatic process that produces 82% of the theoretical yield. Additionally, the biocatalyst step affords improved stereoselectivity of 97%, making it a viable industrial manufacturing process.

Process redesign: We have developed an innovative process for manufacturing a key intermediate molecule, achieving a 63% increase in Cis isomer yield while reducing raw material usage by 30% and cutting residue generation per kg of API by the same percentage. By simplifying the original five-step process to three steps, we utilised selective imine reduction with a metal catalyst, yielding the desired isomer and enabling efficient resolution of diastereomeric Mandelic acid salts. This resulted in a chirally pure API with improved yield and selectivity while reducing Mandelic acid use by 34%. Our process development team's focus on simplicity and safety has fostered breakthrough innovations, leading to cost optimisation and a reduced eco-footprint. Additionally, adopting digital technologies such as IoT, smart sensors, Data Lakes, and Low Code applications has enhanced production efficiencies and streamlined operations.

How is Lupin using AI, ML, and automation to streamline drug manufacturing to ensure consistent product quality?

Lupin has built a strong foundation of extensive sensorization and near real-time data availability through a data pipeline of production and utility parameters.

- Based on this data, the team has built up the availability of equipment information for the shift supervisors so that they can make decisions to reduce cycle time and improve the overall equipment effectiveness (OEE).
- Through the deployment of Low Code and No Code tools, the operational team has gained the capability to resolve quality issues and ensure robust quality, as well as improve yields.
- On high energy consumption equipment, the team is working on prediction using Databricks to run and predict chiller/compressor performance for a stipulated period. This enables the operating team to optimize energy systems most efficiently.
- Through Digital Performance Management & by reporting performance metrics across the hierarchy and roles, we leveraged performance management metrics and enabled data-driven decision making
- By offering gamified learning applications on mobile devices, We are developing knowledge of its personnel beyond SOPs, thus helping create and strengthen the SME system.

How does Lupin balance complex generics growth with sustainability commitments globally?

At Lupin, we focus on optimising legacy and commercial molecules to enhance cost efficiency and environmental sustainability. By integrating advanced route scouting platforms, lean manufacturing, and waste reduction strategies, we achieve energy savings and improve process efficiency. Our development benchmarks include atom economy, e-factor, and PMI. We also explore innovative technologies like flow chemistry for continuous manufacturing, advanced analytics, and green propellants for inhalation products to drive sustainable pharmaceutical advancements.