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Enzyme Enabled Antibiotic Production: Going "Green" in Manufacturing

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Prologue

Manufacturing is the life line and driver of economic development; by producing goods we not only achieve growth but also vastly improve our quality of life. Manufacturing in simple terms means taking certain raw materials and converting them into value added products and invariably nuisance value by-products or creating eco-impact at various levels and with more. In addition, consumption of the key material from the nature depletes the same and without a concerted eco-responsible effort the natural resource is lost for ever. So, what is the viable, scalable and environmentally sustainable alternative?

Green Manufacturing: Enabling Sustainability

A paradigm shift in manufacturing mind-set, defined figuratively as "Green manufacturing" has emerged as a trend in developed economics, though at various levels of successful translation across various geographies. Green manufacturing may be generically defined as "elimination of waste by re-defining the existing production system" which is achieved by adhering to various smarter, benign and eco-efficient strategies. These strategies aim at making products/processes which consume less input, less energy, substitution chemistry (from toxic input to non-toxic input, from non-renewable input to renewable input), reducing unwanted outputs, converting outputs into inputs (recycling) or use of 'smart enzymes" to transform the way the chemicals are manufactured.

Antibiotics Manufacture: Main driver for "Green" Make Over

Green manufacturing approaches in pharmaceuticals assumes prime importance due to its sheer size as well as the overall alleviation effect it potentially brings to already stressed environmentally non-benign chemical process. Apart from reducing the pollution footprint and being cost effective, green approaches leads to cleaner manufacturing shop floors, more purer final products with virtually no impurity carry over and thus reducing the both occupational and consumption health risk perspectives. Moreover, over the years the efficiency of chemical manufacturing process has reached stagnation without further scope for improvement in terms of process times, yield and purity or in some cases conventional chemistry options were limited or non-existent, which necessitated the transformation into more smarter approaches. One of the most exciting, promising, innovative ways that this can be achieved is to use nature's catalysts (i.e. enzymes) to perform chemical reactions more efficiently, and most importantly, under mild conditions which have minimal environmental burden.

Beta lactam antibiotics like Amoxicillin, Ampicillin, and cephalexin form one of the main areas of pharmaceuticals and considering their global demand and impact on environment, shift towards green enzymatic processes was inevitable. One of the latest success story of industrial transformation of chemical process to enzyme mediated green manufacturing process is Amoxicillin, which has reached a critical mass with more companies up scaling the process, though with initial hiccups and challenges, followed by Ampicillin, Cephalexin, Cephadroxil and the other cephalosporin antibiotics. For example, globally, Amoxicillin, is produced to the tune of 50,000 to 80,000 tons per year and with the advent of new age smart enzyme technologies, significant portion of this drug molecule is produced by enzymatic process, across emerging markets in China, India, Middle East and other countries. What is the big deal with enzymatic approach?

Just to exemplify, in conventional chemical process for Amoxicillin, chemicals like triethylamine, pyridine, pivolyl chloride, dimethyl acetamide and toxic solvent like methylene chloride are used under sub-zero temperatures. From an eco-inventory perspective, all these chemicals put together contribute close to a kilogram of hazardous chemical waste for every kilogram of Amoxicillin produced, leaving behind equal amount of hazard foot print which would take years to degrade. Similar arithmetic tantamount for other antibiotics like Ampicillin, Cephalexin, and Cephadroxil as well. On the contrary, none of these chemicals are used in enzymatic process but only in water under ambient temperature conditions. Thus enzymatics becomes a natural choice for eco-efficient, cost efficient and process efficient technologies wherever it is possible for the changeover.

The successful industrial transformation of integrated amoxicillin process by many players primarily across India and China by using enzyme has added fillip as well as improved scale up confidence to other manufacturing process to go green in other antibiotics like Ampicillin, Cephalexin as well as other molecules.

Companies like DSM, Fermenta Biotech Ltd and few others have played pivotal role in scaling up and integrating these enzymatic antibiotics processes across various geographies at various scales. The grand successful story of Sitagliptin (Januvia process) by evolved transaminase by Merck & Co has further inspired many innovative pharmaceutical companies to integrate enzymatic approaches in the respective manufacturing processes for other molecules.

Enzyme Platform; Challenges and Opportunities

The enzyme based bio-industry has been experiencing rapid and significant growth over the past decades and playing a pivotal role in transforming the conventional chemistry processes. However, this transition is challenging against the well-established conventional processes in terms of reaction chemistry, cost, plant infrastructure as well as mind set for a change. From adapting a chemical process to the naturally available enzyme, the emerging approach of evolving a "tailor-fit" enzyme or developing a synthetic enzyme with bespoken reaction engineering attributes like increased substrate concentration, enzyme stability, temperature, pH and solvent resistance etc., has been made possible by the emerging brave new directed evolution platform. While the industry would continue to produce most of the chemicals

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by the conventional methodology, the emergency of these smart and integrated enzymatic technologies offers plethora of viable alternatives for manufacturing companies to collaborate and integrate suitable processes. Even with the today's progressive technology choices, the real challenge still would be the overall economics and the matching efficiency to enable these smart enzyme technologies to replace r the conventional platforms. The emergence of smart, enzymatic technologies and the success stories so far has changed the opportunity landscaping and ushering in a revolution in drug manufacturing. Going forward, the continued synergisms with old and new age manufacturing process augur well for the industry.