BIO-CATALYSIS WORKSHOP

Bio-catalysis – an inspiring technology in green and sustainable API route development

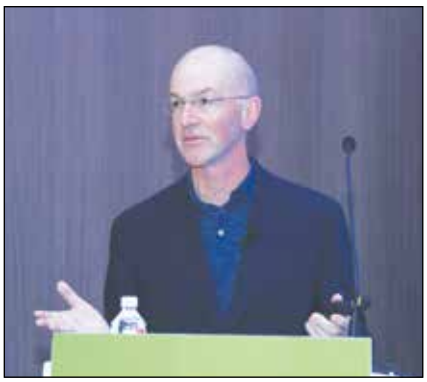
DR. AJIT JOSHI
drjoshi9@gmail.com

Bio-catalysts are more efficient and environmentally safe alternatives to traditional chemical catalysts in several areas including the manufacturing of active pharmaceutical ingredients (APIs) and their intermediates.

Bio-catalysis is a green synthesis strategy, which provides the advantages of chemo-, regio- and stereo-selectivity. It is also an important tool to access enantiomerically pure molecules. Further more, the combination of bio-catalysis and modern chemical synthesis steps, i.e., chemo-enzymatic synthesis, can be used to obtain several drug molecules, with fewer reaction steps, reduced waste production and improved overall synthetic efficiency, both in yields and enantio- and/or diastereo- selectivities, as compared to classical chemical synthesis.

While bio-catalysis is a powerful GC tool, its potential is yet to be fully exploited. But there is growing interest in bio-catalysis in the Indian pharmaceutical industry.

Prof. Nicholas Turner, Professor of Chemical Biology, Manchester Institute of Biotechnology, UK, delivered the keynote address at the workshop by explaining the relevance of bio-catalysis in the pharmaceutical industry. He discussed several topics including the emergence of bio-catalysis in API synthesis; advantages & challenges of using bio-catalysis in various processes; current applications of bio-catalysis in the global pharmaceuticals industry; and future prospects.



Prof. Nicholas Turner

He also covered the tools available for different chemical processes; developing engineered bio-catalysts and applying them on scale; commercialization of bio-catalytic processes and their intellectual property; and future developments including cascade bio-catalysis.

From enabling to inspiring: bio-catalysis in green and sustainable process development

Dr. Guy Humphrey, Distinguished Senior Investigator, MSD (Merck), USA, also discussed the applications of bio-catalysis in the pharmaceutical industry.

Many years prior to the development of the commercial route to *Januvia* (sitagliptin), based on transaminase chemistry, Merck and many other pharmaceutical companies were invested in using bio-catalysis as an enabling, green technology in drug synthesis and production. Thanks to these and similar efforts by other companies, the recent years have witnessed a seemingly endless expansion of chemistries amenable to bio-catalysis. "Coupled with the optimisation of enzyme evolution workflows, this has transformed bio-catalysis into an inspiring technology in green and sustainable API route development," Dr. Humphrey observed.

Several case studies, from recent Merck development programmes, that highlight the transformative potential of this technology were discussed.

Dr. Juan Colberg, Senior Director, Pfizer Inc., USA, noted that bio-catalysis is also reaching further into discovery chemistry, resulting in great impact across all development stages for new drugs.

Applications of bio-catalysis in synthesis of complex APIs

Dr. Ishwar Bajaj, Senior Scientific Manager, Biocon Ltd., discussed the applications of bio-catalysis in synthesis of complex APIs.

One of the focus areas of Biocon, he noted, is to produce complex generics using greener technologies like fermentation and bio-catalysis. "Various bio-catalysts like ketoreductase, nitrilase, transaminase, acylase, hydroxylase, etc. are being used to synthesise otherwise difficult asymmetric carbon-containing synthons. Most of the processes are running successfully at commercial scale," he observed.

The case studies presented by him described the use of a microbial ketoreductase and hydroxylase to synthesise complex intermediates for APIs. High throughput screening was done to select strains that can produce the enzymes required for efficient conversion, following which robust & scalable processes were developed in R&D using these

View of the audience at the workshop

selected strains. These processes were then scaled up to commercial scale, which considerably increased output without using environmentally harsh chemicals. "These processes are running successfully in the GMP facility of Biocon in Bengaluru for commercial supply of APIs to regulated markets," Dr. Bajaj observed.

Mr. Suresh Kumar. K, Project Lead – Technical Services, Advanced Enzymes Technologies Ltd., pointed out that bio-catalytic reactions can be performed both in organic solvents and in water. This allows selective and efficient conversion of both water-soluble and apolar organic molecules using bio-catalytically active cells or molecules. His presentation threw light on synthesis of various APIs using enzymes such as lipases, ketoreductases, transaminases, and nitrilases.

Commercial synthesis of chiral active ingredients

Mr. Sarvanan Jothi, Associate Scientific Manager, Iosynth Labs Pvt. Ltd., noted that enzyme- and whole cell- mediated syntheses of chiral molecules has seen a surge during the last decade, especially in the manufacture of generic APIs. "This is primarily due to a push for green synthesis by regulatory agencies, along with awareness about the harmful effects of heavy metals and hazardous solvents," he noted.

Enzymes also bring cost reduction by increasing selectivity and yields. "It is noteworthy that many generic pharma companies are running enzymatic processes at commercial scale. Hydrolases, as workhorses of bio-catalysis, have taken a lead here. However, big API producers have also used other enzyme classes, like oxidoreductases, nitrilases, transaminases and lipases, at commercial scale. In cost-sensitive processes, Indian generic companies are using whole cells fermentation for production of APIs," Mr. Jothi observed.

Besides pharmaceuticals, bio-catalysis is also making headway in cosmetics and agrochemical synthesis. "Looking at the present industry trends, it is highly likely that commercial chiral synthesis of active ingredients would be soon taken over by enzymes," Mr. Jothi added.