

# Bio-way to drugs

Biotechnological processes are rapidly becoming one of the principal ways of synthesising new drugs. A report by **Gunter Festel, Jürgen Knöll, Hans Götz and Holger Zinke**

In 2010 about 20% of all chemical products will be produced by biotechnological processes, representing a sales value of \$310bn. The highest potential for biotechnological processes is in fine chemicals where 60% of the sales value (\$100bn) will be produced by biotech routes in 2010.

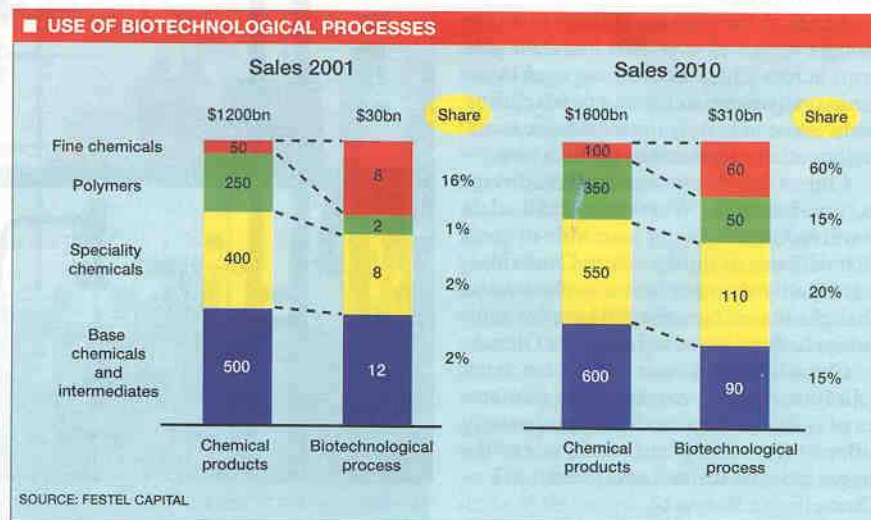
This is expected especially for the production of complex chiral molecules, such as enantiomerically pure active pharmaceutical ingredients (APIs) with chiral centres which can be produced by biotech routes. The increasing requirement for chirality results from parallel regulation policies at the FDA in the US and EMEA in Europe to accommodate the fact that usually only one of the two chemical enantiomers is active and beneficial.

More than 50% of the top 100 drugs are based upon enantiomerically pure molecules and such drugs already exhibit sales exceeding \$100bn. In addition, 60% of the new APIs in drug development phases II and III are chiral and 90% of the new chiral substances are developed enantiomerically pure. Thus, biotransformation will be a key technology for the synthesis of new drugs.

Biotransformation (enzyme catalysis, whole-cell bioconversion) is the conversion of a specific substrate by stereospecific catalysis using isolated enzymes, cells or microorganisms. Enzymatic catalysis increasingly allows higher concentrations of educts and non-physiologic temperatures and conditions. But a single enzymatic catalytic step does not necessarily lead to the desired product, so that the reaction has to be performed in multiple steps. The cell-free biotransformation will nevertheless widely replace fermentation for the production of small molecules.

The technical development has progressed at an enormous rate and will further boost the application potential of biotransformations. Increasing knowledge of enzyme reactions in non-aqueous solution will lead to a broadened spectrum of processes and a greater number of substrates. Due to new developments in reactor and process design, process efficiency will be improved. The versatile application of extremophiles will enable more robust processes, thus increasing the diversity of process conditions and reducing reaction times.

Common use of the directed evolution process leads to the development of tailor-



made and high performance enzymes, particularly when using molecular scaffolds as starting points, derived from the wealth of evolutionary diverse microorganisms. Those organisms which are not cultivable can be accessed by molecular genetics via direct cloning of environmental DNA.

This recent technological breakthrough has led to an enormous boost of the number of available enzymatic systems. The genetically engineered modification of microorganisms will thus result in the implementation of new enzymes and reactions and to new sustainable processes. Recent notable and successful examples are the process for 1,3-propanediol from glucose in *E. coli* by an extensively engineered organism by multiple knock-outs and knock-ins of homologous genes plus trans-

In late 2003, Festel Capital performed an interview-based market study on industrial biotechnology to obtain a clear picture of the current situation and to gain a fundamental understanding of future trends and success factors in fine chemicals. Within this market study, about 20 executives from European chemical and life-science companies (including Bayer, Celanese, Ciba SC, Cognis, Degussa, DSM, Lonza, Merck and Roche) and start-ups (such as AC Biotech, BRAIN, Jülich Enzyme Products, Jülich Fine Chemicals und X-Zyme) were interviewed.

genes of yeast origin (DuPont/Genencor) and the process for 3-hydroxy propionic acid from glucose in *E. coli* by engineering the lactic acid and alanine pathways (Cargill/Codexis).

A decisive driving force for the transfer to biotechnological production processes is clearly the cost factor. As a rule, biotech routes have substantially lower capital and manufacturing costs and allow greater flexibility because the minimum economies of scale are much lower.

In some industrial segments, such as the food industry, sometimes higher prices can be achieved for biotechnological products compared to their chemically produced counterparts. However, factors other than the production costs usually do not play a role in the choice of the production process.

The restrictions of biotechnological production processes are therefore seen primarily on the economic side, eg operative costs, R&D costs and investments.

The notable number of successful implementations of biotech processes clearly shows that the European chemical industry is increasingly using the potential of molecular biology to sustain competitiveness especially with regard to US and Asian challenges. ■

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