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product, is manufactured, apparently competitively, by a chemical route based on dynamic resolution, by a route involving a series of whole cell biotransformations and by a process involving supported enzyme systems. Similarly, chemical and biochemical routes compete in the manufacture of captopril and diltiazem.

It is generally acknowledged that there is considerable pressure on the fine chemicals industry to use 'environmentally friendly' processes and methods and to dispose of its wastes in the same manner. Chlorinated hydrocarbons are regarded as generally undesirable and methylene dichloride is coming under increasing pressure as a reaction solvent, principally in relation to emissions and containment. While oxygenated solvents may be suitable substitutes in some processes, in others there is a need for alternative reaction schemes. Biotechnology methods can provide opportunities for avoiding the use of suspect materials. Other areas for future development include the use of solvent-tolerant enzymes and innovative biochemical engineering.

What is needed in order to develop biotechnology processes successfully? The broad principles are the same for chemical and biochemical syntheses. The difference lies in the biological component. The search for an organism suitable for carrying out a biotransformation, or for one that contains an enzyme that will catalyse the required reaction, may be long and difficult. Even when an organism has been discovered and isolated, the optimum conditions for organism culture and, if appropriate, the biotransformation, have to be established. Increasing the 'activity' of the organism may involve significant strain development, a process which may involve modification of the natural genetic material in the organism (genetic engineering). If the organism is to be used as the source of an enzyme which is to be isolated and further modified, the process is even more complex. Process development will be required to establish the optimum reaction conditions and, at this point, economic issues will begin to become apparent. Separation and purification may present unusual challenges. Co-factors may be needed. Is the precursor easy to synthesise?

Not surprisingly, these issues have daunted most fine chemical producers. Many have not had the resources to address the area seriously, have not been interested or even aware that it exists. However, the evolution of the fine chemicals market, the increasingly discerning attitude of customers, the increasingly stringent regulation of products and process outputs, economic pressures generally and, finally, the number of new products emerging from discovery laboratories, all suggest that the future for processes broadly falling within the definition of biotechnology is full of promise.

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Biotechnology: Responding to the Fine Chemical Market Challenge

Stephen C. Taylor*

The broad range of definitions and products which are increasingly encompassed by the term 'Fine chemicals', is perhaps only matched by the even broader use of the term 'Biotechnology'. To avoid the inevitable pitfalls for anyone trying to define specific boundaries, this paper will simply offer a personal view of the key recent and likely future biotechnology developments that relate to chemicals production. It will thus:

i) map out and illustrate the range of applications of biological methods to the manufacture of chemicals,

ii) seek to identify the key strenghts and weaknesses of biotechnology in this type of use and

iii) consider how the technology might evolve further to meet the future market challenges in particular:
- the need for faster process development and scale-up,
- the continued drive for more cost-effective production methods,
- the rise in biopharmaceuticals,
- the emergence of gene and DNA medicines.

With relatively few exceptions, the focus for biotechnology in the last decade has been firmly on the pharmaceutical industry, perhaps not surprising bearing in mind, the recent dynamics and strong financial performance of this industry coupled with a constant flow of ever more complex new product introductions. Although there are notable examples of biotechnologically derived products to be found in the sphere of agrochemicals and flavours and fragrances, the pharmaceutical sector will be the main theme taken in this paper and should serve to illustrate the major technology issues and development needs.

All biotechnology processes can be broken down into four generic activity boxes (*Fig.*). Anti-infectives derived by microbial fermentation and the newer protein biopharmaceutics draw upon cell manipulation, cell production and product isolation. The concept of biotransformation, where cells or their enzyme products are used to catalyse the interconversion of specific chemicals, is not new and has been practised over much of this century as I and other speakers have often reminded audiences! However, the real strategic impact of this technology has only been recently recognised and accepted, thus in many respects, biotransformation is a child of the 1980s and 90s.

The first two elements underpin all biotechnology products and much of the distinctiveness of individual fine chemical businesses lies in their technology packages in these areas. By way of example, the range of organisms and gene-expression systems used, each with their own advantages and disadvantages, is considerable: *Aspergillus* (*Gist, Genencor*), other fungi, *Pseudomonas, E. coli* (*Zeneca*), yeast (several), mammalian cells (*Celltech*), animals (*Genzyme*), plants (*Monsanto*). Similarly, there is variance and differentiation in cell production methods, *e.g.*, my own business's expertise in large scale continuous fermentation or *Kelco/NSC Technology* expertise in viscous fermentations. Developments in these

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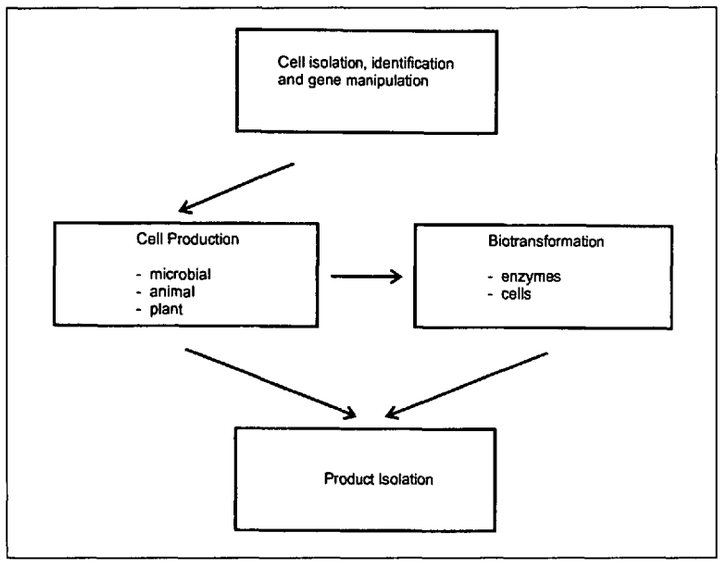

Figure. *Generic process flows*

areas are ongoing and perhaps the most important aspect will be in facilitating faster construction and growth of new strains expressing specific new products through the use of 'generic' organisms and molecular biology cassettes. This will be an essential pre-requisite to meeting the challenging time scales for even faster development being required by the pharmaceutical industry.

Methodologies for the isolation of biotechnological products are many and range from well-proven solvent and chromatographic methods to the newer supercritical fluid extraction systems. Recognising the trend towards lower quantities of more specific, more active and often biological molecules, the point may be near when affinity chromatography starts to realise fully its potential for fine chmicals production.

The growth in biotransformation has probably been the major recent biotechnological development in a fine chemicals context. This development has essentially paralleled the recognition of the importance of chirality to drug development coupled with the lack of good scalable conventional chemical catalytic methods for these compounds. The use of enzymes to resolve racemic mixtures is now well-established at all scales from its application in laboratory screening to over 1000 tpa full scale plant operation with highly competitive economics. Numerous challenges need to be met in order to widen the base of product applications of biotransformation. Perhaps the two major ones are establishing stable biocatalysts that can be even more amenable to routine use and, secondly, establishing cost-effective and robust methods for using reduction and oxidation enzymes in biotransformations. Some recent developments point the way forward such as *Zeneca*'s work on biocatalyst-drying technology [1] and the innovative enzyme-crystal crosslinking techniques of *Altus Biologics* [2]. There are now a few good examples of the use of redox enzymes, largely based on the application of intact, viable microbial cells rather than isolated enzymes [3]. Although effective, this does take it out of the hands of the traditional organic chemist, and history would suggest that without easy application by this dominant community in the industry, the technology may never realise its full potential. However, confidence in biotechnology meeting this challenge remains high in the biotransformation science base.

The recent exciting development of pharmaceuticals based on DNA structures and analogues by biotechnology companies such as *Isis*, offers a new area for applying biotechnology. Whether the production of specific sequences of DNA for gene-therapy treatments comes within the banner of 'Fine Chemicals' may be a point for debate. It is clear however, that if such products are commercially successful, biotechnology will play an important role in the production systems used.

[1] Eur. Pat. 366303, *Zeneca*; 13/12/95.
[2] J.J. Lalonde, C. Govardhan, N. Khalef, A.G. Martinez, K. Visuri, A.L. Margolin, *J. Am. Chem. Soc.* **1995**, *117*, 6845.
[3] Pat. WO 93GB1776, *Zeneca*.

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Fine Chemicals and Biotechnology: How Do Regulatory Aspects Influence the Business and Technology?

Dieter Brauer*

Modern biotechnology consists of a growing range of interrelated techniques, procedures and highly competitive processes for application in the industrial, agricultural and healthcare sectors. The impact of the processes, techniques and procedures crosses a number of sectors where the European Union is highly competitive including agriculture and agriculture processing, chemicals, pharmaceuticals, informatics and environmental remediation.

The sector, where biotechnology-inspired growth has a direct impact, currently accounts for 9% of the European Union's gross added value of ECU 450 billion and 8% of employment. However, biotechnology-based growth in the Union faces a number of factors unique to the structure and operating climate for investment, research and development and labour skills within the European Union.

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