CHIMIA 50 (1996) Nr. 9 (September)

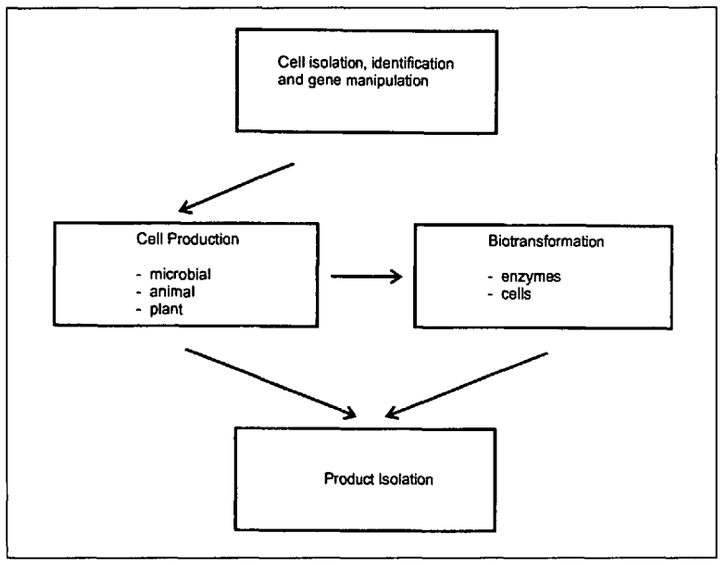

Figure. *Generic process flows*

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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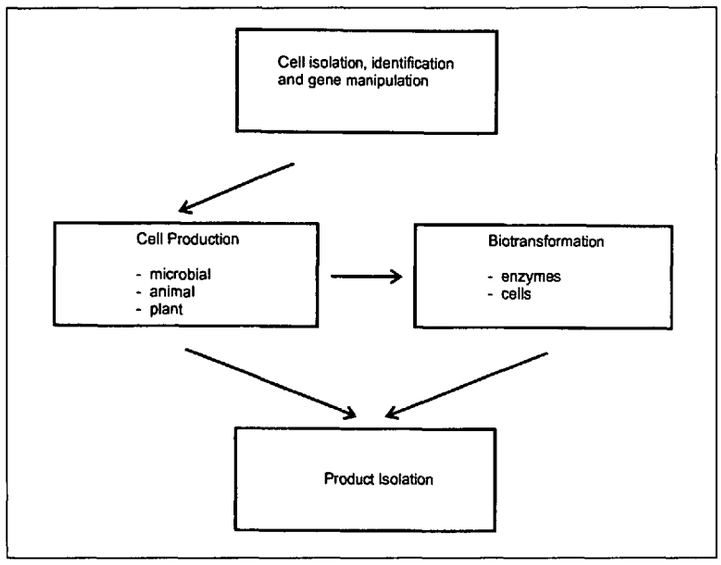

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Table. *Regulatory Issues in Europe*

– Amendments to Directive 90/219 (contained use)
– Amendments to Directive 90/220 (deliberate release)
– Novel food regulation
– Patenting of biotechnological inventions
– Product approval systems (one door – one key)
– Biosafety-protocol

The biotechnological industry has obtained a new dimension recently. The reason for this is an exponential increase in scientific knowledge in the field of recombinant DNA technology over the last few decades. Nowadays, biotechnology is used not only for production, but as a research tool for the development of new drugs as well. Recombinant DNA technology enablesone to produce vaccines in newer and safer ways, and it helps to produce complex proteinaceous drugs like Hirudin. Meanwhile, there is also proof for advantages associated with replacing chemical productions by enzymatic procedures in respect to costs, worker safety and environmental benefits. Screening systems based on cloned receptors or reporter genes are used in search for new drug candidates with an increased specificity. Genetic targeting methods are developed, which allows to target the body's genome itself. Finally, mutated proteins with increased therapeutic values can be constructed, and a rational drug design becomes more and more a reality due to an increased and refined pool of analytical techniques.

However, the European Union's White Paper on Growth, Competitiveness and Employment (1994) identifies the serious social and economic challenges facing Europe for the 21st century. The main causes of the increased challenges for the European Union have been identified as:

- Suboptimal macroeconomic management and insufficient adaption to structural changes in the European economy.
- Lack of adaptation to new technologies, in particular biotechnology.

The root cause of Europe's strategic problem is the political and regulatory climate which is seen to discriminate against modern biotechnology. It is uncertain, unwelcoming and inflexible, while structural and cost barriers to biotechnology entrepreneurship remain relatively high. As indicated in the *Table*, the regulatory issues concern a wide range of topics which include R&D, patenting and product approval problems which urgently require solutions and which are at different developmental stages in the European regulatory process. The existing problems have led to a continuing reluctance to invest in industrial biotechnology in Europe compared with alternative investment sites elsewhere and have prompted the European Commission in late 1994 to propose amendments to the legal system for biotechnology. However, the European political bodies present an ambiguous picture in respect to their willingness to accept the overall positive international experience with modern biotechnology in respect to biosafety, ethical and economic perspectives. Hence, the question arises, whether the slowly developing regulatory reneal for biotechnology will be too late or whether there is still a chance for a competitive European biotechnological industry?

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Toll Fermentation Considerations

Richard I. Mateles*

Toll fermentation is the production of a fermentation (or cell culture) product by a plant (the toll facility or toller) which is not owned by the party contracting out the production. The technology is supplied by the client, and the toller delivers the product to the client. Various arrangements can be made for sharing the different risks involved.

Traditionally, fermentation products were produced in plants owned by the company. In some cases, a manufacturer sought additional temporary capacity by arranging for toll production of some of its needs. However, the industry looked upon manufacturing process as a core component of its proprietary position and was reluctant to open it to others. Even in pharmaceuticals, where manufacturing costs have traditionally not been a subject of great concern, tolling out of production of active ingredients was an unusual event.

The picture has changed over the last decade as a result of several economic realities: 1) as fermentation processes for pharmaceuticals such as antibiotics or steroids have been improved, more and more microbial fermentation capacity has been surplus to the needs of the company; 2) owing to cost pressures, the manufacturing process has received added scrutiny, and the potential advantages of tolling out production, in terms of capital and other savings, has been reevaluated; and 3) with the entry of many new companies into biotechnology, and the highly public failures of several new products, which were in some cases the only product on the horizon for the company, the risks of building plants costing 30–50 million USD based on a single product became apparent. Responsible boards now insist that the operating executives at least consider toll production as a means of reducing risk in the early stages of new product introductions [1].

Today, major multi-national fermentation/biotechnology companies, as well as emerging companies, consider tolling out all or part of their production. Furthermore, several facilities have been built, or are in stages of construction, with the intent that they will operate solely as toll facilities available for production of cell culture or fermentation products. These facilities supplement the use of excess fermentation or cell culture capacity made available by companies whose principal activity is manufacturing and marketing products rather than tolling, but which seek to maximize their return on investment by renting out some spare capacity [2].

There are various motives to engage in or refrain from tolling out production.

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