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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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Likewise, there are various motives for being willing to provide toll production services to another company. An understanding of the possible motives on both sides is important in deciding among various alternative possibilities when seeking a vendor of toll services or a client for a toll service facility.

The supply and demand for toll fermentation services is in reasonable balance at this time, but with important *caveats* relating to the anticipated scale of the demand, as well as to the type of product (*e.g.*, recombinant pharmaceutical protein), GMP needs, and downstream processing requirements.

Although it remains to be seen whether building facilities with the principal purpose of supplying toll services will return an adequate profit, there is no question that toll production, whether crude enzymes as one extreme or of recombinant pharmaceutical proteins as the other extreme, is an option which an intelligent producer must consider carefully.

[1] I.J. Nicholson, P. Latham, *Biotechnology* **1994**, *12*, 473.
[2] R.I. Mateles, 'Directory of Toll Fermentation and Cell Culture Facilities', 2nd edn., Candida Corporation, Chicago, Illinois, 1996.

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Cost Analysis of Fermentation Processes

Leo Hepner*

General Aspects

The fermenter yield represents the most critical parameter concerning the manufacturing cost of a fermentation product. With increasing yield, the manufacturing cost decreases following an exponential curve (*Fig. 1*). In chemical engineering terms the fermenter yield reflects the productivity of the process, *i.e.*, product quantity per reactor unit volume.

Fermenter yield, batch cycle and capacity utilisation determine the annual plant output and control fixed costs, including processing cost (labour, maintenance, depreciation).

The product yield from the fermentation substrate determines variable or raw material cost. In high-yield fermentation processes, the yield on substrate is a critical parameter for the manufacturing cost. In low-yield processes, the yield on substrate is of less relevance. The variable costs and particularly the influence of the fermentation substrate on the manufacturing cost is often negligible for low-yield processes (*Fig. 2*). As a result the cost of fermentation substrate as a proportion of the total manufacturing cost is virtually constant over a wide range of fermenter yields. Any yield improvement in the low-yield range reduces both the absolute variable and fixed cost per kg of product, but does not change their ratios to each other.

In high-yield processes, the fermentation substrate must be increased in parallel with increasing volume productivity. With increasing fermenter yields, the substrate cost as a proportion of the total manufacturing cost increases steadily, whilst the relative impact of the fixed cost decreases. This is illustrated in *Fig. 2* for bulk product, where the carbohydrate substrate at 70% of total manufacturing cost highlights the difference between speciality and bulk products. The recovery yield influences both variable and fixed costs, determining the amount of finished product harvested from a specific yield for given variable and fixed costs.

The *Table* compares the influence of the various factors on the manufacturing cost for low- and high-yield processes:

- the raw-material and variable cost are insignificant in low-yield fermentations, but crucial in high-yield processes.
- fixed cost parameters exert significant influence in the total cost of low-yield processes. Due to the competitive market for bulk products, they are also of relevance in high-yield processes.

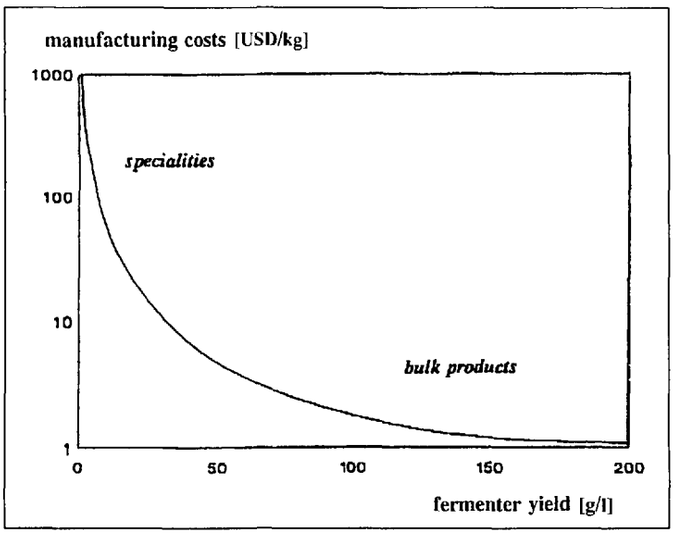

Fig. 1. *Yield impact on manufacturing cost*

Low-Yield Fermentation Processes

In these processes, fixed costs, which depend on the installed capacity and variable cost, including fermentation substrate, are constant. The yield depends predominantly on the genetic characteristics of the production strain. Modifications resulting in overproduction of the desired product improves the fermenter yield based on virtually the same variable and fixed cost

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