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Fine Chemicals and Biotechnology: The Business and the Markets

Michael S. Barber*

Defining 'fine chemicals' is like describing an elephant! It is not easy to do, but you know one when you see one! It is difficult to value the market for fine chemicals but a broad assessment of the value of the market for the various segments of the business is shown in *Table 1*. These figures are indicative only and are not intended to be an accurate representation of market sizes.

If it is difficult to define fine chemicals, it is even more difficult to define biotechnology! If the narrow definition of biotechnology as the manipulation of the genetic material of living cells in order to produce in quantity a natural substance that cannot be obtained by other means, the direct impact of biotechnology on fine chemicals is minimal and will remain so.

Biotechnology is an enabling technology and has evolved to become the application of molecular biology to chemical processes. The old name for this, biochemistry, has been regarded by chemists as something that took place in living organisms, with minimal relevance to industrial processes. Fermentation processes were used to produce useful substances but this was not, of course, biotechnology! A greater understanding of the role of enzymes in fermentation and biochemical reactions, and the use of isolated enzymes as chemical catalysts, led to the view that the demarcations were no longer appropriate. Fermentations gave rise to biotransformations, to processes involving simple reactions with cell-free enzyme extracts and to processes utilising enzymes immobilised on solid supports. The need to improve the yields of the end products from these various processes led to intensive research on the genetics of the microorganisms used and to the discovery of ways of manipulating genetic material to bring about the improvements required. Thus, the application of biotechnology to the fine chemicals business can be considered to embrace the whole range of bioprocesses and biochemical methodologies. These may be superior to conventional chemical processes (most antibiotics), competitive with them (L-lysine and (–)-D-(*p*-hydroxyphenyl)glycine) or uncompetitive. Whatever the competitive status in economic terms of any particular process is, 'biotechnology' methods now have to be considered as legitimate means for making many types of fine chemicals. Examples of typical biotechnology-based fine chemicals are shown in *Table 2*.

These examples are representative of biotechnology methods in fine chemical manufacture, and cover chemicals made on scales many thousands of tonnes (lysine, vitamin C, penicillin) down to a few thousand kilograms (prednisolone).

While there is no obvious connection between most of the products listed in the table, closer examination reveals many of the products could also be obtained by purely chemical methods, that the target molecule itself is labile and may be sensitive to chemical attack from conventional reagents, or that several of the products listed are required in homochiral form. While a discussion of chirality would not be appropriate to this paper, it is worth noting that the increasing use of computer-assisted molecular design techniques in discovery processes is generating an increasing requirement for stereospecific-synthesis capability. Indeed, if a molecule is required in homochiral form, a biochemical (or biotechnology) route should be considered from the beginning.

Whether or not a biochemical method is finally chosen often depends upon comparative economics and there may be no *a priori* reason why one method should be more efficient than any other. (–)-D-(*p*-Hydroxyphenyl)glycine, a homochiral

Table 1. *Indicative Value of Fine Chemical Market Segments – 1996*

	[billion USD]
Pharmaceutical active ingredients and auxiliaries	25–30
Crop protection and pesticides	7–8
Food and feed chemicals, vitamins, flavours and fragrances	8–12
Dyestuffs, pigments, colourant, polymer chemicals and additives	6–8
Other special effect chemicals	6–8
Total approximately	55–60
Less high-volume bulk products – say	10
Total – fine chemicals	45–50

Table 2. *Examples of Biotechnology Processes and Products for Fine Chemicals*

Technology	Products
Fermentation	Antibiotics – penicillin, erythromycin, *etc.*; Amino acids – lysine, MSG; Vitamin B_{12}; Acids – citric, gluconic, lactic acid
Biotransformation	Vitamin C – sorbitol/L-sorbose; Steroids – prednisone, prednisolone Acrylamide, nicotinamide; (–)-D-(*p*-hydroxyphenyl)glycine Cefuroxime; Captopril intermediate; (*S*)-2-chloropropinoic acid
Cell-free enzymation	(–)-D-(*p*-hydroxyphenyl)glycine; Aspartame Captopril intermediate
Supported enzyme systems	6-APA, 7-ADCA, 7-ACA; (–)-D-(*p*-hydroxyphenyl)glycine; Malic acid; Diltiazem intermediate

**Correspondence*: Dr. M.S. Barber
Michael Barber and Associates
18 Croydon Road
Caterham
Surry CR9 6QB, UK

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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

**Correspondence*: Dr. S.C. Taylor
Zeneca LifeScience Molecules
BioMolecules
P.O. Box 2
Belasis Avenue
Billingham, Cleveland, UK