Small molecules: down but not out

Rumours of the imminent demise of small molecules are greatly exaggerated, says Dr Rob Bryant, as he outlines the impact of biopharmaceuticals on the fine chemical industry

Since the mid-1990s, the pharmaceutical fine chemical industry has had to tackle an array of challenges created by changes within pharma itself. These have included an expansion of the generic sector and its supply-base, evolving customer-supplier relationships driven by industry restructuring; increasing cost pressures; and growing recognition of the capability of the newly emerging fine chemical suppliers.

Understanding the new technologies of one's customers has always been a critical aspect of the fine chemicals business but recently, as biopharmaceuticals* have come more to the fore, it has begun to appear that the latest client requirement might involve abandoning chemistry as a core skill altogether.

The increasing number of new drugs based on biopharmaceuticals has significantly reduced the market share of 'small molecule' drugs in the innovative sector over the past five years (see Figure 1). And estimates for new biologics projects, published by US market research company IIR, point to their continued growth. IIR forecasts that between 2005 and 2010, 155 facilities will be built, valued at US$8.86 billion, compared with 100 formulation projects, valued at US$3.7 billion.

Importantly, however, Figure 1 also demonstrates an absolute drop in US approvals, reflecting the failure of the innovative sector to develop new products at similar levels to those achieved in the 1990s. Thus, the apparent lack of new projects has as much to do with the research-based failure to invent new drug candidates in the past five years, as it has with the popularity of biopharmaceutical candidates.

These twin trends have led to a dearth of new 'small molecule' drugs and a perception that the demand for pharmaceutical fine chemicals (PFCs) may be in long-term decline. Western PFC producers offering their services to the innovative sector have also found it harder to win new business as companies from the generic API sector and Asian suppliers have begun to make serious inroads into their profits. For all these reasons, it is not surprising that many companies have considered moving into the biopharmaceutical contract business.

Nevertheless, such a major change is not suited to most PFC producers since it involves acquiring a new set of technical capabilities (bioengineering rather than chemical) and significant capital investment. The impact of such changes on existing chemical operations and company morale also cannot be underestimated.

In any case, biopharmaceuticals cannot replace all traditional chemical treatments. Their limitations include their high costs, the need to administer by injection, difficulty maintaining uniform batch-to-batch quality; emerging problems with patient allergic reactions; and their unsuitability for treating a number of classes of illness.

On the other hand, a key factor in their appeal to the R&D-based drug industry is that the major determinant of quality is the process used (rather than the usual array of analytical tests used for chemical APIs), allowing one to expect limited competition after patent expiry. Another important benefit is the potential of biopharmaceuticals to treat otherwise intractable conditions, particularly cancer and inflammatory diseases caused by defects in the auto-immune system.

Impact of new technology

The impact of this new technology has been varied but one can reasonably expect that in time it will take its place within the overall pharmacopaeia, rather than replace small-molecule products. Indeed, such is the convenience of small molecule pharmaceuticals that even established biotech companies such as Amgen are developing them as part of their new product pipeline. There even appears to be a growing group of researchers that considers monoclonal antibodies to be useful as research tools for identifying new chemical leads.

In the developed world, to date, the effect has been that companies with the financial resources – big pharma and the larger fine chemical groups – have made investments in biopharmaceutical technology and production facilities. Their more successful products are the leading exponents, both in the invention and marketing of biopharmaceuticals and in their manufacture. However, the financial risks mean companies, inventors, marketers and producers can all collapse if products fail. This is particularly true in mammalian cell production facilities, the costs of which are a factor higher than for biopharmaceuticals made from recombinant microbes.

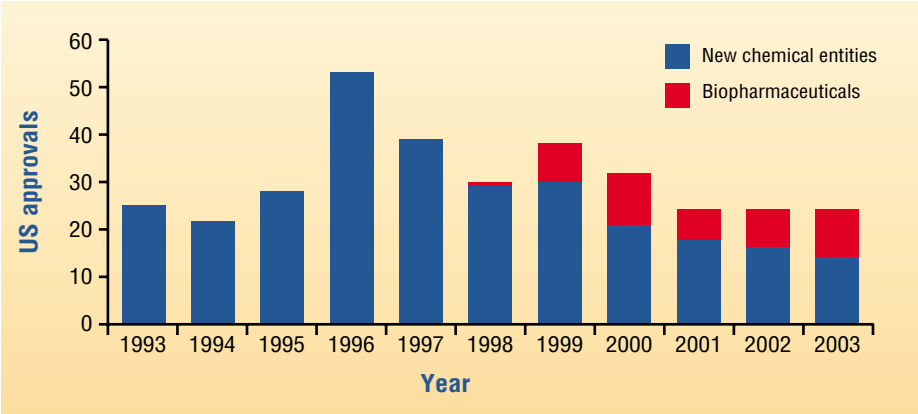

Figure 1: The proportion of new US approvals based on biopharmaceuticals can only increase as the number of new chemical entities declines.

*In this article, biopharmaceuticals (called biologics in the US) are defined as human proteins produced by recombinant organisms (mammalian cell cultures or micro-organisms), grown in a suitable bioreactor. It is important to note that capital investments are much greater (by an order of magnitude) for recombinant mammalian processes than for microbial ones.

Illustration by Rob Wilcockson

The superiority of large-molecule biopharmaceuticals over their chemical counterparts in attracting the attentions of big pharma is by no means a foregone conclusion. The smaller, niftier chemicals have life in them yet.

In the developing markets, companies can become biopharmaceutical producers at significantly lower risk than their Western competitors by cherry-picking the best biogeneric opportunities. But the whole area already shows signs of becoming a legal minefield, with good patent lawyers becoming as important as biotechnologists. Indeed, a recent article in the Indian newspaper, *The Financial Express*, suggests the term 'biotechnology' is rather loose with inflated revenue claims for India's fledgling biotech sector – reminding older industry observers of the over-hyped claims for the growth of 'chirals' in the 1990s.

What is clear, however, is that the 'small molecule' specialists in the developed markets – which don't have anything to do with biopharmaceuticals – will experience greater competition in the supply of services and products during the early part of a drug's life cycle, as deeper inroads into this sector as well in GMP production are being made by companies based in Asia. Greater participation in the non-proprietary sector by PFC companies headquartered in developed nations could help to offset the loss of business and maintain volumes, but this is likely to be at the expense of profits.

Thus, although the continued growth of the value of pharmaceutical products lacking proprietary exclusivity (which includes old branded and generic products) will fuel growth in the overall volume of PFCs, the demand for new small molecules is likely to be reduced over the next few years.

Return to the past

In a sense, one can see a return to the PFC industry structure before the influx of chemical company investment, where small-to-medium-sized operations were the norm. The dominance of big capital projects in biopharmaceutical manufacture fits better with the chemical industry model than that of the fine chemical business. This is clearly the case with biopharmaceutical players' sub-contractors, many of which are chemical industry-based companies such as DSM, Dow (which has, however, recently withdrawn from the sector) and Avecia. It is noteworthy that Lonza and Cambrex both espouse process development as their key strengths rather than announcements on new capacity reflecting their different approach to business development, although the former has made a major investment in mammalian cell capacity in the US. Another fine chemicals-based company, Merck Darmstadt, has pulled out of this activity and has sub-contracted Boehringer Ingelheim to produce its biopharmaceutical needs.

The emergence of opportunities to produce biopharmaceuticals has offered some PFC producers the chance to create significant new revenue streams at a time when business has become increasingly difficult. Those with the resources and management backing have made investments and secured new projects which, should they reach full commercialisation, ought to be easier to retain over the product's lifetime. The impact for these companies has tended to be mixed. Even well-resourced companies have experienced process development problems that have strained customer relationships and created divisions within their workforces as the new skills required have sidelined the chemists and brought biotech engineers and biochemists to the fore. Separation of the operating divisions has alleviated these operational problems, but has then highlighted the financial risks involved. These growing pains will ease with success and the impact on the PFC division will be reduced. Where success has been more elusive, the impact on the business will have been quite serious, given the levels of investment and running costs required.

However, with business-entry barriers so high, small-to-medium-sized companies would be better advised to stay with small molecules. Although biopharmaceutical process development contractors have begun to emerge as a specialist sector, a typical PFC company would have little technical expertise to bring to this lower-capital-cost route into the industry.

In any event, there is a case to be made for small-to-medium-sized players maintaining the 'small molecule' area as their prime focus. Fine chemical development remains an area where really skilled practitioners can make their mark. Even though the numbers of new APIs that reach the market has declined, there is still a strong commitment to these traditional drug actives by the research-based industry. Structures continue to be complex and challenging to synthesise, thus offering good rewards to companies able to devise robust processes for them. And as more basic research is being carried out by smaller companies that may have few chemical development skills, the role of the process development specialist is becoming more critical in the complicated business of bringing a new drug to market. SM

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