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Pharmaceutical Issues in Perspective

Fine tuning the fine chemicals market to satisfy pharma

Dr Rob Bryant considers the evolving business landscape for companies making pharmaceutical fine chemicals over the next five to ten years and asks if there is a better way to do business

Fine chemical producers, like any other commercial concern, have always had to anticipate the changing demands of the companies they serve if they want to stay ahead and win the higher margin contracts. For the fine chemical industry, this has meant keeping abreast of how pharmaceutical R&D changes with the times. And it is as important now as it has ever been. Indeed, the recent sharp fall in the share-price of Bayer, following its withdrawal of Baycol, demonstrates one such change: the need for the major groups to insulate themselves from the risks of drug innovation.

But this case, to which we will return later, is unusual in that it was prompted by failure. In the main, the changes in R&D focus over the past century have been prompted by the industry's success. As new drugs have transformed therapeutic areas so the need for new remedies in those areas has became less pressing. From antibiotics and analgesics, the focus shifted to cardiovascular, anti-asthmatic, and anti-ulcer drugs. More recently, it has shifted again to central nervous system drugs, antivirals and anticancers.

The lead time between scientific discoveries and practical breakthroughs in these three broad categories is roughly of the order of a generation. The categories themselves have led to three equally broad types of products available today. These are:

•A core of tried and tested remedies that have been in use for a generation or more. These **mature products** are usually off patent and available in most markets as branded (by multinationals) or unbranded (by regional and generic companies) medicines. Branding can be supplemented by special formulations and delivery systems to differentiate them from the competition.

•Newer, often speciality, products that have been on the market for a sufficient period of time to confirm their safety and efficacy. These **establishing pharmaceuticals** are the mainstay of the multinationals, although they are also available as unbranded products in some markets because of regional legislation on generic substitution or product patents. During their 10-15 years of patented sales, their future as mature products or eventual failures (once patent protection expires) becomes evident.

•Recently launched or **development products**, where their true potential, clinical and financial, remains to be proved. This is the traditional province of the innovative sector, which has always consisted of both large, maturing companies and small research-based operations that are either publicly or privately funded firms or government-funded research institutions.

Pharma survival strategies

The emergence of companies specialising in these three sectors has begun to change how the global industry organises itself. Some changes are already evident and can be seen, for example, in big pharma acquiring 'pipeline rich' smaller companies and redeveloping existing drugs to extend their period of profitable exclusivity.

As these stop-gap solutions have failed, a new focus on cost-reduction has emerged, squeezing the pharmaceutical fine chemical (PFC) industry to the extent that it can be fairly said that its prospects have never been more confused or gloomy. The contractual terms now being offered are often unacceptable both in terms of reward and the sharing of commercial risk. It therefore seems a good time to ask whether it wouldn't be in the best interests of pharma to reorganise itself so that the companies supplying it with PFCs have a better chance of survival.

One trend that can be observed is that the larger pharma companies are becoming increasingly focused on the marketing and distribution of mature and establishing products, thus becoming more like the food multinationals. These companies will in-license important new drugs, having the resources to develop and market them on a global scale. Moreover, the withdrawal of Baycol, coupled with other recent dramatic post-launch failures will tend to encourage later and later in-licensing. And it may be that launches by the innovative sector – but indirectly funded by big pharma – will be limited to selected markets so that any major side-effects can be picked up prior to global launch. As a result of greater in-licensing, the majors will increasingly divest their innovative R&D operations, considering them to be too risky for their shareholders to tolerate.

Big pharma is becoming increasingly focused on the marketing and distribution of mature and 'establishing' products, like the food multinationals

These global brand leaders will source established active pharmaceutical ingredients (APIs) from low cost producers and add value via their branding power, thereby outsourcing risk and increasing investor confidence. Overall profits may not be as high but more predictable returns help keep

Source of new products	Major drug groups
Considerable in-licensing	American Home Products, Bristol-Myers Squibb, Pfizer, Johnson & Johnson, GlaxoSmithKline, Novartis
Balanced portfolio	Aventis, Pharmacia, AstraZeneca, Schering-Plough
Self-sufficient	Abbott, Bayer, Lilly, Merck, Roche, Takeda

Figure 1: Pharma players are moving away from self-sufficiency in drug production in favour of in-licensing.

Illustration by Rob Wilcockson

The outlook for the pharmaceutical fine chemicals industry has never been more gloomy…

investors sweet. The fact that Pfizer, the world's biggest pharma company, has evolved from a commodity chemical firm within the past 50 years by following this exact strategy is indicative that the formula works. An attempt to illustrate the current move towards greater in-licensing is presented in Figure 1.

Another trend, not entirely unrelated to the first, is that established APIs will be produced by high capital investment plants owned increasingly by the major chemical concerns. Much of the integrated chemical manufacturing capacity of the multinationals will be spun out as they move away from this non-core activity. In this regard, the recent investments in chemical production by Pfizer were exceptional and special factors, such as the tax benefits available in certain locations and coping with massive cash inflows, were at play.

Regulatory compliance in supplying APIs will take on greater importance, as will the use of cGMP-regulated production units and the resources to make significant capital investments well ahead of perceived pay-back times. As production facilities meet these higher standards, it is predicted that the current trend towards greater outsourcing of mature products will also be seen with the 'establishing products'. The driving force will continue to be the reduction of costly fixed assets in order to increase margins.

Companies marketing unbranded products and regional pharma companies will continue to serve local markets with 'me-toos' or cheap versions of branded products. APIs for these non-branded drugs could be sourced from the same suppliers as the branded products (compare the way food commodities are sold) or from less sophisticated PFC producers which serve less stringently regulated markets. Medium-sized companies with sales of between US$200million and US$1billion in the US, Europe, India, China and Japan form the core of this group.

The pharma industry in Japan is something of a special case in that its many small- to medium-sized companies have been able to move from producing copy products to become truly innovative. During this process, the companies have remained relatively small, perhaps enhancing their ability to innovate successfully.

From this heterogeneous group, new multinationals will emerge through major product successes (Astra and its blockbuster, omeprazole, is a recent example) or by mergers. US generic legislation has acted as a spur to the creation of multi-billion dollar companies that carry out virtually no new chemical entity (NCE) discovery. Some of these are now becoming global players and might eventually join the ranks of the major brands, especially when one considers the rise of global generic product companies in other industries, such as Wallmart.

This part of the industry, although recently associated with the major multinationals, will return to its entrepreneurial roots, with smaller, development-based pharma companies inventing and developing new APIs. The companies operating within this sector will tend to avoid getting involved in chemical development and manufacture and will sub-contract out work to development-based PFC companies. The biotech industry is an expression of this trend, as is the rise of new, small pharma companies formed by groups of individuals looking to free themselves from the bureaucracy and political infighting of the major companies. The prime objective will be to invent and develop innovative drugs that, once proven in limited launch markets, can be wholly or partly licensed to the branded sector. Where global sales are expected to be limited, these companies will retain the rights to the new products.

Investment in this sector will be recognised as high risk and facilitated mainly by the multinational drug companies, as well as institutional investors looking for capital growth. This sector has been pioneered by the US biotech industry, which was set up outside big pharma precisely because the technology was speculative and risky. There have been some spectacular successes (see Figure 2) as well as many well-publicised failures.

The first generation of entrepreneurs were, perhaps, too often those who could tell a good story rather than those with a rough diamond tucked under their arm. There are signs, however, that the newer discovery groups may contain a higher percentage of important technologies than the first and that investors are becoming a little more savvy about the investments they make. It really does make more sense for big pharma to foster smaller, specialist discovery groups from a safe distance and only crank up funding when it becomes clear that an important new compound has been uncovered.

Reacting to the new landscape

As this new landscape emerges from the confusion of the past five years, a new and exciting phase in the development of the PFC industry will unfold. In order to reflect the differing needs of the pharma industry sectors described above, the diverse collection of PFC companies will reform into one of three main types:

•Capital intensive and regularly inspected cGMP operations that focus on producing mature and establishing APIs for the major brands. World scale plants will be able to generate good margins, since continuing production will enable process parameters to be closely defined, improving quality and regulatory compliance. This group will include multinational drug production, which is predicted to be increasingly spun out; divisions of chemical companies (often built up by acquisition); and larger PFC companies such as Lonza, Omnichem and Siegfried.

•Less well-endowed PFC operations will

produce APIs in non-registered plants for less demanding customers and established intermediates for the big cGMP units. They will want to evolve into companies that can serve the branded sector. Southern European companies once dominated this sector. Now, and in the future, companies in India and China will increasingly serve this market, with Western operations acting as sales, administrative and quality control agencies.

•Companies serving the innovative sector will be small- to medium-sized, responsive companies which can cope with technically challenging API syntheses that require new skills in chemistry, engineering and biotechnology. These players will operate in a wide range of niches, primarily defined by their technical skills and the development stage(s) in which they specialise. Operating in this sector will demand greater emphasis on good process development not only to meet development deadlines, but also cost targets. However, with less need to launch products globally as quickly as possible, all aspects of development should be undertaken with greater thoroughness than is currently the case, hopefully reducing the number of late stage clinical failures.

These companies will need to operate to GMP standards but will retain some flexibility at the early stage of development so that the increasingly challenging process chemistry can be made to work properly prior to scale-up. Maintaining this balance between innovative technology development and regulatory compliance will be a managerial problem that has been solved, so far, by very few companies.

The demand for new technologies involved in developing and producing novel APIs has spawned an increasingly heterogeneous mix of firms. These companies, and that can be divisions of larger groups but more usually are small start-ups, create new niches during the initial phase when business success is less than certain. As products reach the market and demand rises, other companies try to win a share of the business with me-too technologies, or by acquisitions.

Technology niches, as they mature, become relatively stable with fewer more-established players – at least, until new developments attract new entrants. Such technological niches include fluorine chemistry, nitrations, phosgenations, cyanations, etc. Indeed, developing a reputation as a technology leader in one or more particular fields is a kind of branding exercise and offers significant commercial advantages, if not necessarily a premium.

As long as small molecules (organic chemicals with molecular weights generally under 1,000) continue to be required, then demand for custom synthesis services, in which more general organic chemistry skills are required, will continue. The key ability in this vast area, claimed by most but absent in many, is to produce a small amount of the target material quickly and efficiently. This skill is found at the core of all successful companies and must be maintained and updated continuously.

Claims that larger groups can integrate such small synthesis companies within a 'one-stop shop' have been made but never successfully demonstrated. There is a major difference in mentality between people who like the continuous challenge of a stream of target molecules and those who take pride in producing batches of fine chemicals within closely set parameters day-in day-out. Keeping such people under one roof has never been easy and has led to many break-ups. Customers appear to understand this better than the PFC industry and most major outsourcing operations have two distinct groups to deal with what AstraZeneca now calls tactical outsourcing (for small amounts of new lead compounds) and strategic outsourcing (for advanced development contracts).

The more mature sector

Once full-scale production is required, pharma tends to favour the PFC companies with the larger operations. But while size is important to ensure continuity and sufficient capital investment for regulatory compliance, a counter-tendency towards bureaucracy and process optimisation (rather than development) tends also to kick in. And this type of contract manufacturing is not necessarily suitable for undertaking effective process development.

Traditionally, the major drug companies have undertaken much of their own process development and manufacturing in-house. Most still maintain that this is the best way to ensure security of their process secrets (undeniable) and that they never run low on APIs, which is more debatable. Many now concede that third parties can offer many advantages but most remain shackled with chemical manufacturing capacity which is hard to off-load. Indeed, Aventis' inability to sell its Romainville site is a recent demonstration of this problem. Given time, captive chemical production will become less important, preferably through closure rather than sale, since the results achieved by PFC producers who have taken over pharmaceutical plants have generally been disappointing. While a capacity overhang exists, major pharma companies will continue to produce in-house.

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In the future, the major chemical companies and their subsidiaries will be the natural providers of services to this group. The top 15 companies, by fine chemical sales (see Figure 3), offer interesting insights into this type of producer. All, with the exception of Bayer, BASF and Siegfried, have grown through the acquisition of smaller compa-

Technology	Examples of companies
Peptides	Bachem, Synthetech, Avecia, Chiratec, Peptisyntha, Senn Chemicals, Degussa
Combinatorial chemistry/ high throughput screening	Paradigm, Combichem, 3-D Pharmaceuticals
Process development	Medichem, Onyx, SynProTec
Carbohydrates/glycoproteins	Pfanstiehl Laboratories, Oxford Glycosystems, Inalco, Dextra Laboratories
Protected nucleocides	Degussa (Raylo), Ajinomoto, Samchully
Chirals/biotransformations	DSM Fine Chemicals, Kaneka, Dow (ChiroTech/Celltech), Oxford Asymmetry, Synthon, Mitsubishi Rayon, Chiragene
Asymmetric synthesis	Sepracor (Chirex), Takasago, PPG-SIPSY, ChiroTech
Chiral separations	Daicel (Chiral Technologies), Novasep, UPT, Degussa
Biotechnology (microbial and mammalian cell culture)	Akzo (Covance acquisition), Lonza Biologics, DSM

Figure 2: There is no shortage of successful new technologies coming from fine chemical companies.

Illustration by Rob Wilcockson

…and prospects will only pick up if fine chemicals companies can adapt to the changing needs of pharma.

nies. Some, such as Lonza, have become larger by organic growth and others, such as Cambrex and Honeywell, are the result of a campaign of acquisitions.

Although there are wide variations in these companies' structures and financial performances, most share features which are attractive to the major drug companies:

•They have the resources to invest in expensive fixed assets to satisfy both customers and national regulatory agencies.

•All derive some income from producing basic chemical intermediates, which helps to define their technology platform.

•They are mainly based in mainland Europe, where investors have traditionally not expected the high returns on investment demanded by US and UK companies.

•Most would be considered less as custom synthesis (where route definition is included) specialists, than as contract manufacturing (where the customer's process is operated, often under their R&D control) specialists.

Process implementation

The culture of the technologists in these companies tends to be dominated by process implementation rather than process development, although there are exceptions. The loss of senior individuals who were responsible for building up the acquired company after the acquisition is now almost accepted as the norm, as is the departure of the more ambitious juniors for more dynamic environments. This is one important reason why dynamism tends to drain out of companies as they grow in size.

For the same reasons, the cultural fit between such companies and their large, multinational customers is good. The argument for separating innovation at drug discovery level from big pharma finds its equivalent expression in the need to separate creative organic synthesis and process development from big PFC companies. Creativity always finds its best expression outside large organisations. A less familiar idea is that chemical process development is creative and worthy of investment. Herein lies the paradox of the industry; that billions are spent on blue-sky R&D to identify a new API (US$38 billion by the global drug industry in 2000, according to one source). And virtually nothing, by comparison, on process development to make that API.

It is as though the most expensive and time-consuming part of man's learning to fly was for Leonardo da Vinci to draw his first helicopter. The reality, as Edison so brilliantly observed, is that 99% of an invention is perspiration. Thus it was that 'daring young men in their flying machines' contributed this lengthy, expensive and risky part of getting manned flight established.

There can be no doubt that the complexity of the problems facing these businesses has, in part, been created by the scientific breakthroughs in medicine over the past ten years. The predictions in this review have been for the next five-ten years. Beyond this, the impact of some of the more exciting new developments in the understanding of genetics will be such that the PFC industry will need to make more dramatic adjustments to its structure.

What can be said is that chemical active ingredients will continue to be a keystone of therapeutic intervention, but will probably no longer hold the primacy they have today. This is probably just as well, given the decline in the popularity of chemistry as a subject of study in the world's seats of higher learning. SM

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Company	Head office location(s)	Sales revenue 2000 (E million)
DSM Fine Chemicals	Netherlands	900
Clariant	Switzerland, Germany	575
Lonza	Switzerland	398
Degussa Fine Chemicals	Germany	397
Cambrex	US	334
Bayer Fine Chemicals	Germany	296
BASF Fine Chemicals	Germany	275
Dow Fine Chemicals	US	268
Honeywell	US	250
Great Lakes Chemicals	US	216
Eastman Fine Chemicals	US	216
Diosynth	Netherlands	210
Rhodia	France	205
Siegfried	Switzerland	203
Avecia	UK	200

Note: these sales data include non-pharmaceutical fine chemicals business

Figure 3: The top 15 fine chemicals companies by sales revenues.
Source: Merrill Lynch

