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Pharmaceutical Fine Chemicals

Global Perspectives 2000

by

Dr Rob Bryant

An Informa Chemicals Industry Report
now distributed by

Brychem Business Consulting

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Dr Rob Bryant was born in Chingford, England, in 1948. He married his wife, Michelle, while at university and was awarded a BA in Natural Sciences at Peterhouse, Cambridge, in 1971. He subsequently undertook research in the synthesis of prostaglandins for his doctoral thesis, receiving an MA and PhD from Cambridge in 1974. After three years' post-doctoral work in Heidelberg, Germany, then in Lyon, France, and Bangor, North Wales, he and his wife started a family that eventually included a son and two daughters. From between 1979–88 he was employed in the pharmaceutical fine chemical industry. He worked in process research and development at three UK-based companies: Sterling Organics (now Chirex), Orsynetics (now part of Thomas Swan) and the then Glaxo subsidiary, Macfarlan Smith). He has been a consultant since 1987. He spent five years with the international group, Chem Systems (now part of IBM), where he was a partner and headed the consultancy's fine chemicals practice. He set up Brychem in 1992 to concentrate upon providing consulting services to the international fine chemical industry, particularly in the area of pharmaceuticals and agrochemicals. In 1997, he acquired the specialist US agrochemical publishing business, Ag Chem Information Services, and relaunched it under the name Agranova.

Acknowledgements

I should like to thank first and foremost my wife, who has put up with me for nearly 30 years, having helped to fund my education and bore the brunt of the work in bringing up our three children. Secondly, I wish to acknowledge all the individuals who have retained my consulting services over the past 20 years, without whom I could not have learned enough about the fine chemical industry to make an attempt at this biography. Thirdly, I should like to thank the following friends who kindly read through the manuscript and/or offered useful comments and additional data: Dr Maris Bite (who manfully checked the initial draft!), Dr Yusuf Hamied, Pang Feng, Dr Arthur Jackson, Martin Paltnoi, Dr Sidney Smith and Brian Tarbit. My final acknowledgement is to Noemie De Andia and Martha Kürzl for their part in helping to produce this book. The author is grateful to Edwin Bailey for returning his copyright.

ISBN 1 86067 4755

Code: P2597

Copyedited and typeset by Martha Kürzl, martha@kurzl.softnet.co.uk

Printed and bound in Great Britain by Copyspeed Printing PLC, Concorde House, 56 Station Road, Finchley Central, London N3 2SA, UK.

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EXECUTIVE SUMMARY

What is PFC industry?

My primary intention in writing this report is to provide a scientifically literate reader with a basic picture of the pharmaceutical fine chemical industry. In doing so, I have striven to define and separate the components of what is too often described as the 'pharmaceutical industry' or the 'chemical industry'. Why should this matter? It matters because many interested parties looking at the industry from the outside, create problems for themselves and the various industries involved because of this confusion. Two examples illustrate this:

- Would-be investors in a new fine chemical start-up might expect a 30–40% profit before tax on sales (commonly achieved by large innovative pharmaceutical companies), when in fact such profitability is unusual for such a company. A biotech start-up would not be expected to deliver any profits for the first 5–10 years; a generic pharmaceutical company might achieve much higher profits. These companies all operate under the broad pharma industry umbrella, but are in fact as different as chalk and cheese.

- Managers moving from a pharmaceutical company to a fine chemical company (or vice versa) tend to create terrible problems because their previous experience usually proves to be more of a hindrance than a help.

With this laudable objective in mind, care has been taken in this report to describe the relationships between the pharmaceutical fine chemical (PFC) industry and the other inter-linked industries that are involved in the delivery medicines to the general public.

Evolution of PFC industry

After a brief description of how the modern PFC industry evolved, Chapter 1 provides an introduction to some of the terms and concepts required to understand the main body of the report is provided.

Demand for PFC

Chapter 2 then describes how the demand for PFCs arises, the market value of this demand and the types of operations set up to fulfil this demand.

Supply of PFC

In Chapter 3, a basic review of the supply of PFCs is given. Information is presented on the way basic chemical raw materials are converted to the complex active ingredients used in medicine today.

The sub-title of this report, 'A Profile of an Industrial Business' reflects an important reality about the fine chemical industry in general and the pharmaceutical fine

chemical industry in particular; that it requires more than an ability to invent processes for and make fine chemicals. An enormous amount of energy must also be spent in providing customers with a high level of service. Chapter 4 describes some of these business aspects in more detail and includes sections on the development of a new pharmaceutical chemical (a 'new chemical entity') and the business opportunities that arise at each stage of a new compounds life, from 'cradle to grave'.

Business aspects

The pharmaceutical industry

A PFC industry view of its customer, the pharmaceutical industry is presented in Chapter 5. After a section on the big US, European and Japanese innovative pharmaceutical companies, which are the power-houses of the industry, descriptions of the other types of customers are provided: medium-sized and regional companies, the generic industry, the newer biotech companies and, finally, other PFC companies.

PFC companies

In Chapter 6, a detailed survey of the PFC companies themselves shows the differing niches within the industry. Examples of typical players are given to round off this chapter.

Technology involved in PFC processing

In a rather technical Chapter 7, the technology involved in carrying out pharmaceutical fine chemical processing is presented. Chemistry and engineering graduates might find this section helpful to develop a better understanding of modern industrial chemical synthesis. In omitting chemical engineering aspects, the author makes no apologies. The PFC industry is founded on the development and operation of synthetic chemistry. Although the laboratory equipment and manufacturing technology used in fine chemical factories is important for a successful operation, it has no more place in this review than a detailed description of pots and pans does in a cookery book. Some effort has been made to provide a forecast of some of the chemistries that will become more important in the coming 5–10 years.

Topical issues

The final chapter 8 consists of short reviews on a number of topical issues and maps out some of the challenges the industry faces now and in the near future.

A bibliography is provided in the appendix.

CHAPTER 1 INTRODUCTION

HISTORY AND BACKGROUND ON THE DEVELOPMENT, PRODUCTION AND SALE OF PHARMACEUTICAL FINE CHEMICALS

Since the earliest times, humans have used extracts of plants and animals to treat injuries and diseases. Although the basis for the efficacy of these natural cures was not understood at the time, previous generations discovered many useful treatments eventually by trial and error. Among the most useful were psychoactive materials (such as coca leaves and opium), pain relievers (such as willow bark) and the more recently discovered heart remedy, digitalis (from the leaves of the foxglove). Inorganic treatments such as mercuric salts (used for treating a number of diseases) have also been used for many centuries.

During the 19th century, improvements in the technical expertise of pharmacists led to the isolation of reasonably pure 'active principles'. The concept of a pure compound was also developed by chemists and the two hitherto separate branches of scientific research began to benefit from one another's findings. The advances in organic chemistry that occurred in the latter part of the nineteenth century were transferred quickly into a newly formed chemical industry, where the development of synthetic dyes was the key driving force.

At that time, a multiplicity of pharmacies carried out much of drug production in laboratories behind or close to their retail outlets. The processing was generally one of extraction of plant (and animal) material in order to produce purified active ingredients. The chemical industry provided solvents and simple reagents for preparing salts and esters of the basic natural extracts. Many of the familiar multinational pharmaceutical companies were formed from such pharmacies, including Merck (which traces its history to a 17th century pharmacy in Darmstadt, Germany) and SmithKline and French (a Philadelphia-based group of pharmacies). In Europe, major producers of natural products emerged; they included Merck & Co., Boehringer Söhne, Knoll, T.H. Smith and J.F. Macfarlan.

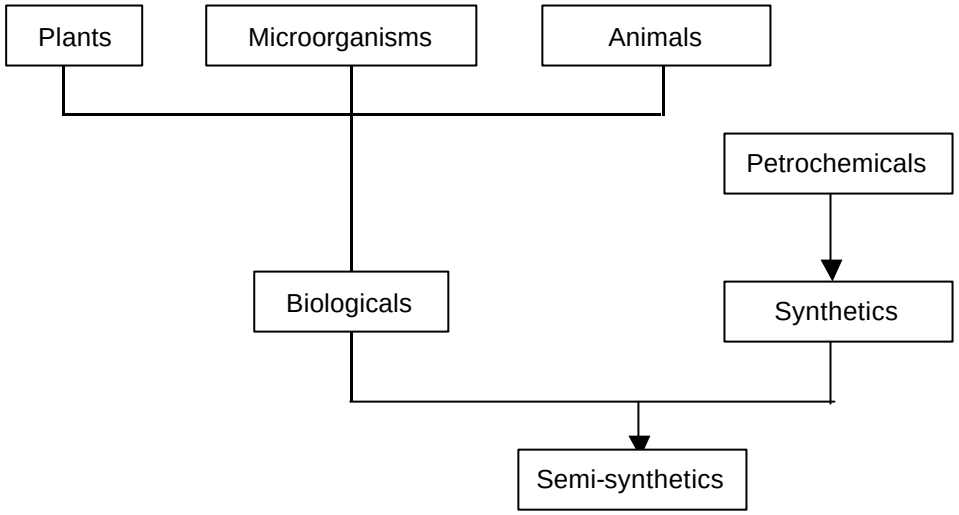
As the range and sophistication of the active ingredients increased, particularly as synthetic drugs began to appear, these relatively modest facilities became too small and the first bulk pharmaceutical factories were set up. New entrants to the business such as Bayer and Roche, who were introducing synthetic drugs, used their organic chemistry skills to invent new pharmaceuticals. Aspirin was one of the first of what was to become the dominant type of pharmaceutical product during this century – totally synthetic drugs, often without similarity to naturally occurring medicinal chemicals. Greater specialisation in the technologies required in the production of pharmaceuticals led to an increasing number of specialist producers.

By the middle of this century, the foundations of the modern drug industry had been established in Europe and the US. Rapid development of a host of new compounds, many (but not all) based upon natural products, led to increasing numbers of pharmaceutical

companies, some formed by mergers, others by organic growth. A supply industry grew up, offering basic raw materials, intermediates and even active ingredients.

Pharmaceutical ingredients may be sub-divided into three basic classes, 'biologicals', 'synthetics' and 'semi-synthetics'. In Figure 1.1, these basic classes are divided into other sub-categories. The important point to be made here is that only synthetics and semi-synthetics require the use of chemical synthesis. For the purposes of this review, only these two sub-classes will be discussed in any detail.

Figure 1.1: Sources of pharmaceutical active ingredients



Source: Brychem

Pharmaceutical fine chemicals (PFCs) can now be usefully classified into several categories:

- Active ingredients (or bulk actives) – responsible for the primary activity of the finished formulation.

- Key (pivotal or critical) intermediates – elaborate fine chemicals that can usually be only used for producing one or two pharmaceutical actives.

- Basic intermediates – relatively simple multi-outlet chemicals, used as the building blocks for pharmaceuticals and/or other types of performance chemical.

Development of pharmaceutical production outside of Europe and the US has occurred since the 1960s. Generally these developments have been driven by the need for developing countries to secure an independent source of essential drugs at moderate prices. In these countries a fully integrated capability has been developed, with pharmaceutical fine chemicals being manufactured from a combination of locally made and imported raw materials. The three most important Asian regions for pharmaceutical fine chemicals illustrate this.

- In India, import substitution was enforced by a combination of import tariffs and patent legislation. A major boost to the indigenous industry was provided by the

government's 1971 withdrawal of product patent legislation, thus allowing local companies to produce copy products at a fraction of the imported price.

- In China, use of so-called Western drugs, started with the 1951 introduction of synthetic chloramphenicol, produced by a Beijing company. Patent protection for multinational company inventions has only recently been provided.

- In Japan, the local industry has benefited from the rapid growth in Japanese economic power, coupled with a healthcare system that encourages innovation and a population used to 'popping' pills. Exports of Japanese pharmaceuticals (both as bulks and finished goods) to Asian markets have also meant that Japan's industry has prospered.

These three countries have become important sources of PFCs over the past 10 years, particularly for markets where the control of drug pricing is an issue. As the dominance of Italy (and more recently, Spain) as bulk drug suppliers to the US generic market (resulting from their special patent status within Europe) wanes, India and China are expected to become increasingly significant as PFC exporters to Europe and the US.

Elsewhere, most countries have been content to import mainly branded drugs (countries such as Australia and South Africa) or locally marketed generics (Canada, Argentina, Brazil, the Middle East). In Africa cheap, essential drugs supplied through the WHO have been all that can generally be afforded.

REVIEW OF THE PHARMACEUTICAL FINE CHEMICAL INDUSTRY – BASIC FACTS AND FIGURES

Commodity chemicals are manufactured from (mainly) petrochemical feedstocks in very large quantities and are sold on the basis of their composition. This means that the buyer (always another industrialist, never a final consumer) requires only a guarantee of chemical purity to an agreed specification. Unless small amounts of specific impurities might create processing problems, no performance guarantees are normally needed. Prices are low and are calculated on a cost-plus basis. Fine chemicals are small volume, high value chemicals which are sold, like commodity chemicals, on the basis of their *chemical composition*. The cut-off between commodity and fine chemicals is an arbitrary one, but it is generally agreed that fine chemicals generally have prices greater than US$5–10/kg. Fine chemical price levels are established on the basis of the level the market will bear (not on a products/cost–plus basis). Fine chemicals may be contrasted with performance chemicals, also sold in modest quantities compared to commodity chemicals and intermediates, which are sold on the basis of their *performance*. This performance is usually, but not exclusively, achieved using carefully controlled mixtures of fine chemicals. In the US, the term specialty chemicals is used to denote both fine and performance chemicals. Pharmaceutical products represent a relevant example of a performance product; others include agrochemicals, perfumes, industrial biocides and health supplements. An example will clarify these relationships: Phenol (commodity chemical) is transformed first into salicylic acid (fine chemical intermediate) and then

aspirin (bulk pharmaceutical active ingredient), which is formulated into a tablet and sold as a headache cure (performance product).

Fine chemicals are produced worldwide for a number of important performance product manufacturing industries. The main outlets are listed in Table 1.1. The value of sales shown in this table must be treated as broad estimates, rather than accurate statistics. Reliable calculations are made difficult by the secrecy of much data, double-counting problems created by a high percentage of captive manufacture and by confusion created by misleading published data.

Table 1.1: Customers of the fine chemical industry

Customers for fine chemicals	Estimated sales of fine chemicals (US$bn)[a]
Pharmaceutical industry	60
Agrochemical industry	10–12
Food industry (additives and flavours)	5–10
Animal health and nutrition	5
Cosmetics (fragrances, adjuvents and vitamins)	2
Industrial chemicals	1–2
High-performance polymers	< 1
Dyes and pigments	< 1
Total	80–90

[a] Includes captive and third-party sales.

As with fine chemicals in general, quantifying the value of the sales achieved by the pharmaceutical fine chemical industry is not easy. One important reason is that statistics on the production and sale of fine chemicals are not in the public domain; rather they are closely guarded commercial secrets. Consumption data (in volume terms) must be back-calculated from the sale of finished dosage forms (available in terms of value), information on which is available, although not freely, since it is expensive to collect. From this data, estimates of the production of active ingredients and intermediates may be calculated. Ideally, reconciling feedstock production data with these consumption figures should make an independent verification of the estimates possible. The whole exercise is time-consuming and requires specialist skills if reasonably reliable data is to be obtained.

Another source of difficulty results from the problems associated with the complex industry structure. During the conversion of a raw material to a finished bulk pharmaceutical, as each step is undertaken manufacturers might often ship the chemical intermediates between companies several times. Thus the total sales of the industry will be greater than the actual sales value of the business through double-counting. These provisos should be borne in mind when reading Table 1.2.

Statistics on the sale of pharmaceutical finished products (tablets, injections, etc) are collected in most major markets. In Table 1.2 the global pharmaceutical finished dosage

sales for 1998 are listed by these main country markets. One should take care when interpreting these figures. In different markets, statistics are reported on differing bases, since the channels of distribution vary. In general, sales of pharmaceuticals outside of pharmacies (important in the US) are not included. For example, the US Veterans Administration is a major purchaser of pharmaceuticals and is responsible for buying a high proportion of certain products. The main outlets in the US are retail pharmacies (80%) and hospital sales (around 20%). In Europe, the hospital sales (8%) account for a smaller proportion of the total. The reliability of the statistics collected in much of Asia is questionable, both in terms of reliability and accuracy.

Table 1.2: Global pharmaceutical sales by leading country markets (1998)

Country	1998 sales (US$bn)	Global share (%)
US	99.5	39.7
Japan	38.8	15.4
Germany	18.2	7.2
France[a]	14.1	5.6
Italy	10.9	4.3
UK	10.2	4.1
Brazil[a]	6.5	2.6
Spain[a]	5.3	2.1
Canada	4.9	1.9
Argentina[a]	3.6	1.4
Other	39.3	15.7
Totals	251.3	100.0

[a] Excludes hospital sales.

Source: IMS Health, London

The total sales in major markets estimated by IMS should be augmented to calculate a reasonable global figure. Taking into account the estimates of sales (at the retail level) in other important markets including China (US$12bn), Russia, Central and Eastern Europe (US$8bn) and Africa (US$5bn), the global market is calculated at around US$275bn. The value of these sales at the bulk level is estimated at around US$60bn, with perhaps 70% of this total being captive production by the companies that market the finished formulations. The independent manufacturing sector, valued at approximately US$18bn is divided into three main areas of activity:

- Production of bulk actives (valued at around US$10bn).
- Advanced intermediates (valued at around US$5bn).
- Basic intermediates/raw materials (valued at around US$3bn).

The vast majority of this *merchant* business is handled by companies located in Europe and Japan, with the US accounting for a relatively small proportion, compared to these regions. Although China and India are securing an increasing

market share of the merchant market, it is from a small base and consists mainly of basic intermediates. The US has a major share of the *captive* business, however, being the base for the world's largest and most successful pharmaceutical companies.

There are five classic ways in which a company can build up a fine chemicals business. These are examined briefly below. In reality, most companies operate a mixture of more than one of these strategies, but the separation of the approaches is useful because each requires different resourcing and each demands a different level of customer service.

Exploitation of a basic raw material position

The company has a basic position in a commodity (such as chlorine) or chemical intermediate (such as diketene) that it manufactures on a cost-effective scale. It exploits this favoured access to a raw material and produces a range of downstream products (some of which may be relatively small volume chemicals with quite complex structures) at competitive costs. These chemicals are generally offered to the customers on a cost–plus basis, although where access to a raw material is an important advantage, custom products can be made at a premium price. Feedstocks for these raw materials can include petrochemicals, natural products such as sugar or (more recently) biotechnical raw materials (for example, erythromycin).

German and Swiss majors have generally adopted this approach. It has some major disadvantages in that the balance between the intermediates produced is dictated to a considerable extent by the technology, whereas the demand is dictated by the customer base. The two are never equal and this leads to pricing complexities that have rarely been resolved. Another growing problem with exploiting basic raw materials is the competition from companies producing these relatively simple chemicals in India and China. Many companies have, nevertheless, built up useful businesses using raw materials as an important technical strength. Some examples are given in Table 1.3.

Table 1.3: Exploiting a raw material strength – examples

Raw material	Important producers	Important derivatives
Chlorine	Many	Chlorotoluenes, chlorophenols, alkyl chlorides, chloralkanoic acids, trifluoromethyl-aromatics
Acetic acid	Clariant, Wacker, Lonza	Acetic anhydride, diketene, sorbic acid, propiolactone
Hydrogen cyanide	Degussa, Lonza, ICI, DuPont, RP	Sodium cyanide, cyanuric chloride, adiponitrile, methionine, phenylacetic acid
Phosgene	PPG, SNPE, BASF	Diisocyanates (for PUR's), chloroformates, carbamates, acid chlorides
Penicillin	Antibioticos, Chinese, SB, Gist brocades, Synpac, Clariant	6-APA, 7-ADCA, penicillin salts, penicillamine
Poppy straw	Macfarlan-Smith, Noramco, Francopia	Morphine, codeine, thebaine, buprenorphine

Exploiting a technology

Building up a range of standard and custom intermediates can also be carried out by operating a particular technology. Examples are shown in Table 1.4. Opportunities to exploit niche technologies abound. Companies that can develop new solutions to chemical production by combining the skills of engineers and chemists effectively have the potential to develop lower cost processes and secure profitable business.

Table 1.4: Exploiting a technology – examples

Technology	Important producers	Important derivatives
Nitration	EMS-Dottikon, Dynamit Nobel, Olin, Angus	Nitroaromatics, nitrate esters, nitromethane
Gas phase reactions	Laporte, Weyl, Nippon Shokubai, Nepera, Reilly, BASF	Pyridines, anisaldehyde, cresols, cyclopropane derivatives
Aluminium alkylations	Albemarle, Lonza	2,6-dialkylbenzenes
Aerial oxidations	Clariant (Hoechst), Toray	Phenol derivatives, benzonitriles
Chiral technology	Chiroscience, Oxford Asymmetry, SIPSY, Sepracor	Chiral intermediates for agrochemicals and pharmaceuticals
Peptidisation	Bachem, Synthetech	Peptides, small proteins

Toll (contract) manufacture

Traditionally all fine chemical companies carry out some toll production. This technique for developing business is quite straightforward: the contractor makes available his spare capacity for a customer so that it can transfer its ready-developed process into the contractor's facilities. It requires a maximum of engineering expertise and a minimum of chemical expertise. Business is developed by ensuring customers are aware of the equipment available. Differentiation is difficult, but particular skills in certain technologies can help to secure contracts. There is therefore considerable overlap with the second strategy described above.

Toll manufacture is an essential part of the activities of most fine chemical producers, but it does not offer on its own an effective way to develop a successful business, unless the customer is also the owner. Profits are low, reflecting the low risks involved. However, contracts are unpredictable and if several are cancelled at the same time, this can be very disruptive!

Custom synthesis (manufacture)

The essential difference between custom synthesis and toll manufacture is that the former approach includes the development of the process to be operated. The company therefore requires a good team of process *development* chemists in addition to the usual resources required of a fine chemical company. The word development is important. Many companies are able to optimise, adapt, tweak or maintain a process, but it takes special skills to come up with a workable process starting from scratch. On the other hand, companies with the necessary skills to come up with a novel *synthesis* too often lack the ability to develop a viable *process*.

Companies operating in this area tend to concentrate upon process development or custom manufacture (where a collaboration with the customer's chemists is required to co-develop the process). 'One stop shops', where a customer merely specifies the molecular structure to be made, are rare; they are usually large companies that possess several different types of operation. Table 1.5 lists some of these companies.

Table 1.5: Examples of companies in custom synthesis and manufacture

Custom synthesis	Custom manufacture	Full custom service
ChiroTech	High Force	Laporte Fine Chemicals
Oxford Asymmetry	Chirex	DSM Fine Chemicals
Lancaster Synthesis	Aerojet	Cambrex
Melford Laboratories	Calaire	Lonza
NSC	Eastman	Kaneka Fine Chemicals
CTI (Daicel)	Reilly Chemicals	PPG-SIPSY
Bachem	Omnichem	Phoenix

Bulk drug manufacture

Production of pharmaceutical bulk actives is a specialist activity, which requires rather different resources from those needed for the production of fine chemicals. When supplying Western markets, close attention must be paid to the regulatory and analytical protocols that the customers and the national and supranational regulatory bodies demand. The impact of these regulations upon the level of resources (personnel and manufacturing facilities) is such that this is a niche activity that is largely occupied by a group of companies that do not participate in the main stream fine chemical industry. The two main sectors are the captive manufacturing units of pharmaceutical companies and the independent group of producers, traditionally involved in supplying the generic market. Examples from both sectors are listed in Table 1.6.

Table 1.6: Bulk drug producers – examples of captive plants and independent producers

Captive producers	Independent producers
Abbott Fine Chemicals	PFC (Alfa)
Pharmacia & Upjohn, Portage	Farmhispania
Glaxochem	Orgamol
Novartis Generics (Biochemie)[a]	Macfarlan Smith
Cheminor Drugs [a]	Shasun Chemicals & Pharmaceuticals
Recordati [a]	Ganes/Siegfried
Knoll Pharmachem	Catalytica (Greenville)

[a] Also supply generic pharmaceutical companies.

CHAPTER 2: DEMAND FOR PHARMACEUTICAL FINE CHEMICALS

A BREAKDOWN OF THE MARKET BY PHARMACEUTICAL FINE CHEMICAL REQUIREMENTS

Pharmaceutical fine chemicals (PFCs) are used by pharmaceutical companies to manufacture finished pharmaceutical products and by fine chemical companies for producing bulk actives. Companies involved in supplying animal health products and human food products are also minor customers. Many fine chemical companies buy PFCs in order to add value to intermediates which are then sold for further processing or formulation into finished products. Ultimately PFC demand is created by pharmaceutical companies.

Pharmaceutical companies fall into several categories, all having differing fine chemical requirements. The main types are:

- Innovative pharmaceutical companies.
  - The most important companies (in terms of market share) are integrated producers and marketers of finished proprietary products. Many are multinational groups with commercial and technical operations located around the globe. These companies are mainly based in the US and Europe, although Japan does have some international companies as well. These companies' prime strengths are in inventing, developing and marketing innovative medicines which they are able to sell at significant premiums because of the exclusive marketing rights conferred upon them by patents.
- Medium-sized, domestic pharmaceutical companies.
  - Similar to the major multinationals, but largely limited to smaller markets (single countries or restricted regional areas), this type of company usually license its discoveries to the majors in order to derive the maximum benefit from their period of exclusive marketing. This benefits the multinationals too, since it provides an important supplementary source of new products to their own R&D efforts. Japan, France and Italy are characterised by such companies, reflecting special circumstances in these countries. These companies require a very similar range of services from the PFC industry as the multinationals.
- Smaller, discovery companies.
  - These research-based pharmaceutical groups spring up continuously, as individuals identify opportunities to exploit new areas of medicine. They are able to exploit the relatively easy availability of start-up finance for this type of activity and thus develop new drugs to the point where their efficacy and potential can be properly judged. Usually the company then licenses the successful candidates to a major company, which then provides the marketing 'clout' needed to recover the investment and bring the product to market. In the US and Europe, such companies are now generally called 'biotech' companies, but the phenomenon is not new. Very few of these companies survive as

independent entities, although several US biotech companies have done so. Generally, these small pharmaceutical companies offer interesting prospects for the PFC producer, since they usually lack chemical process skills and commonly obtain active ingredients from third parties. Such contracts can be threatened by subsequent license agreements with larger, integrated companies that generally prefer to maintain control of the manufacture of their own new products.

- Generic producers.
  - Once the period of exclusivity for a pharmaceutical product is finished (this is very often significantly later than its patent expiry), any company is able to register and then market its own version of the branded medicine. In markets where government legislation has lowered the entry barriers to registration (especially in the US), these 'generic versions' can achieve high market shares. Supply of bulk actives to this market sector makes significant extra demands upon the would-be supplier, but the rewards can be great. Such suppliers also create new opportunities for suppliers of intermediates, although such supply will often be only won at the expense of supply contracts to the originators. The volume of the active ingredient consumed is usually sustained, but the value of sales can often decrease drastically, particularly when Chinese and Indian companies become involved. A redistribution of the market shares of the intermediate suppliers is often inevitable, particularly where the drug has been highly successful.

    Where the global sales of a product are relatively small or where legislation is unfavourable for the development of generic markets, off-patent (more precisely, non-exclusive) products continue to be marketed solely by originators and their licensees. Supply opportunities by independent companies to these companies can often arise at this stage, since protection of the process technology of a smaller product is less critical. This tendency has increased as the industry has matured and perceived cost pressures have led to plant closures (or divestments) by the major companies.

- Private and government-funded research institutes.
  - The needs of such groups rarely extend beyond the provision of kilo-quantities of active ingredients and advanced intermediates. Much of what was said for small research-based companies applies to this sector.

SUPPLYING PHARMACEUTICAL FINE CHEMICALS TO COMPANIES INVOLVED IN PHARMACEUTICAL INNOVATION

From the perspective of the supplier of pharmaceutical fine chemicals, the key to maintaining a successful business lies in identifying the particular technological niche in which to operate. One of the most rewarding is in the supply of fine chemicals to companies developing new pharmaceutical compounds.

The invention of novel pharmaceuticals which are safe, efficacious and cost-effective, is difficult, slow and expensive. The risks of failure are high, so a developer must be prepared to accept that the majority of the candidate compounds he takes through his research 'pipeline' will fall at one or other hurdle. During the early years of the industry, setting about identifying candidate drugs was mainly a hit-and-miss affair. Leads derived from natural products that were known to have a beneficial therapeutic effect were the most likely sources of inspiration. Indeed, programmes based upon the identification and modification of natural products continue to be a useful source of new activity.

More recently, identifying pharmacological activity based upon an understanding of how organisms work at the molecular level has enabled the industry to discover many new groups of successful drugs. These work by interfering with the activities of enzyme and protein receptors, including the β-blockers (heart drugs), H_2-antagonists (for treatment of gastric ulcers), ACE-inhibitors (control of hypertension), calcium channel blockers (heart drugs) and the newer COX_2-inhibitors (anti-inflammatories).

As the science of genetics has progressed, new therapies based upon disrupting the interaction between the normal operation of an organism's basic blueprint, its genes, and the pathogenic processes have been developed. Although still in its infancy, success has been obtained with this approach, with antiviral compounds for a number of intractable diseases such as AIDS, herpes and influenza being successfully developed. Other techniques such as gene therapy and the use of antisense polynucleotides may soon deliver their first successful products.

One of the most challenging aspects of drug discovery lies in the difficult task of generating sufficient high-quality leads to guarantee a regular succession of new products. Rapid methods for synthesising many close analogues of initial leads (combinatorial chemistry, or combichem), combined with automated screening techniques to check these compound libraries (high throughput screening or HTS) have been widely adopted during the past 5–10 years. The success of these techniques remains controversial, but it appears that they are helping to generate more candidate compounds than was possible before their introduction.

Bringing a promising new pharmaceutical candidate (a new chemical entity, NCE) to market represents a major team effort and the process is beset by difficulties. At the early stage of development, when the new compound is undergoing initial testing, involvement of a fine chemical producer can be beneficial, since it allows the drug developer to concentrate its efforts on orchestrating the clinical development of the NCE. The fine chemical supplier must, however, offer a flexible service if it is to win the ultimate goal of a manufacturing contract for the supply of an intermediate or active ingredient for the manufacture of the final commercial product. The drug development process is represented schematically in Table 2.1.

Table 2.1: Development of a new pharmaceutical compound		
Pre-clinical	Lead discovery ↓ Lab tests to verify in vitro activity ↓	*milligrams – grams*
Phase I	Tests on acute toxicity in model animals (rats, mice, guinea pigs) ↓ Small scale clinical trials to confirm in vivo activity ↓ Start of long term toxicity, oncology and teratogenicity studies ↓	*10-100 grams* *kilogrammes*
Phase II	Trials on healthy volunteers to establish dosage and serum levels ↓	*10s – 100s kilogrammes*
Phase III	Large scale double blind trials to establish efficacy and safety in a large sample patient population ↓ Registration studies, followed by submissions for marketing approval ↓	*1-5 metric tons*
Pre-launch	Pre-launch marketing and production of stock ↓ Launch	

Each phase demands a different response from would-be suppliers, with much of the chemical development often being retained within the pharmaceutical company's own chemical manufacturing and development divisions:

- *Invention:* Opportunities exist to supply analogue libraries for laboratory testing.

- *Pre-clinical:* At this stage fine chemical companies can offer small quantities (1–1000 g) of lead candidates (generally active ingredients, but also complex or advanced intermediates) for further laboratory tests. Development of improved synthetic methods (custom synthesis) is also appropriate at this early stage of development.

- *Phase I/II:* Clinical trials create the need for 'kilo' quantities of material, with a potential demand for larger scale business in the 25–500 kg range. Generally, responsibility for the production of the bulk active is retained by the developer (there are exceptions, where this is not feasible and where specialised fine chemical companies can undertake this manufacture).

- *Phase III:* This is the awkward stage in the development process for the fine chemical supplier. These large scale trials can often take up to four years, and during this time stockpiled material is drawn down from stock, so there is usually not a great deal of business for the suppliers. The chance of failure for the NCE is lower than earlier on, but the consequences are more serious. Recent drives to accelerate the drug development process appear to have created a higher risk of Phase III failure, and many of the major players have been forced to withdraw otherwise promising drugs at Phase III.

- *Pre-launch:* Even before approval is believed to be imminent, launch supplies of bulk active need to be built up and final arrangements for out-sourcing bulk active production or intermediate procurement must be made. Typically sufficient material for 6–12 months in the launch market(s) is built up.

- *Post-launch:* As experience with the production of the bulk drug is developed, process improvements are made and projected demand falls. Obviously the success (or otherwise) of the product also determines the material requirements and many examples exist of both underestimated demand (leading to major difficulties in keeping up with demand) and over-optimistic forecasts (leading to a dip in requirements for year two, as stocks are drawn down). In extreme cases, demand is drastically reduced or ceases altogether, when the clinical performance of the new product is found to be compromised.

- *Pre-patent:* During the period of exclusivity, which lasts for up to 15–20 years, the fine expiry chemical requirements for the product becomes stabilised after the major launches worldwide have been successfully completed. It is rare, although not unheard-of, for new supply arrangements to be made during this time. Exceptions to this rule occur when the costs of the final product limit sales and an improved process is developed, or when new improved processes for intermediates become available.

  As their period of exclusivity draws to a close, minor drugs are increasingly out-sourced (the originator arranges for the active ingredient to be produced by a third party under sub-contract). New opportunities also arise to supply bulk actives to generic pharmaceutical producers when the patents on successful drugs expire. Suppliers of intermediates can also participate by offering advanced intermediates to companies making the active ingredient, since these companies tend not to be back integrated.

- *Post-expiry:* As the market share and prices are eroded by the entry of new producers, the degree of change in the market for the fine chemicals required for making the bulk drug is determined by several factors. The most important are the product's level of sales in important generic markets (US, Germany) and the product defence strategy of the inventing company. If it is able to launch a new improved version in a timely manner, the company may reduce the market for its original product to a sufficient degree that launching a generic copy becomes unattractive (this tactic is termed cannibalisation). There are other, generally less effective, defence strategies, but cannibalisation is the most effective.

This brief outline of the life cycle of a pharmaceutical product provides an essential backdrop to the differing roles that pharmaceutical fine chemical companies are able to play. These differing roles largely determine the varying technical and commercial structures of the numerous companies involved in this industry. More will be said about this in Chapters 3 and 6.

SUPPLYING PHARMACEUTICAL FINE CHEMICALS TO GENERIC PRODUCERS

The generic sector is driven essentially by government legislation. In many healthcare markets, government agencies are directly or indirectly the ultimate customers for a major proportion of finished pharmaceuticals. Control of drug pricing by legislation is a favourite way for governments to be seen to be making an effort to control healthcare spending (in spite of the fact that it represents approximately just 7–15% of total healthcare spending). The high profits achieved within the pharmaceutical industry are tolerated because otherwise (the argument goes) new R&D would not be funded and the continued advance in medical science would be threatened. These profits are secured by granting product patents (generally of twenty years duration) and exclusivity extensions (various mechanisms exist for this type of extension to the basic period of monopoly).

In the US, in particular, the end of exclusivity has become a significant event through the enactment of two important pieces of legislation:

- *Waxman-Hatch:* Once a product reaches the end of its period of exclusivity, US companies can register new formulations of the innovator's product relatively cheaply by demonstrating the 'bio-equivalence' of its new product (this means that the pharmacological performance of the generic version is similar to that of the original drug). The copier can make reference in its application for a marketing licence to the registration data (on toxicology, oncology and efficacy) submitted by the original inventor. This constitutes a major saving for the generic companies and has allowed relatively small companies to compete with the major multinationals in the US market.

- *Roche-Bolar Amendment:* This important piece of supplementary legislation allows generic companies to begin development of a copy product well in advance of patent expiry, ensuring that competitive products reach the market the first day after exclusivity ends.

Although generic markets exist outside the US, nowhere else provides a comparable market size combined with such a favourable legislative environment. Other significant generic markets exist in Canada, Germany, the Netherlands and the UK. In other parts of the developed world, government support is much feebler, and the generic sector is relatively weak, although moves are afoot in Japan and France to change this situation.

The fine chemical needs of the majority of generic companies are relatively straightforward. Lacking any chemical manufacturing capacity themselves, they require their suppliers to manufacture the bulk active ingredients for them. In

developed markets, special attention has to be paid to the control of the manufacturing plant and the requirements of the US Food & Drug Administration (FDA) have become the standard by which bulk active manufacturing operations have been judged. The key requirements are that detailed records are kept of the sourcing, processing, testing and distribution of the products made at the plant. Important procedural recommendations have become mandatory for success in this business. Most important of these is *current Good Manufacturing Practice* (cGMP, often shortened to GMP), which lays down the FDA's view on the (current) minimum standards for running a pharmaceutical chemical process plant. Would-be producers for the US market need to submit a lengthy document (drug master file, DMF), before they are able to register as suppliers of individual products. Only some time after the generic company's documentation is received by the FDA will these submissions be checked. Failure at this late stage is disastrous, so most companies have no option other than to 'play safe' and over-invest in their FDA compliance. The UK's Medicine Control Agency (MCA) and the European Union's new pharmaceutical registration agency have different, and in some ways more demanding, registration formalities.

It is noteworthy that supply of bulk drugs to the US market has been dominated traditionally by the Italian PFC industry. Although this pre-eminence has largely waned, following changes in Italy's once favourable patent legislation/enforcement, Italian companies still maintain a disproportionate market share in this sector.

SUPPLYING PHARMACEUTICAL FINE CHEMICALS TO MARKETS WHERE PRODUCT PATENTS ARE NOT ENFORCED

During the late 1970s and 1980s, when the US generic market was established, many countries in the developing world had little product patent legislation or poor enforcement of the laws they had enacted. A flourishing 'B'-market (as opposed to the 'A'-market in developed countries) existed in these markets. Important examples included China, India, Spain, South America, Mexico and Canada. In Table 2.2, a list of dates when product patent legislation was adopted in relevant markets is presented.

Table 2.2: Dates of product patent enactment in selected markets

Country	Date introduced
China	1993
Czech Republic	1991
India	1995
Italy	1978
Japan	1976
Korea	1987
Poland	1992
Spain	1992

Although the value of the pharmaceutical markets were relatively low in finished product value terms, they were attractive in terms of the volume/value of PFCs required. A slightly less laudable fact was that quality standards were also generally (but not always) laxer. Many fine chemical companies have been able to develop expertise in the manufacture of newer pharmaceutical actives by selling into these markets prior to the expiry of major developed markets exclusivities. In this way, they have been able to fund development costs well ahead of patent expiry. An important feature of the processes used in this sector is that they are generally copied from the originators' original registration filings. They are therefore generally not particularly efficient and often breach process patents that remain valid after product patents expire. Originality in process chemistry has not been a hallmark of this sector for this reason.

In the larger markets where product patents were not enforced, indigenous PFC industries have been able to develop by virtue of their ability to make and sell new products shortly after their introduction in the West. In certain markets, fully integrated pharmaceutical companies have developed in this way, particularly in China and India. Elsewhere, imports of bulk drugs have supported the local formulation-based companies. Through lack of raw materials and other technical constraints, some producers in these markets have developed original process technologies. In India, in particular, alternative routes have often been invented. However, the advantages this could have bestowed have been limited by two negative factors. Using available raw materials has not always guaranteed the lowest costs (especially as India has enjoyed a buffer of high import taxes). Most damagingly, however, Indian companies find it impossible to protect their trade secrets, because of the common transfer of technologies by unscrupulous individuals (this is a problem everywhere, but in India it is endemic).

Over the past thirty years, the 'B'-market has been supplied by PFC companies operating in Italy, Spain, Ireland, India and China. As international agreements on product patents have been enacted, such commerce has either been transferred abroad or 'gone underground'.

During the 1990s, even China and India have finally been obliged to adopt such legislation, following threats of trade sanctions from the major trading nations if they did not. It is difficult to moralise on this thorny issue, without risking bias, but the greed of a few (on both sides) has inevitably led to an uneasy compromise that is by turns fair and unfair, depending upon one's perspective.

In spite of the increasing constraints on this sector, it is one that can be rewarding if the PFC producer is able to develop original, cost-effective process technology and thus enjoy higher margins than the majority of the players in what is a largely non-innovative sector of the industry.

SUPPLYING PFCS TO BULK PHARMACEUTICAL PRODUCERS

As has been stated above, manufacture of bulk actives has become a specialised activity in response to the demands made by customers and legislative authorities. Most bulk producers prefer to source key intermediates from third parties, rather than

build up their own capital-intensive production operations. In this, they have generally copied the bulk manufacturing divisions of the major pharmaceutical companies, albeit with a much greater tendency to outsource intermediates. Many have also, wherever possible, chosen to avoid chemical processing altogether, preferring to purify (or produce the salt of) cheaply sourced bulk active ingredient.

Suppliers of intermediates have often had to make difficult choices about supplying these independent producers. Since many intermediates are unique (or nearly so) to a specific product, intermediate producers have to weigh up the merits of eventual supply to the generic sector or risk losing existing contracts to the originator that may become much smaller post-patent. Attempts to do both tend to lead to discovery, although there are exceptions; for instance, Japan's complicated industry structure has allowed it to supply both markets without apparent detection.

A second important problem with the major producers in this sector has also been their inability to control prices as competition increases. They often try to pass on drops in their prices to their suppliers in order to maintain margins. Given the fact that most companies generate excellent margins, despite a generally modest technology-base, these demands are often unreasonable. The intermediates business then often goes to Eastern suppliers, which are able to drop their prices to a greater extent than Western firms (often through the economic advantages flowing from their participation in the supply of the corresponding finished pharmaceutical to their local markets).

CHAPTER 3: SUPPLY OF PHARMACEUTICAL FINE CHEMICALS

MATERIALS DERIVED FROM PLANTS, ANIMALS, FERMENTATION PRODUCTS AND PETROCHEMICALS

Medicinal chemicals were originally wholly obtained from natural sources, but as the importance of the application of chemistry in drug discovery increased, this pre-eminence waned. Today, natural products are still important (particularly if fermentation products are included within this category), but usually as raw materials for semi-synthetic compounds. The most significant of these active ingredients and raw materials are listed in Table 3.1.

Table 3.1: Leading natural products used in producing pharmaceutical actives

Raw materials	Source(s)	Major products
Opium alkaloids: morphine, thebaine	Opium poppies	Codeine, morphine, buprenorphine
Digitalis alkaloids	Foxgloves	Digoxin
Other alkaloids	Pilocarpus sp, Belladonna, etc	Pilocarpine, atropine
Penicillins	Penicillium sp.	Ampicillin, amoxicillin, cefalexin
Cephalosporins	Cephalosporangium sp.	Cefazolin, cefotaxim, cefaclor
Other antibiotics	Range of soil micro-organisms	Erythromycin, vancomycin, etc.
Baccatin anticancer drugs	Pacific yew	Taxotere
Amino acids	Animal products, bacteria	Cysteine, glycine, phenylalanine
Blood products	Animals, humans	Vaccines and sera
Steroids	Soya beans, Mexican yams	Corticosteroids, sex hormones

The majority of modern medicinal chemicals are now synthesised from simple organic chemicals produced from petrochemicals. A few illustrative examples are presented in Table 3.2.

Table 3.2: Producing pharmaceutical actives from petrochemicals

Raw materials	Intermediates	Major products
Hydrogen sulphide	Cysteamine hydrochloride	Ranitidine, cimetidine, nizatidine
Benzene	Phenol	Aspirin, paracetamol (acetaminophen)
Propylene	Epichlorohydrin	Atenolol, metoprolol, timolol
Aniline	Aminosulphanilyl chloride	Sulphamethoxazole, sulfadiazine
Propionic acid	α-chloropropionic acid	Ibuprofen, naproxen
Diphenylamine	Substituted phenothiazines	Chlorpromazine, perphenazine
p-cresol	p-trifluormethylphenol	Fluoxetine hydrochloride
Collidine	4-methoxy-2-hydroxymethyl-3,5-lutidine	Omeprazole
Benzaldehyde	2-R-hydroxyphenylbutanoate	Enalapril, lisinopril, etc.

Biotechnology has recently increased greatly in importance as a source of medicinal chemicals, with many naturally occurring products now being produced by genetically engineered micro-organisms. Examples of active ingredients made in this way include human insulin, erythropoeitin and the interferons. Synthetic chemists also use extracts of such micro-organisms to catalyse chemical reactions so as to create homochiral intermediates (possessing specific stereochemistry), which often offer improved medical benefits. In Table 3.3 a listing of the most important pharmaceutical fine chemicals made by fermentation is presented. Fermentation is a well-established method, whereby a carbohydrate is 'fed' to a broth containing specially prepared, rapidly growing micro-organisms (usually a bacteria or fungus) and a useful fine chemical extracted from the broth at the end of one to five days. During the processing, many separate reactions (both degradative and synthetic) occur, prior to the final reaction that leads to a commercially viable accumulation of product.

Table 3.3: Producing pharmaceutical fine chemicals from micro-organisms by fermentation

Chemical	Volume (metric tons)	Price (US$/kg)	Sales value (US$m)
L-Lysine	400,000	4.9	1,960
Penicillin GK and VK	40,000	40.0	1,600
Monosodium glutamate	350,000	4.1	1,435
L-Phenylalanine	15,000	20.0	300
Erythromycin	3,200	0.0	250
L-Tryptophan	650	84.0	85
Streptomycin	2,000	0.0	80
L-Lactic acid	40,000	1.7	70
Oxytetracyclin	2,500	0.0	25

Source: Brychecm

Fermentation is distinct from a newer and more general biotechnological process, called a biotransformation, in which a preparation containing fully-grown cells or an enzymic cell extract is used to catalyse a single chemical transformation. In Table 3.4 a selection of the most important biotransformations is shown to illustrate this type of biocatalytic processing.

Table 3.4: Producing PFC from micro-organisms by a biotransformation process

Chemical	Raw material/enzyme	Volume (metric tons)	Sales value (US$m)
Fructose (Isoglucose)	Glucose/isomerase	8,000,000	1,000
Fatty acids and trigylceride oils	Natural fats and oils	0	1,000
L-Malic acid	fumaric acid/fumarase	>25,000	>25
L-Aspartic acid	Fumaric acid/aspartase	40,000	0
L-Carnitine	/hydrolase	150	20
Phenylacetylcarbinol	/pyruvate decarboxylase	300–500	0
6-APA	Penicillin G & V/amidohydrolase	11,000	490
7-ADCA	Penicillin G S-oxide	2,000	150
Aspartame (Holland Sweetener)[a]	D,L-Phenylalanine, L-aspartic acid/ thermolysin	1,200	60
β-Cyclodextrin	/glucanotransferase	800–1,500	0
L-Dopa	/tyrosine phenol lyase	50	0
(S)-2-Propionic acid	(R,S)-Propionic acid/dehalogenase	1,600	0

[a] The world's major producer, Monsanto, uses chemical coupling of L-Phe and L-Asp.

Source: Brychecm

The more recent impact of genomics (the science of manipulating genes outside of the cell) has been to revolutionise the ability of biotechnologists to tailor-made micro-organisms that can fulfil specific functions. Of particular importance is the technique for the insertion of genes that carry out useful transformations from a difficult-to-grow micro-organism (such as a fungus or alga) or cell (from a higher organism such as a mammal) into an easy-to-grow micro-organism, such as E Coli. An example of some economic importance is the manufacture of L-phenylalanine (raw material for aspartame, the world's most valuable high performance sweetener) using a recombinant E Coli (a fermentation, see Table 3.1).

FINE CHEMICAL INTERMEDIATES

As has been touched upon in the preceding section, access to fine chemical intermediates has become vital for the production of a vast majority of the active ingredients currently being manufactured. An exact definition of an intermediate is impossible, but a useful working definition is the following: a chemical compound that is produced and sold on the basis of its composition alone, for which a relatively limited number of outlets exist. A pharmaceutical fine chemical (PFC) is one produced to the exacting specifications required for further processing into a pharmaceutical active ingredient. Sometimes, intermediates have useful physiological activity and so can be considered active ingredients as well. Generally PFC intermediates are made by chemical and fine chemical companies, only rarely being produced by backward-integrated pharmaceutical companies. The number of chemical components and operations needed to build up a complex pharmaceutical active can often be very substantial. Synthesis routes generally fall into one of three main categories:

- Semi-synthetic processes:

  In a semi-synthetic process, the functionality of a complex starting material, obtained from a natural source or by fermentation, is modified by a limited number of chemical steps. The objective is to alter the activity or pharmacodynamics of the natural compound, so that its medical value is enhanced. Sometimes the resulting active ingredient is still a natural product, but the semi-synthetic route is more economical. There are many such examples, including codeine (produced by the methylation of morphine), the penicillins (in which the natural 6-amide side-chain and/or the 3-carboxylic ester is modified to produce a wide range of semi-synthetic penicillins) and the cephalosporins (in which the side-chains are similarly modified).

  Intermediates for semi-synthetic compounds are often simple molecules, but they may be sometimes quite challenging. Their production lies firmly within the province of the fine chemical intermediates industry, although there are exceptions; SmithKline Beecham, one of the world's leading multinational drug discovery companies, continues to be a major producer of D-(-)-4-hydroxyphenylglycine for amoxicillin, for instance.

- Linear processes:

  This type of process is one in which a final product is made by adding small components to a basic starting material in a linear fashion. Thus paracetamol (acetaminophen) is produced from nitrobenzene by reduction to p-aminophenol, followed by acetylation to p-acetylaminophenol. Many simple active ingredients are produced by such routes, but as the number of stages increase, the efficiency of a linear synthesis decreases. Sometimes long linear syntheses appear to be unavoidable (often the case in steroid synthesis), but chemists generally manage to find a better, convergent route. A good example of this is the synthesis of prostaglandins, where the original linear routes of Corey have mainly been overtaken by convergent syntheses developed by Noyori and others.

- Convergent routes:

  When a relatively complex compound is to be assembled from scratch, a convergent route is much preferred. A good example of this approach is the

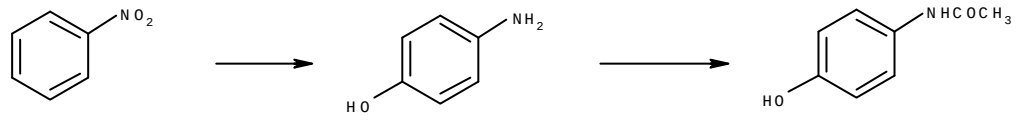
production of the H_2-antagonists such as cimetidine and ranitidine. Three fragments are assembled in the penultimate step, making the actual processing by the bulk active producer relatively straightforward. There are additional practical advantages to such processes:

– Special technologies can be practiced on a site well away from the plant where the final product is made. Thus one component of the two H_2-antagonists mentioned above is cysteamine hydrochloride. Production of this intermediate involves handling sodium sulphide and (in some cases) ethylene imine, both highly toxic substances.

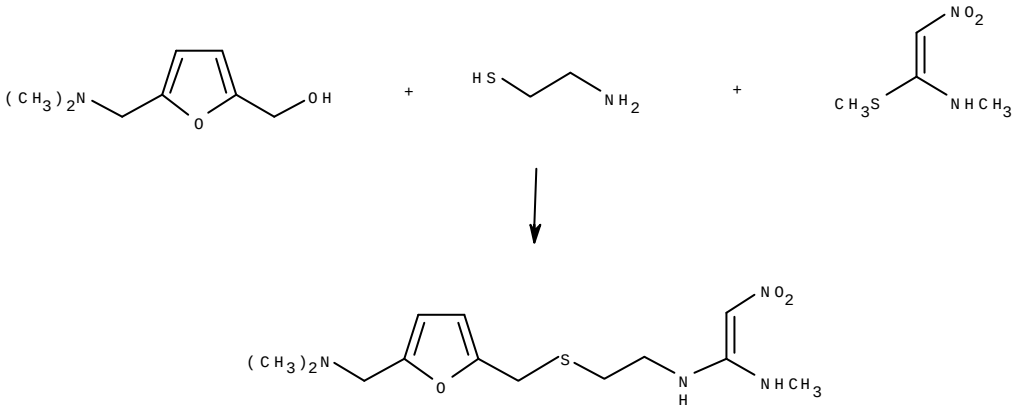
– The production of the key intermediates can be undertaken by the most efficient producers, since fewer compromises on qualifications need to be made. Again, in the case of ranitidine, the companies that make cysteamine are not necessarily qualified to produce the nitroguanidine intermediate, which involves handling nitromethane and carbon disulphide.

In order to illustrate these concepts, two of the syntheses mentioned above are presented in Figure 3.1.

Figure 3.1: Different types of fine chemical processes



Linear synthesis of paracetamol



Convergent synthesis of ranitidine

Source: Brychem

Although it would be impossible to describe the source of all the basic intermediates required to produce the vast number of pharmaceutical actives available today, a partial list is presented in Table 3.5. Several important facts emerge from a consideration of the chemical industry and its relationships with the industries it serves:

- Although the products of the chemical industry are vital for the production of pharmaceuticals, this revenue from the products of the pharmaceutical industry to the chemical industry is trivial, in comparison with that from other end-uses. The major part of the petrochemical industry's output goes into materials (particularly plastics), solvents and fuels.

- The major part of the value added between petrochemical feedstocks and a finished pharmaceutical occurs within the pharmaceutical industry, so the apparent attractiveness of the pharmaceutical fine chemical industry to the wider chemical industry stems from a fundamental misconception. This topic will be discussed later in greater depth.

Table 3.5: Chemical industry output and applications

Chemical industry's 'big seven' feedstocks	Main applications
Methane	Carbon monoxide, hydrogen cyanide, methanol, chloromethanes, acetylene, formaldehyde, acetic acid
Ethylene	Polyethylene, ethylbenzene (→ styrene), vinyl chloride, ethylene oxide, ethylene glycol, vinyl acetate, ethanol
Propylene	Polypropylene, epichlorohydrin
Butane/Butadiene	Styrene-butadiene, ABS, neoprene, adipic acid, HMDA, MTBE, maleic anhydride
Benzene	Cumene (→ phenol/acetone), cyclohexane, nitrobenzene, aniline
Toluene	Toluene diisocyanate (TDI), phenol, benzene, caprolactam, p-xylene
Xylenes	p-xylene, phthalic, isophthalic and terephthalic anyhydrides

It would not be helpful to list the intermediates that are used in the pharmaceutical fine chemical industry, since they are so numerous that this entire report would be too small to list even a fraction of them. As the complexity of a chemical intermediate increases, the number of applications decrease, with the majority of fine chemical intermediates being used for a single application. Basic intermediates such as p-nitrotoluene or benzyl chloride are employed in the production of many 'downstream' fine chemicals. These are generally called chemical intermediates rather than fine chemicals. Some of the more important basic intermediates are listed in Table 3.6.

Table 3.6: Chemical intermediate applications

Chemical intermediate	Important fine chemical applications
Carbon monoxide	Phosgene (→chloroformates, acid chlorides, isocyanates), ketones
Diketene	Acetoacetates
Ethanol	Ethyl esters, solvent
Epichlorohydrin	1-amino-2-hydroxypropane derivatives
Formaldehyde	Aldehydes, methylene-bridged compounds
Hydrogen cyanide	Nitriles, aryl acetates, amides, heterocycles
Methanol	Methyl esters, solvent
Toluene	p-nitrotoluene, chlorotoluenes

There are also some 'multi-outlet' fine chemical products that find broader application. A few examples are listed in Table 3.7.

Table 3.7: Multi-outlet fine chemical applications

Fine chemical	Main applications	Examples
6-APA	Semi-synthetic penicillins synthetic cephalosporins	Ampicillin, amoxicillin, cefalexin
7-ADCA	Semi-synthetic cephalosporins	Cefazolin, ceftazidime
α-chloropropionic acid	NSAIDs	Naproxen, ibuprofen
Corey lactone	Prostaglandins	$PGF_2\alpha$, alprostadil
Cysteamine HCl	H_2-antagonists	Cimetidine, ranitidine, nizatidine
16-DPA	Corticosteroids	Cortisone, hydrocortisone, triamcinolone, betamethasone
Epichlorohydrin	β-blockers	Atenolol, metoprolol, propanolol
p-chloroaniline	Benzodiazepines	Chlordiazepoxide, diazepam, lorazepam, nitrazepam
Ethyl 4-(R)-hydroxy-butanoate	ACE-inhibitors	Enalapril, lisinopril
Methyl acetoacetate	Calcium channel blockers	Nifedipine, amlodipine
Thebaine	Semi-synthetic opioids	Buprenorphine, etorphine, diprenorphine, oxycodone

PHARMACEUTICAL ACTIVE INGREDIENTS

The majority of proprietary pharmaceutical active ingredients are produced by the companies that have invented and developed the products for the market. Although sub-optimal in strict economic terms, the benefits of retaining total control over the supply of a proprietary product are regarded as of greater importance than reducing manufacturing costs by having the bulk drug produced by a specialist. For this reason, the market for proprietary bulk pharmaceuticals is practically non-existent, since outsourced material would generally be obtained via a confidential manufacturing contract.

Once the patent protection on a product has expired, other independent producers are able to participate in the production of the actives. The majority of these bulk pharmaceutical companies, be they multinational innovators or small independents, generally prefer to minimise the number of process stages in their production routes. Most processes consist of two to three steps in which up to three major components are assembled, usually using relatively benign reaction conditions (there are of course exceptions to this general rule). The key skills required for a successful operation are:

- Access to at least two suppliers of these key intermediates.

- Well-organised production facilities which are operated according to the basic principles of good manufacturing practice.

- Trained personnel who understand the importance of the concepts of quality assurance: that materials are not only produced to a high, constant specification, but also can be proved to have been so produced, by keeping the appropriate process records.

The additional costs (in capital and extra personnel) of running this type of operation are borne by the customers because the governments in the developed markets insist on this degree of compliance. It is clear that bearing such overheads in the manufacture of simple intermediates would be unreasonable and lead to uncompetitive costs when compared with those of a normal fine chemical intermediates plant.

Until recently there has been, however, one major exception to this rule: antibiotics. Many major innovative pharmaceutical companies have maintained their own production of penicillins, cephalosporins and other antibiotics. The capital investments in fermentation plants are much greater than for an equivalent fine chemical plant and the necessary investment in a small-scale production unit has been difficult to justify. Over the last ten years, with the increasing maturity of the antibiotics industry, consolidation of the wide range of products has allowed a number of major products to develop sufficient demand for this high-cost entry factor to decrease in importance. Most major pharmaceutical companies now source their fermentation-based antibiotic intermediates from a handful of independent producers, such as Gist Brocades (the Netherlands), and Antibioticos (Spain). Newer producers in Asia are rapidly eroding markets shares of these companies and this will create further disruption or consolidation in the near future.

The total number of pharmaceutical active ingredients in use around the world probably exceeds 3,000 (with many tens of thousands of formulations containing combinations of these ingredients). Of these, perhaps around 500–600 are of significant commercial value (that is, with sales exceeding US$1m at the level of the finished dosage form). The number of fine chemical intermediates used to produce these important final products runs into many thousands. From the perspective of the pharmaceutical fine chemical industry, classification of these active ingredients by their therapeutic activity (a useful system for pharmacologists) is not very useful, since this approach mixes a wide array of different compounds. Classifying them by their chemistry would be a lot more useful. Examples from a list of the top twenty pharmaceuticals (by both sales and volume), classified in this way is shown in Table 3.8

Table 3.8: Leading pharmaceutical chemistries

Chemistry	Major technologies involved	Active ingredients
Peptide	Chiral synthesis, amidations, use of protecting groups	Enalapril, lisinopril
Steroid	Functional group changes, selective oxidations	Ethinylestradiol, estrogens
Pyridine	Aromatic substitution	Omeprazole, lansoprazole
Fluorinated	Halogen exchange	Fluoxetine
Fermentation[a]	Penicillium, pseudomonas	Clavulanic acid, amoxicillin
Tetrahydropyridine	Acetoacetate/aryl aldehyde condensations	Nifedipine, amlodipine
Piperidine	Acetoacetate/aryl aldehyde condensations	Paroxetine
Indole	Indole ring synthesis	Atorvastatin, sumatriptan
Aromatic	Aromatic substitution, functional group changes	Acetaminophen (paracetamol), loratidine, aspirin
Chiral chemistry	Introduction of chirality	Diltiazem, sertraline, paroxetine
Mammalian cell[a]	Fermentation using GMOs	Erythropoetin

[a] Not strictly chemistries, but it is important to include these to maintain a balanced view.

Further useful listings of pharmaceutical active ingredients are presented in the appendix.

OPERATIONAL ASPECTS: QUALITY ASSURANCE AND REGULATORY COMPLIANCE

Mention of the importance of quality assurance and regulatory compliance in the pharmaceutical fine chemical industry has already been made in the previous section. These additional demands on a fine chemical company that wishes to supply advanced pharmaceutical intermediates or active ingredients are generally lumped under the heading of GMP, or more correctly cGMP. This set of guidelines for setting up and running a PFC production unit are laid down by the US FDA, and cGMP has become a *de facto* global standard. Without going into a great deal of detail, only the basic principles can be described within the remit of this report. These basic guidelines for the submission of a drug master file (DMF) for authorisation to produce PFCs for production in or import into the US include:

- A careful definition of the location and facilities to be used for the PFC manufacture, giving the names and responsibilities of the most important personnel and the basic layout of the unit.

- Segregation of materials and well-designed, clean warehouses must be available. Final products must be isolated in specially prepared clean rooms, where air quality and cleanliness are high priority concerns.

- Training procedures for personnel, careful control against cross-contamination (using validated cleaning procedures) and close attention to warehousing, weighing and packing the raw materials, intermediates and final products must be documented and controlled.

The information for this submission is not product-specific and used to be called a Type I DMF. From 12th July 2000, such submissions will no longer be required and old ones will not need updating. Product-specific submissions are made for each PFC and are called Type II DMFs.

- Production processes must be developed to a sufficiently high level of reproducibility that they can be described in reasonable detail in the manufacturing submission to the US FDA. Major deviations from this formula must be advised in writing to the FDA. The intention is that such a process will be incapable of producing seriously contaminated material.

- Off-specification material must be recycled into the previous stage using a validated process, so that all materials have a uniform quality. Strict records of all process deviations must be kept for inspection.

- Analytical methods for the control of the quality of raw materials, intermediates and final products must be described in detail and quality assurance (QA) procedures designed so that a uniform final product quality is maintained within closely defined limits.

- Stability tests on stored materials at normal working temperatures in the intended packaging (and at higher temperatures to mimic longer-term stability). This helps to ensure that the products will maintain the standard quality over a claimed shelf life (can be as little as one year or as much as five years, depending on the fine chemical).

CHAPTER 4: PHARMACEUTICAL FINE CHEMICALS – THE BUSINESS ASPECTS

VALUE-ADDED CHAIN FOR PHARMACEUTICAL PRODUCTS: VALUE AND PROFITABILITY OF BUSINESS

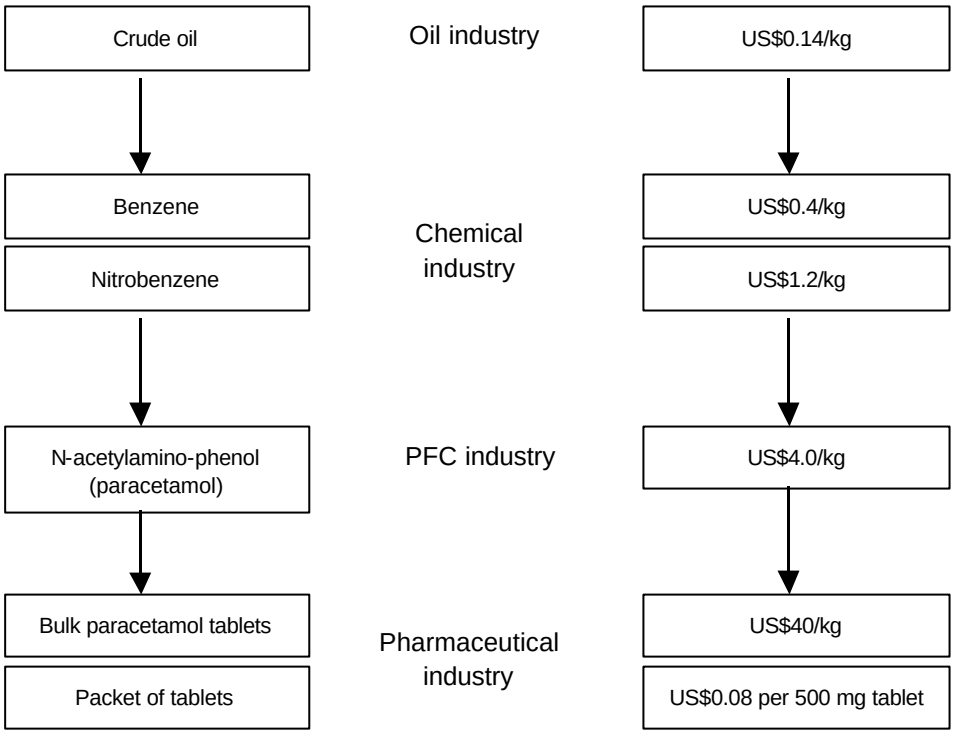
It is very commonly stated and believed by outside commentators that the pharmaceutical industry is a sub-sector of the chemical industry. Nothing could be further from the truth, and many investors will vouch for the fact that the valuations of pharmaceutical companies, based upon historical 'earnings multiples' and the prospects for future profit growth, bear no comparison with those of chemical companies. It is verging on the incomprehensible why anyone who has studied the industry should confuse the two industries. They are as different as apples and pears, two fruits commonly confused by engineers, if only in jest!

The pharmaceutical industry has more similarities to the hi-tech end of the electronics consumer goods industry than chemicals, with sales, marketing power and distribution being important in maximising the revenue from the company's range of finished products. Developing innovative products that can be marketed as an exclusive brand is the other key activity for successful growth in both sectors. The suppliers to both industry sectors are a combination of captive and outsourced production, with the bulk of the design work remaining within the realm of the inventor, but an increasing proportion of manufacture being undertaken in Asia. The comparisons should not be pushed too far, but they may help the reader gain a better understanding of the role of the pharmaceutical fine chemical industry as a supplier to its customer, the pharmaceutical industry.

If the structure and resources of the pharmaceutical fine chemical industry has little to do with its customers, then this is equally true of its relationship with the chemical industry. Commodity chemicals and basic organic intermediates are made and sold by capital intensive companies that must ensure that they are competitive in terms of scale and technology (generally there are only a small number of cost-effective choices for the latter). Core technical skills are the design and construction of production plants, which demands the participation of engineers of various disciplines, but very few chemists.

Reference to Figure 4.1 will help to illustrate these relationships in a graphical fashion. It shows the value-addition chain and the industry sectors involved, in producing a packet of paracetamol (acetaminophen) tablets. The majority of the valued addition occurs at the level of the pharmaceutical industry, with the added value involved in converting nitrobenzene to paracetamol being lower, although not as low as at the chemical industry level. Note that the price of paracetamol is rather low compared with the majority of bulk pharmaceuticals, very few of which are priced below US$10/kg. This is because it is relatively simple to make and it is a large-scale commodity (with its patents having expired many years ago).

Figure 4.1: Value-addition and industry sectors in making a paracetamol (acetaminophen) tablet



Source: Brychem

The chemical extraction industry is, in general, very profitable, when compared to the chemical industry; the extraction of oil is no exception. The value addition in the commodity chemical industry is greatly inferior to that obtained by pumping oil out of the ground. An important reason why forays into chemicals, and especially fine chemicals, by the oil industry have been generally disappointing is that the economics and manner of running these businesses is too different for most managements to combine effectively. Efforts by bromine producers to develop profitable business downstream of bromine have been similarly hampered by this profit differential.

More could be said about the pricing structure within the pharmaceutical industry and the fine chemical industry. The most important factors that bear upon the price of a fine chemical are its cost of production and its scarcity. Demand for new pharmaceutical fine chemicals is created by pharmaceutical companies, which therefore maintain ultimate control over the market. Cost is determined by a combination of the costs of the raw materials and reagents used and the additional processing needed to make the final product. Choosing a good chemical route reduces all these costs and an innovative route can offer costs that allow a higher margin than is achieved by competitors. Developing a cost-effective process and operating it efficiently is the major factor within the control of the fine chemical producer.

In order to review these two competing factors in greater detail, it is best to consider their impact at various times within a pharmaceutical product's life cycle.

Development phase

When initially developing a new drug candidate, there will often be neither a source of supply of the active ingredient nor of its advanced intermediates. At this stage, opportunities arise to supply these scarce materials at high prices, but in relatively low volumes. By offering a quick and effective service, companies can hope to develop a relationship with the developer that can assure higher sales as demand for the new product increases. An early initial exposure to the new intermediates also provides the company with time to improve and refine its technology, thus helping to prepare the way for scaling up the process, if and when the product is launched.

Prices at this stage can typically vary between US$5,000–20,000/kg. Orders rarely exceed five kilogram at these prices, however. Pharmaceutical companies can also obtain these initial small-scale quantities of material by hiring the services of a chemist, plus support staff/facilities at a monthly rate. Prices in Europe and the US range between US$12,000–25,000/month, depending upon the size and reputation of the custom synthesis company.

Small/medium-sized custom synthesis companies concentrate their efforts at this market sector, although many larger companies are beginning to focus on providing a service at this stage, so as to secure higher volume orders later on. Their approach has to be different to the smaller companies, since their cost base is too high for a reasonable return for the production of such small amounts. They generally negotiate terms, perhaps informally as a 'gentleman's agreement', which means they have a good chance to secure the large-scale business if the drug comes to market.

Clinical trial phase

Once significant quantities of active ingredient are needed to carry out tests in the clinic (typically volumes required are around 25–250 kg of active ingredient), the requirements of the customer are different. If the outsourced fine chemical is an advanced intermediate or bulk active, strict cGMP must be operated in producing the products. This can be ensured by working in a 'kilo lab' or small pilot plant, especially adapted for the production of pharmaceutical fine chemicals. If cGMP is required, higher prices will be paid, in order to cover the extra labour costs and capital recovery. Although volumes are higher, prices can be still quite high, although there are usually at least two suppliers (plus the customer's in-house facilities) involved at this stage. Price competition begins to become an issue, particularly if the initial tests are encouraging.

If a large-scale fine chemical producer has supplied material up to this phase, its overall profit is unlikely to be very worthwhile and it may have lost money. The real reward comes as the stocks for the launch are built up, the pre-launch phase. Opportunities for small companies to secure this type of business often require too high an investment (with no guarantee of success) for them to risk going ahead, so larger companies can generally pick up such contracts at this more advanced stage.

Pre-launch phase

The capital investment by the fine chemical supplier has been relatively modest up to this point, but as the new drug reaches the pre-launch phase, investments in plant modifications must be made in order to secure a commercial contract. Price negotiations now involve orders in the two to five metric ton per year range, so the

price/kg has decreased substantially. The customer will generally be trying to get the lowest price from its suppliers, so there is pressure on them to offer reduced prices and take smaller margins.

The more astute pharmaceutical company outsourcing agents will have a reasonable idea of the costs of his suppliers, so he will feel comfortable about setting prices at a level based upon his assessment of the suppliers' costs. Fine chemical producer margins can be better than the customer expects if the supplier has developed better than anticipated chemistry. Scope for this is clearly much greater for non-cGMP intermediates, where only general route information need be declared.

Post-launch phase

Once full-scale manufacture gets underway and, assuming the product is selling well, the suppliers can begin to generate good profits from the business, after around four to six years of anticipation. Many fine chemical companies have established themselves as the result of being a prime supplier to a blockbuster drug. Two examples include Fine Organics (selling intermediates for cimetidine and ranitidine) and Kaneka Fine Chemicals (selling the side-chain for amoxicillin and captopril). Margins of 60–100% ought to be achievable at this stage, although this depends upon the technology involved. Successful pharmaceuticals attract fine chemical companies like bees around the honey-pot. This allows the customer to put pressure on its current suppliers to reduce prices as contracts come up for renewal (annual or biennial contracts are usual). Where the technology is challenging, or the raw materials or reagents used are hazardous or polluting, this competitive pressure can be less and profits better.

A good example of how a fine chemical intermediate can generate good profits is when clever technology (and perceptive marketing) is used. In the production of the fluoroquinolone anti-infective drug, ciprofloxacin, cyclopropylamine is used as an intermediate. When the drug was introduced, methods for the production of this deceptively simple intermediate involved converting γ-butyrolactone to its 2-chloro derivative, cyclising this under basic conditions and then converting the cyclopropylcarboxylic ester to the final intermediate by the Hofmann degradation. Costs were based upon this multistage route and so, therefore, were prices (which were, for many years, in the US$50–60/kg range). Chemists at BASF developed an elegant gas phase process using isopropenyl acetate and ammonia, where the fully recovered costs could not have been greater than US$5/kg. What was even cleverer, was the fact that the company kept this technology coup a well-guarded secret, thus securing many years of profitable business by virtue of its ingenuity.

Pre-patent expiry

As the sales of the pharmaceutical product flatten out and growth all but disappears, cost pressures on suppliers reappear. The probable launch of new versions of the drug by unlicensed pharmaceutical companies (often, but not always, these are generic versions) stimulates the development of new processes and market entry by new fine chemical producers.

The general result of patent expiry is that prices of the finished product will again begin to fall, sometimes quite drastically, if the product has been a major success. This is well illustrated by the price history of captopril, presented in Table 4.1. Major

product patents for captopril expired during the period 1995–97. Before this time, the free market for captopril was less than 10 metric tons, whereas afterwards it jumped to around 100–150 metric tons, so the economies of scale will have reduced the profit slide, which was rather less.

Table 4.1: Price history of Captopril (1990–2000)

Year	1990	1992	1994	1996	1998	2000
Price (US$/kg)	1,250	850	650	450	220	85

Clearly, prices of the intermediates do not decline to the same extent, although the more advanced ones do also suffer considerable price erosion.

'Sunset' phase

Good drugs are often like old soldiers: they don't die, they just fade away. As the product sales decrease, the number of suppliers also decreases and prices can begin to make some small gains. Indeed, in certain cases where the drug cannot be readily replaced, the prices can jump up as the scarcity value again becomes a factor. The natural product sector is particularly prone to this type of reversal. An example of this is illustrated by the way in which pilocarpine prices rose sharply in the late 1980s, as the supply of the active ingredient was finally reduced to just one company, which had secured the only regions in Brazil, from where the raw material could be obtained.

In certain cases, pharmaceuticals become so well-established and the volumes consumed so large that they attain commodity status. It is at this stage that a chemical company has a real chance of becoming involved, since the opportunity presents itself for a large scale, dedicated plant to be built. The parameters for processing and the scale of operation are well-defined and this fits nicely with the chemical company way of doing business. Examples of such drugs include: aspirin, paracetamol (acetaminophen), ibuprofen and amoxicillin. The low margins for the production of these products are compensated by the high volumes, predictable prices and low sales overheads.

ACTIVE INGREDIENTS, INTERMEDIATES AND RAW MATERIALS: VALUE AND VOLUMES

Information on the market value and volumes of pharmaceutical fine chemicals is generally a closely guarded commercial secret. Competitive advantage is protected by such lack of openness and, as has been already stated, much of this business is conducted under confidential contracts. There are companies that provide information on the volumes of active ingredient being consumed (derived from audits of finished dosage sales), but this data is not entirely reliable and is expensive to buy, so it is not readily available.

In spite of this, those within the industry can generally derive a working understanding of this type of statistic by comparing consumption and production data

on intermediates, raw materials and bulk actives. Such a 'bottom-up/top-down' analysis allows more reliable information to be derived.

Information derived in this way on a representative group of bulk pharmaceuticals is presented in Table 4.2.

Table 4.2: Estimated value and consumption of a selection of bulk pharmaceuticals (1998)

Bulk pharmaceutical	Consumption (metric tons)	Value at bulk level (US$m)
Acyclovir	450	140
Amoxicillin	9,000	450
Ampicillin	2,000	90
Captopril	280	35
Cimetidine	1,300	33
Ciprofloxacin	600	50
Diclofenac	750	18
Diltiazem	850	160
Enalapril	90	45
Etodolac	160	55
Famotidine	60	15
Fluconazole	15	8
Fluoxetine	20	15
Glibenclamide	25	5
Guaifenisin	2,000	16
Ibuprofen	12,000	145
Lisinopril	55	45
Metformin	1,100	10
Nabumetone	550	60
Naproxen	1,600	120
Nifedipine	260	17
Nizatidine	220	35
Omeprazole	65	60
Paracetamol (acetaminophen)	60,000	300
Paroxetine	15	14
Ranitidine	1,400	70
Salbutamol	35	5
Sertraline	110	85
Theophylline	950	8
Verapamil	600	80

Prices and consumption/production statistics for pharmaceutical intermediates are even harder to discover than for the active ingredients into which they go. An approximate idea of volumes can be estimated, however, if details of process yields are available. It is generally necessary to carry out detailed market research in order to get a reasonable idea of this type of information.

INVESTMENT AND RETURNS

The risks, investments and returns of setting up and running a fine chemical operation are neither particularly high, nor low. Although some practitioners can be certainly classed as 'high-tech', other companies are able to operate in low investment plants supplying established markets in which modest returns can be predictably achieved. This makes this sector of the industry particularly suitable for private investment, since the returns are generally not sufficient to attract the attention of venture capitalists looking to make 25% and more per annum. A return of 10–15% on sales per year is a more likely result.

The commercial and operational structures of several types of pharmaceutical fine chemical companies are analysed in Table 4.3, which presents a useful impression of the financial performance of typical fine chemical producers.

Table 4.3: Comparative financial performance of typical fine chemical companies (converted to US$m)

Company	Assets	Sales	Gross profit	Operating profit	Net income
Laporte 1998	599.00	438.00	–	71.80	–
Cambrex 1998	617.00	442.00	163.00	73.00	39.00
Siegfried 1997	660.00	520.00	190.00	66.00	52.00
InSpec 1996	–	480.00	–	62.00	37.00
Phoenix 1994	1.60	2.40	2.30	–	0.75
Chiroscience 1993	5.97	2.56	1.77	(1.99)	–

Public companies in this business sector have traditionally adopted a relatively low profile and have not attempted to 'talk up' their stock in the way that pharmaceutical and biotechnology companies have done. Usually, when this occurs, the investors are beguiled into believing that the fine chemical company is somehow caught up in the glamour and high risk/high reward ethos of these 'high-tech' stocks. When reality eventually makes an appearance and the good, but not spectacular returns emerge, the investors realise their mistake and sell their shares, creating a sudden rude awakening for the fine chemical company inside the pharmaceutical 'Trojan horse'.

Without going into unnecessary detail, it can be stated that the essential investments required to produce fine chemicals for the pharmaceutical industry are:

- Laboratories for process development, with access to a wide range of analytical equipment.

- Production facilities that allow reactions to be carried out in vessels having the following range of capacities: 50–9,000 L, together with centrifuges, drying equipment and other isolation facilities.

- Warehousing and environmental treatment facilities (for treating and discharging solid and aqueous effluents and capturing and treating gaseous emissions).

- A team of chemists, technologists and operatives to develop and produce the fine chemicals.

- Management and financial services.

A minimum investment of US$200,000 will buy a small manufacturing site in India, a laboratory-based custom synthesis unit in the UK or a centrifuge in the US. Capital investment does not drive the business; clever process technologies do. When analysing the costs of production of a fine chemical, the following useful rule of thumb is helpful in allowing 'back of the envelope' calculations: in a linear synthesis, the final cash cost of production (which does not include recovery of depreciation charges) is generally around 2–3 times the variable costs (raw materials and services). The higher factor refers to US and European operations, the lower one to Asian plants. Although approximate, this 'guesstimate' usually works out quite well. Another, more cynical, rule of thumb is that the fully recovered cost of pharmaceutical fine chemical is equal to the selling price advertised by Chinese traders! Try it, it works!

BUSINESS RELATIONSHIPS BETWEEN SUPPLIER, PRODUCERS AND CUSTOMERS

The interface between the pharmaceutical customer and the source of its pharmaceutical fine chemicals must be managed by individuals with rather different qualifications than those that are responsible for developing and making the products. This role has been traditionally undertaken by one of three groups, which can be used singly or in combination:

- A sales/marketing operation within the PFC company.

- An agent that represents the company exclusively or non-exclusively in one or more country markets.

- An external marketing group responsible for representing the interests of a number of production companies, typically in a single important region.

There are pros and cons for each type of representation. The size of the manufacturer is important in determining the best option. Large companies have the resources and sales to do everything themselves, although they may appoint some agents/marketing representatives in specific markets. (Japan, for example, is a market where having a

local agent is generally a must for all but the biggest companies.) In contrast, small companies tend to depend to a greater extent on agents, as do many medium-sized companies.

Rather than laying down specific rules or formulas, a wise company, whatever its size and resources, will make use of all three interfaces for the following reasons:

- Securing a contract to supply a PFC requires more than technical competence and timely delivery. It also requires getting a fair hearing. The clamour from outside a multinational pharmaceutical fine chemical purchasing agent's door is such that an offer from 'the best man for the job' does not always reach the table.

- Gaining contracts in this business requires a lot of work. Understanding how the company being represented is viewed at the outset can save a lot of wasted effort. Companies with several ways available to make an approach can benefit from the broader sharper picture such resources can present.

- Use of an agent or other-third party representative can overcome unfavourable personal relationships, which may have arisen from direct contacts on previous project work. Representatives with strong people skills and good relationships with customers can rebuild trust.

- Cultural and language barriers may need to be overcome by a local agent.

- The mechanics of doing business may be difficult to get right, without the help of specialists.

For all these reasons, a mixture of different interfaces with customers, which address specific customer and regional needs, is often the best solution to representation. This applies since the use of external agents certainly has its downside as well. Apart from the fact that they inflate the price (from the customer perspective) or reduce the profits (from the producer perspective) of PFCs, they can also create problems when they feel they are being 'cut-out' of a deal. Whether they are justified in this concern (many producers feel no compunction about doing this) or not, the disputes that follow are usually bad for everyone except the customers, who will often create the situation in order to drive down prices.

The best marketing representatives are worth their commission and do not deserve to be treated as parasites, as some companies treat them. Rather their contacts and customer service can often be far superior to the degree of professionalism within a fine chemical producer.

The worst kinds of agents, however, are secretive, greedy and inefficient. They will create problems between supplier and customer, which ought not to exist.

CHAPTER 5: CUSTOMERS FOR PHARMACEUTICAL FINE CHEMICALS

INTRODUCTION

The global pharmaceutical industry is intensely studied by many groups of analysts, since it is one that interests medical science, the healthcare industry, investors, government regulatory bodies, suppliers and (increasingly) the ultimate consumers of medicines (to name a few). The industry is also extremely competitive, so its participants spend large sums studying one another. The problem, then, in attempting to develop a working understanding of the pharmaceutical industry, is to sift out the 'wheat' from the huge amount of 'chaff' in the mass of information and data that can be found on the subject.

In order to develop a reliable picture of the customer base for pharmaceutical fine chemicals, it is necessary to break them down into comparable entities. Using sales revenue as the basis is the traditional way of creating a basic pharmaceutical company ranking (see Table 5.1), although financial analysts prefer a ranking that measures earning potential or market capitalisation (see Table 5.2).

However, from the perspective of a PFC supplier, a company's revenue is not necessarily the best indicator of potential sales volume, since the price of drugs varies widely around the world. Classifying company sales on a regional basis can be helpful in eliminating this bias, although the multinational players will, of course, figure highly in most countries' top tens. More will be said about individual markets later on in this chapter.

When developing business with pharmaceutical companies, fine chemical producers need to recognise a number of differences in the type of service required by the types of companies that sell pharmaceutical products. The most useful way to sub-divide this group of customers is in terms of their size and the market sector in which they operate. The balance of this chapter explores this classification and the different approach to doing business with such companies.

Table 5.1: Pharmaceutical companies by pharmaceutical sales revenue (US$ bn, 1998)

Company	Sales revenue[a]	Sales revenue[b]	Comments
Aventis	13.3	10.8	Proforma sales (HMR and Rhône-Poulenc Rorer)
AstraZeneca	11.2	10.6	Astra and Zeneca merged in 1999
Novartis	9.7	10.6	Ciba Geigy and Sandoz merged in 1998
Merck & Co.	13.7	10.6	
Glaxo Wellcome	13.1	10.5	Glaxo and Wellcome merged in 1997
Pfizer	9.2	9.9	Made a hostile bid for Warner Lambert in late 1999
Bristol-Myers Squibb	9.9	9.8	
Johnson & Johnson	7.7	9.0	
American Home Products	7.9	7.8	Acquired Cyanamid in 1994
Roche	6.6	7.6	Acquired Syntex in 1994, Genentech 1998
Eli Lilly	7.4	7.4	
SmithKline Beecham	7.3	7.3	Expected to merge with Glaxo in 2000
Warner Lambert	3.6	6.0	Sales grew rapidly in 1998. Pfizer is likely to acquire during 2000
Schering Plough	5.7	5.7	
Abbott Laboratories	6.9	5.5	
Sanofi-Synthelabo	4.9	5.0	
Bayer	4.9	4.6	

[a] Scrip Magazine (January 1999). [b] Merrill Lynch (December 1999) The differences in these estimates are the result of using different product-type and year definitions. Clearly, care needs to be taken when analysing such data.

Table 5.2: Pharmaceutical companies by pharmaceutical market value (US$bn, 1999)[a]

Company	Country of origin	26.11.99
Merck & Co.	US	191.5
Bristol-Myers Squibb	US	151.2
Pfizer	US	146.4
Johnson & Johnson	US	144.4
Glaxo Wellcome	UK	111.3
Novartis	Switzerland	111.1
Roche	Switzerland	110.8
Eli Lilly	US	82.5
AstraZeneca	UK/Sweden	80.8
Warner Lambert	US	80.7
Schering Plough	US	79.1
SmithKline Beecham	UK	76.2
American Home Products	US	68.6
Abbott Laboratories	US	59.9
Amgen	US	52.6
Takeda	Japan	45.7
Aventis	France/Germany	35.8E

Source: Merrill Lynch (1999)

[a] The US and (to as lesser extent) the UK companies tend to generate better profits, thus producing higher valuations than Swiss, German, French and Japanese companies. Aventis' low valuation is particularly striking.

MAJOR MULTINATIONAL COMPANIES

All major multinationals have major investments in chemical manufacturing facilities, so that one might expect there to be little opportunity for third party suppliers to sell fine chemicals to these majors. Although the manufacturing divisions certainly do represent the major source of PFCs for the multinationals, this does not necessarily mean that each company's chemical divisions are fully self-sufficient. In spite of a strong tendency for many companies to make their own pharmaceutical bulk active ingredients, a significant degree of cross-company chemical production occurs. Chemical manufacture has been considered, until recently, an important aspect of the business, particularly (but not exclusively) in European-based companies. In Table 5.3, a few examples of the companies known to supply PFCs to their pharmaceutical competitors are presented. (Many of these companies have

recently sold or are expected to sell these chemical businesses.) As investor-power has spread to Europe, many pharmaceutical companies have felt the need to dismantle or divest some of their manufacturing operations in order to improve their level of profitability. Although usually retaining much captive production, this reduction in available resources and manufacturing capacity has led to new opportunities for third party producers to offer out-sourcing services. However, the degree of new PFC business being spun out to third parties has been far less than many had anticipated and the reality remains that the majority of active ingredient production (by value, if not volume) is still in the hands of the multinationals.

Table 5.3: Multinational companies with important third-party fine chemical businesses

Company	Fine chemical business – technology/products
Bayer	Fluoroquinolones, benzimidazoles
Pharmacia & Upjohn	Steroids, prostaglandins
Abbott Laboratories	Antibiotics, especially erythromycin
DuPont	Wide range of technologies
Rhône-Poulenc Rorer	Fluorinated intermediates
Hoechst (now spun off)	Fluoroquinolones, biaryls

Running the operating companies within the chemical manufacturing divisions of many major multinationals is not a particularly easy proposition. The management has to deal with relatively short product lives, a high proportion of new projects under active development at any one time and a high project failure rate. However, the major challenge is that of dealing with the senior managers of the pharmaceutical divisions. They tend to look upon their manufacturing colleagues as the 'poor cousins' and tend to create problems, through this lack of appreciation of the value of this part of their company's operations.

One serious trap into which many companies have fallen, is to invest in chemical development and manufacturing facilities so as to dispose of the large cashflows that a successful drug can create. During the heyday of the hugely profitable sales of Zantac (ranitidine), Glaxo invested vast sums in this fashion; less than ten years later it is 'down-sizing' in order to reduce running costs and improve its profitability. This situation has been more marked in US and UK companies than in Japanese, German, Swiss or French companies, although this variation by region is gradually disappearing. Up to five years ago, most companies in mainland Europe considered the lower profits achieved overall to be no problem at all. These companies (such as Bayer, Hoechst, Ciba Geigy, Sandoz, Rhône-Poulenc Rorer) operated within a different financial system that did not require that huge dvidends be paid out to directly investors. Whatever the rights and wrongs of the argument, the globalisation of the industry and the increasing power of US-dominated international finance have led to a radical change and these companies have felt obliged to change their ways. For example, Hoechst in Germany has recently gone through an extremely painful restructuring in which its pharmaceutical and agrochemical divisions have been separated from its manufacturing divisions, which have themselves been split up by industry application.

A special case of the isolation of pharmaceutical manufacture from the mainstream of the company is the tax-efficient bulk pharmaceutical production units set up in Puerto Rico, Bahamas, Ireland and Singapore. Although multinationals consider these to be a great success, mainly because these regional supply centres offer very substantial tax savings (through the generous incentives offered by the governments of these countries). However, the tight central control of the development and operation of the processes used in the factories, means that little stimulus to local skills has actually been forthcoming. Thus the local economy is not as enriched as has been intended, although nearly full employment has been achieved. Also many pharmaceutical chemical sites have been sold off in Puerto Rico and the Bahamas. The trend has been that the major drug companies have sold capacity once the benefits dry up.

The independent sector of the fine chemical industry has been an essential complement to the captive industry for several important reasons:

- It has offered its customers access to skills and technical know-how outside of the range to be expected within a pharmaceutical operation.

- Small/medium-sized companies or fine chemical divisions of chemical companies have offered greater speed and flexibility than its customers' own chemical groups have been able to deliver.

- Development of new technologies to solve the continuing challenges set by medicinal chemists has improved the range of building blocks available to the pharmaceutical industry.

- The industry's operating costs have generally been significantly lower than their customers', enabling them to supply PFCs at lower *real* cost to the customer (although this has not always been properly appreciated, since the pharmaceutical companies have usually not compared out-sourced prices with their costs on a fully rational basis).

Given the degree of change in the way pharmaceutical companies run themselves, it is hard to offer a reliable commentary on the balance between captive and third party business that the major multinationals undertake. A semi-qualitative summary is presented in Table 5.4.

Table 5.4: Multinational companies and captive versus third-party manufacture (intermediates and active ingredients)

Highly self-sufficient	Intermediate	Out-sources a great deal
Abbott	AstraZeneca	American Home Products
Aventis	Astra[a]	Pfizer
Bayer	GlaxoWellcome	Johnson & Johnson
HMR[a]	Merck & Co.	Schering Plough
Pharmacia & Upjohn	Novartis	Eli Lilly
Roche	SmithKline Beecham	Warner Lambert
Zeneca[a]	Rhône-Poulenc Rorer[a]	

[a] Before merger.

In this report, outsourcing means the buying of fine chemical intermediates or bulk actives by a pharmaceutical company in order to avoid the need to produce them itself. In some companies outsourcing is taken to mean the replacement of existing bulk active production by buying the material from a third party. Not all consider that chemical intermediates are 'out-sourced', even if the demand for the fine chemical is only for their own product, preferring to lump them in with solvents and other 'chemicals'.

The way in which a multinational pharmaceutical company secures the services of a third party varies both from company to company and by project to project. Nevertheless, some useful generalisations can be made:

- Standard chemical intermediates and solvents are sourced on the simple basis of price and quality. Price differences between (a usually good selection of) suppliers are small, and changing the source is not difficult, so these chemicals are non-strategic.

- Advanced and critical intermediates are supplied by two to three approved sources, the most important of which will supply around 70% of the contract. The process technology for making the fine chemicals is quite often based upon the customer's own route; therefore, there has often been a degree of risk sharing in arriving at the supply contract. Thus the suppliers have often tended to develop a working partnership with the customer so that contracts can often have a medium or even long-term value.

- Active ingredients may be produced under sub-contract or on another exclusive basis (for example, the supplier may have a patented process for the product, or it may operate a proprietary technology). Because of regulatory constraints, such contracts are usually long-term. Increasingly, such supply relationships have arisen through the divestiture of the pharmaceutical company's chemical manufacturing site.

Much is made of the increasing tendency towards a restructured pharmaceutical industry, in which the multinational companies have a two-tier supplier base, where preferred partners win the most lucrative contracts and the majority of the other business. Under this model, the second tier companies must satisfy themselves with the 'crumbs from the rich man's table'. This prediction is largely a self-serving one that is supported by the larger fine chemical producers and their mouthpieces. In reality, the psychology of the supplier-customer relationship, which is continually being renewed as younger executives move into the decision-making management positions, is simple. Bias towards reliable suppliers is likely to become established, but when the purchasing management changes, these favoured partnerships can change abruptly. The most efficient, cost-effective producer who delivers at the right quality and price will secure the business, if all other things are equal. When a fine chemical company provides this type of service, repeat contracts are likely to be offered.

The importance of the caveat about 'all things being equal' cannot be overstated. Many buying decisions are made on the basis of insufficient evidence, expediency, laziness or 'understandings' (whereby sweeteners are paid to decision-makers). Much is made of the special relationships that exist between companies, but the truth is that they exist between *individuals* and are based on trust or self-interest. If the relationship exists, it must be nurtured on both sides (whatever its basis) and it can

always become unstuck by external factors. Indeed, the ultimate 'special relationship' is ownership and this demonstrably does not guarantee good performance!

MEDIUM-SIZED PHARMACEUTICAL COMPANIES

The trend towards a larger and more globally based pharmaceutical industry has been driven by the disproportionate size of the world's single biggest market – the US. In Europe, many countries (for example, France, Italy and Spain) have sustained an industry consisting of many local producers, whereas other countries (such as the UK, Sweden and Switzerland) have developed multinational businesses. In Japan, special circumstances have led to the creation of a valuable internal market that has enabled many medium-sized and small companies to thrive. Marketing agreements between the local Japanese companies and the multinationals have benefited both sides by providing the Japanese companies with a flow of new pharmaceutical products and, in exchange, lucrative licensing deals to derive income from their own discoveries in foreign markets, with a minimum of risk.

Outside of these major markets, many countries developed a local industry consisting of small companies that generally licensed new products from foreign companies. This led to a very fragmented industry across the world, with the multinationals usually supplying (directly or indirectly) the active ingredients for local formulation. Where multinationals were discouraged from developing a market (particularly in China and India), their activities have been more curtailed. With recent changes in patent legislation, this situation has begun to change and many are now actively developing their presence in (from the early 1990s) China and (from the mid-1990s) India. Brief profiles of these regional markets are presented in the following few sections.

Medium-sized companies in Europe

A list of some of the local pharmaceutical companies (excluding major multinationals) in Western Europe is presented in Table 5.5. It is beyond the scope of the present report to characterise each national pharmaceutical market, but the survival of these local companies has much to do with the differing pharmacopoeiae that are used in European countries. France is particularly well known for this and over 50% of the drugs prescribed there in the 1980s were said to be unique to that market. The influence of the multinationals has, nevertheless, steadily eroded the power of local and regional companies, so that this figure would be very much lower today.

In the early 1970s, the French authorities changed the formula by which the prices of new pharmaceuticals were calculated. It included a component relating to the cost of manufacture, and this meant that it became advantageous that companies were able to produce their own active ingredients. This led to the foundation of many small bulk pharmaceutical plants, somewhat along the lines found at that time in Italy. The French companies were strongly tied to their mother companies at first. However, as time passed, several emerged as important producers of PFCs for third parties, particularly in the US. A representative list is presented in Table 5.6. Many have now been sold, as their value to their pharmaceutical company owners became less important and the costs of maintaining these operations became burdensome.

Table 5.5: Medium-sized regional pharmaceutical companies in Western Europe	
Company	**Country of origin**
Novo Nordisk	Denmark
Guerbet	France
Fournier	France
Jouveinal	France
Servier	France
UPSA	France
Asta-Medica	Germany
Boehringer Ingelheim	Germany
Byk-Gulden	Germany
Merck KgaA	Germany
Schering AG	Germany
Menarini	Italy
Recordati	Italy
Akzo-Nobel	The Netherlands
Almiral	Spain
Esteve	Spain
Serono	Switzerland
Celltech Chiroscience	UK
Galen Pharmaceutical	UK
Medeva	UK
Shire Pharmaceutical	UK

Table 5.6: Pharmaceutical companies		
Company	**Original ownership**	**Current ownership**
Expansia SA, Aramon		Expansia SA
Finorga SA, Chasse-sur-Rhône	Synthelabo	Finorga SA
Hexachimie	UPSA	Archimica (BTP), UK
Lipha Chimie Fine, Lyon	Lipha Group	Lipha Group
SIPSY SA, Avrille	Groupe Jouveinal	PPG, US
Simafex SA, Marans	Groupe Guerbet	Guerbet Groupe
Synkem, Plasto SA, Chenove	Groupe Fournier	Fournier Groupe

In Italy and Spain, a similar situation has existed to the one found in France, although much of Spain's pharmaceutical industry is now owned or controlled by multinational companies.

In Germany, the pharmaceutical industry has been dominated by the multinational companies Hoechst and Bayer (both of which acquired smaller local companies as their empires expanded). There are, nevertheless, three medium-sized companies that have overseas presence, but could not be considered as fully-fledged multinationals. These are:

- Schering AG, based in Berlin, a specialist in steroid-based drugs.
- Boehringer Ingelheim, based near Frankfurt.
- Merck KgaA, based in Darmstadt; specialising in proprietary radio-opaques and generics.

Byk-Gulden and Asta-Medica are two other smaller companies. There are also many small/medium-sized companies that have concentrated on the sale of generic pharmaceuticals (see belowlater). The generic pharmaceutical industry in Germany has a number of special features, the most important of which is that 'generics' are branded, so that consumers are aware of which generic company's product will be prescribed at the point of dispensing. Recently, the German authorities have directed funds into the creation of a biotechnology industry, and small biotech companies are beginning to appear in Germany.

The situation in the UK is broadly similar to that in Germany, although generics are prescribed anonymously. The biotech industry is better established in the UK, but its leading companies have had mixed fortunes with their lead developmental products over the past three years, and some of the confidence in the sector has been lost by the financial community.

The Netherlands has one large pharmaceutical company, Akzo-Nobel, which is a regional rather than a global player.

In Belgium there are two well-known companies:

- Janssen (a subsidiary of the US multinational, Johnson & Johnson), which has a remarkable record for discovering new classes of pharmaceuticals.
- UCB, a small pharmaceutical subsidiary of a chemical company, with just one major product to its credit.

Of the three Scandinavian majors, Astra, Pharmacia and Novo Nordisk, only the last remains as an independent entity. Pharmacia was merged with Italy's Farmitalia and then bought by the US multinational Upjohn (now called Pharmacia & Upjohn). The leadership of P&U swung decisively over to the US company as the result of the mess that the Italian company's management made of Pharmacia.

Astra recently merged with the UK's Zeneca, with control marginally on the UK company's side. Although Sweden's Astra created the world's biggest selling pharmaceutical to date, Losec (omeprazole), its management was unable to come up with a replacement when Losec's patents expired in 1997/8, leading to an opportunity

for the UK company to make its merger approach at a time when it felt compelled to increase its overall size.

Denmark's Novo Nordisk is a specialist in pharmaceuticals derived from biotechnology (for example human insulin). It remains independent, being part of a large speciality chemical group with a core business in manufacturing industrial enzyme.

In Switzerland, there are several small/medium-sized companies, the most significant of which is Serono, which has invested heavily in the biotech field and more recently in genomics.

Central and Eastern Europe

Table 5.7 lists medium-sized regional pharmaceutical companies in Central and Eastern Europe.

Table 5.7: Medium-sized pharmaceutical companies in Central and Eastern Europe

Company (owner)	Country of origin	Sales 1997 (US$m[a])
ICN in CEE	Russia	350
LEK	Slovenia	295
Krka	Slovenia	275
Gedeon Richter	Hungary	270
Pliva	Croatia	220
Bryntsalov	Russia	180
Leciva	Czech Republic	175
Egis (Servier)	Hungary	165
Chinoin (Sanofi)	Hungary	160
Slovakofarma	Slovakia	150
Starogard	Poland	120
Biogal (Teva)	Hungary	85
Galena (Ivax Corpn)	Czech Republic	80
Alkaloida (ICN Pharmaceuticals)	Hungary	75
Poznan	Poland	70
Tarchomin	Poland	65
Biotika	Slovakia	60

[a] Brychem estimates.

Japan

Japan's pharmaceutical market is the world's second biggest country pharmaceutical market after the US. The disproportionate size of the Japanese market stems from the unusual financial structure of the country's healthcare system, which the government has been attempting to rationalise over the past few years. The market value has hardly grown over the past decade, as the result of this governmental action, the economic downturn in Asia and the general policy of the National Health Institute (NHI) to reduce drug prices regularly. In 1999, however, prices were not cut for the first time in several years and so the industry experienced its best trading results for some time.

There are many pharmaceutical companies in Japan and few are really large in comparison with the US and European multinationals. The top companies by sales income are listed in Table 5.8. Within the top ten are several companies that have significant income from overseas, either via direct investments or through licence income.

Table 5.8: Medium-sized regional pharmaceutical companies in Japan

Company	1998 pharma sales (US $m)
Takeda	869
Sankyo	630
Yamanouchi Pharmaceutical	438
Eisai	309
Daiichi Pharmaceutical	288
Fujisawa Pharmaceutical	278
Yoshitomi Pharmaceutical	236
Tanabe Seiyaku	216
Banyu Pharmaceutical	147
Ono Pharmaceutical	117
Kissei Pharmaceutical	53
Taisho Pharmaceutical	26

Source: Merrill Lynch (1998)

Most companies, however, are relatively small and operate only in the domestic market. Historically, the Japanese market has been extremely insular, with direct access by the major multinationals being blocked. Most participated via joint ventures, many of which are now being dismantled, as the market is slowly opened up to foreigners. Nevertheless, there still remain many barriers to a more open market. Peculiarities include the continuing need to retest drugs approved elsewhere, as the result of a general perception that Japanese are not racially distinct. Access by foreign companies to inspect Japanese production facilities is also still not as straightforward as elsewhere.

In spite of the resistance to change, the need for Japanese pharmaceutical industry to globalise is now recognised by many companies, and as this trend continues, the entry into Japan by foreign corporations will also accelerate.

Asia and the Pacific Rim: India and China

The growth of the Indian pharmaceutical industry over the last thirty-five years has been phenomenal. From sales valued at US$100m in 1965, it grew to US$2.52bn in 1994 and by last year had reached well over US$3.5bn. This growth has been almost entirely due to the expansion of the domestic pharmaceutical industry, which has fuelled the development of the Indian bulk medicinals industry. The liberalisation of the Indian economy during the 1990s has further boosted this growth and 'unleashed' the Indian pharmaceutical industry.

The major producers of pharmaceuticals in India have invested in their bulk drug businesses not only to assure supplies of reasonably priced active ingredients, but also because these operations produce good profits too (especially exports). This contrasts with the economics of most multinational companies. The relatively low profitability of the finished pharmaceuticals business is a result of the Indian government's restrictive drug pricing policy, which ensures that the overall profit of pharmaceutical companies does not exceed 8–13% of pre-tax sales. This disadvantage has been effectively counter-balanced by the favourable patent policy and regulatory climate for bulk medicinals manufacture in India. These policies have helped the establishment of a strong, locally owned company sector (accounting for 70% of domestic sales and 85% of bulk medicinal sales). This contrasts to the industries in much of the developing world, where multinational companies tend to dominate. In Table 5.9, the leading domestic pharmaceutical companies in India are ranked by their drug sales (not *total* sales). Of the top fifteen companies, only five are multinational companies (Glaxo, Hoechst-Roussel, Knoll, Pfizer and Novartis).

The manufacturing operations of most Indian pharmaceutical companies are of much greater commercial importance than is generally the case in the West due to its higher relative profitability. Since the sales of the bulk and finished businesses are not usually separated, the task of defining the size of the industry and the ranking of its major players is difficult. In order to achieve reasonable profits companies have a mix of new and older products. The major companies' bulk medicinals businesses contribute between 10–20% of their total sales and profits.

As in India, traditional herbal medicines have been the mainstay for the Chinese physician for many centuries. Use of Western pharmaceutical products was introduced in the late 1940s and grew slowly until the mid-1980s, from when the industry really started to develop in earnest. By 1996, annual sales had reached US$10.4bn, with sales projected to reach US$18bn by 2000.

This spectacular rise has been generated largely from within, although multinational companies have been active in China and represent an important proportion of these sales, usually by way of local joint ventures. As has been the case in India, China's patent laws have not offered sufficient protection and drug prices have been too low to have attracted major investments by the multinational companies until quite recently. With China's accession to the world patent convention and its adoption of product patents in 1993, the climate for foreign involvement has been greatly improved. There are over 5,600 pharmaceutical companies in China, the majority of which carry out the manufacture of finished products from basic raw materials.

Table 5.9: Regional pharmaceutical companies in India (ranked by sales[a] in 1999)

Company	Town	Overall sales (US$m)	Market share
Cipla	Mumbai	184	4.25
Ranbaxy Laboratories	Delhi	374	3.34
Wockhardt Merind	Mumbai	–	2.37
Zydus Cadila	Ahmedabad	–	2.34
Sun Pharmaceuticals	Ahmedabad	103	2.21
Cadila Pharmaceuticals	Ahmedabad	–	2.18
Lupin Laboratories	Mumbai	–	2.17
Nicholas Piramal	Mumbai	110	2.07
Alembic	Delhi	–	2.04
Alkem		–	2.02
Total domestic share in top 15	–	–	24.99
Five multinationals in top 15	–	–	15.33

[a] Value of total pharmaceutical sales was Rupees128bn, equivalent to US$3bn.

Source: ORG, India (based on surveys for January–December 1999)

Although inefficient by Western standards, this multiplicity of companies is sustained by the political organisation of the country, in which each province has a high degree of autonomy. In spite of the preponderance of small companies, a number of bigger companies have begun to emerge, a list of which is shown in Table 5.10.

Table 5.10: Regional pharmaceutical companies in China

Company	Town, province	1998 sales (US$m)
999 Group (Shenzhen Nanfeng)	Shenzhen, Guangdong Province	558
North China Pharma Group	Shijiazhuang, Hebei Province	337
Shijiazhuang Pharma Group	Shijiazhuang, Hebei Province	275
Xian-Janssen	Xian, Shaanzi Province	225
Shandong Xinhua Pharma Group	Zibo City, Shandong Province	222
Harbin Pharmaceutical General Factory of Harbin Pharma Group	Harbin, Heilongjiang Province	180
Sino-American Tianjin SmithKline & French	Tianjin, Province	141
Northeast General Pharma Group	Shenyang, Liaoning Province	127
Livzon Pharma Group	Zhuhai,Guangdon Province	124
Wuhan Heart K. Group	Wuhan, Hunan Province	120

Source: Beijing Cons-BioTech

The Chinese pharmaceutical industry has developed a strong export business for bulk pharmaceuticals and their intermediates by offering them at very low prices. Their main objective in developing these sales has been to generate foreign exchange, an essential activity for these companies, since they need many imported materials in order to supplement domestic supplies.

In the region, Korea and Taiwan are two powerful economies that both have strongly westernised pharmaceutical industries, although traditional herbal medicines continue to be important, particularly for treatment of chronic conditions. Companies in Taiwan have invested heavily in Chinese pharmaceutical capacity and have helped to fund the development of the industry in Shanghai and Guangdong. This financial and pharmaceutical technology exchange between these two countries has benefited China and goes some way to explain the greater rate of growth of the Chinese industry compared to that in India.

Rest of the world

The local companies in *South America* are generally structured similarly to what would elsewhere be called generic pharmaceutical companies. An important difference, however, is that generic products sell at around the same price as branded drugs sold by the local multinational operations. Multinationals supply finished formulations, while Italian and Spanish producers supply the majority of the region's bulk drug needs. Suppliers from China and India are beginning to make inroads into this market, but they still account for only a minor percentage of sales.

Before the abolition of apartheid and the election of a multiracial government in *South Africa* in 1994, the organisation of the pharmaceutical industry was similar to the one in the US and Europe. Since then, the new government has been putting pressure on the multinationals and their local partners to reduce the price of drugs (so as to make them affordable to the black majority). With the spread of AIDS becoming a major concern, threats have been made to repeal product patents, so that the newer anti-AIDS treatments can be made available by local manufacture (based on Asian imports of active ingredients). Asian pharmaceutical groups have been investing heavily in South Africa in order to develop the sale of cheaper drugs in this country and, indeed, throughout Southern Africa.

Elsewhere in *Africa*, supplies of drugs are very limited, with aid agencies supplying much of the continent with older, cheaper products supplied as formulations under tender.

In the *Middle East, Israel and Iran* are the dominant markets. Israel has its own multinational pharmaceutical company, Teva, which has grown by acquisition to be a leading US generic company. It has begun to develop its own compounds, with the first, Copoxone, recently launched for the treatment of multiple sclerosis. The majority of the Israeli market is supplied by US and European generic companies. In Iran and elsewhere in the Middle East, local producers are important, with many multinationals excluded for political reasons. These companies import bulk active ingredients from unlicensed producers, mainly in India and China.

GENERIC PHARMACEUTICAL COMPANIES

The word 'generic' is, like the word 'pharmaceutical', often loosely used to indicate the producers of finished formulations as well as the producers of bulk drugs. This is most misleading, since the two industries are as different as steel-making and the selling of canned food. Back-integrated production of generic pharmaceuticals is the exception rather than the rule.

Generic pharmaceutical companies manufacture finished dosage forms of pharmaceuticals which are no longer covered by product patents. They sell them through the usual outlets under a generic (non-branded) name in most markets, although in Germany only 'branded generics' are allowed. Thus, in the US, SB sells Tagamet, Mylan sells cimetidine, both equivalent treatments for the control of peptic ulcers. The leading generic companies in the US are presented in Table 5.11. Mylan is the biggest seller of US generics today if one omits other sources of income. Ownership has quietly passed almost entirely into the hands of the multinational pharmaceutical producers over the last five to ten years. Examples of these transfers of ownership are shown in Table 5.12.

Table 5.11: Ownership and sales of leading US generic companies

Company	Specialisation (formulations)	Ownership	1995 sales (US$m)
Ivax	Oral	Public	1,260[a]
Teva Pharmaceuticals	Oral/injectable	Public	900[a]
Alpharma	Oral	Private	521[a]
Forest Labs	Oral	Private	405
Mylan Labs	Oral	Private	396
Barr Labs	Oral	Private	200
Copley Pharmaceutical	–	HMR	142

[a] Includes other sales.

Table 5.12: Three leading US generic companies now absorbed into acquirers

Company	Specialisation (formulations)	Ownership	1993 sales (US$m)
Rugby Laboratories	Oral	HMR	500
Schein Pharmaceutical	Oral/injectable	Bayer	400
Geneva Pharmaceuticals	Oral/injectable	Novartis	240

They are supplied by PFC producers which often specialise in the production of bulk actives. These companies are often referred to as 'generic producers' or 'pirates' by

the more aggressive employees within the innovative pharmaceutical industry. Most suppliers to the generic pharmaceutical industry should not be so damned, since the majority are breaking no laws and are indeed run using the same business principles as the multinational companies. It is also true that there are a number of outright rogues operating in the industry.

These generic pharmaceutical companies present an important outlet for PFCs and have excellent growth prospects, as the pharmaceutical industry and its products continue to mature. They have access to the market, and the better ones have invested in the facilities, quality assurance systems and regulatory approvals which are vital for continuing success.

In order to ensure continuity of supply to their customers, bulk pharmaceutical companies are increasingly looking for sources of competitive technology (to improve their processes and their margins) and suppliers of advanced intermediates. Changes in the importance of regulatory compliance and customers' expectations mean that this sector is particularly attractive for the more technologically oriented fine chemical intermediates producers. Price differentials between 'DMF bulk actives' and 'USP bulk actives' are always significant (usually 50–100% higher for the 'regulated market') and sometimes enormous (cimetidine sold at around US$150–180/kg in the US after its patent expiry, compared to US$50–60/kg in the EC/Japan and US$22–35/kg in other markets). Needless to say, costs are nowhere near as different, so profits are better. A representative selection of leading European generic pharmaceutical companies is presented in Table 5.13.

There are relatively few international generic pharmaceutical companies (see Table 5.14), although some have begun to emerge as the industry continues to consolidate. The sales of these emerging companies are significant and likely to grow through further acquisitions and consolidation.

Table 5.13: Location and ownership of leading EC generic companies

Company	Country	Ownership
Ratiopharm	Germany	Merckle GmbH
Azupharma	Germany	Gehe
AWD	Germany	Asta (Degussa)
Klinge-Natterman	Germany	Fujisawa-RPR
Durachemie	Germany	Cyanamid (AHP)
Hexal-Pharma	Germany	Strungmann
Heumann Pharma	Germany	Searle (Monsanto)
Sanorania	Germany	Pharmacia & Upjohn
Centrafarma	Netherlands	Stada
Multipharma	Netherlands	Novartis
Pharmachemie	Netherlands	OPG / co-mktg DuPont
Magnafarma	Netherlands	ACF (DSM)

Table 5.13: continued		
Company	**Country**	**Ownership**
Albic	Netherlands	Sanofi-Winthrop
Amerpharm	Netherlands	E Merck (51%)
Generics UK	UK	Amerpharm (E Merck)
Norton	UK	Ivax
Cox	UK	Hoechst UK
Evans-Kerfoot	UK	Ivax
APS/Berk	UK	Teva
P Drugs	UK	Akzo
Wallis	UK	Private
Wyeth Generics	UK	Wyeth (AHP)
Servipharm	Switzerland	Novartis

Table 5.14: Leading international generic companies			
Company	**Markets**	**Ownership**	**1993 sales (US$m)**
Merck KGaA	World	E Merck/Public	2,100
Faulding	Australasia, US	Private	1,010
Novopharm	Canada, US, Europe	Teva (acquired 2000)	650
Apotex	Canada, US, Spain	Private	600
Genpharm	US, Canada, South Africa	Private	400

BIOTECH INDUSTRY

The smaller research-based drug discovery companies, in the so-called biotech sector, rarely have their own manufacturing capabilities. These companies, the majority of which are based in the US, the UK and Germany, offer excellent opportunities for fine chemical suppliers as their R&D pipelines mature. A list of the leading US Biotech companies is presented in Table 5.15.

These companies usually sell the marketing rights to successful drugs (at around phase II-III in the development process) to multinational licensees in order to ensure that the maximum potential sales can be realised. This can cause dislocations if the licensee has a strong commitment to ‘making’ rather than ‘buying’ or has a different

attitude towards the existing suppliers. In general, however, the supply relationships already set up are preserved.

Table 5.15: Leading US biotech companies

Company	Sales 97Q1 (US$m)	Earnings 97Q1 (US$m)
Amgen	576	180
Chiron	330	15
Genentech	257	32
Genzyme	145	21
Biogen	100	17
Biochem Pharma	46	24
Centocor	45	3
Agouron	39	-5
Immunex	39	-9
NeXstar Pharmaceuticals	21	-10

In some instances manufacturing is wholly retained by the company and this is often because it has a strong pharmaceutical fine chemical partner. For instance, Biochem Pharma and Agouron have granted marketing licences to major multinationals, while maintaining control of chemical manufacture. This sector will create continuing opportunities for independent fine chemical companies over the coming years.

It is an interesting fact that the majority of drug candidates emanating from the biotech sector are small molecules such as heterocycles, oligopeptides, aromatics and peptidomimetics. Gene therapy and products resulting from molecular biology are still in the minority and will continue to be so during the next ten years. There will continue to be a strong need for chemical synthesis, albeit with more complex structures being needed than has been the case before.

FINE CHEMICAL PRODUCERS

Independent producers of bulk pharmaceutical actives buy advanced intermediates from fine chemical companies and are therefore customers as well as producers from the perspective of this report. It is not worthwhile to go into this in any great detail, except to remark that these companies represent a growing source of income for producers of intermediates. In Europe and the US they generally may be expected to resist the temptation to back-integrate their operations and are therefore potentially more secure customers than in Asia, where such a tendency is rather more common.

CHAPTER 6: COMPANIES INVOLVED IN PRODUCING PHARMACEUTICAL FINE CHEMICALS

BRIEF OVERVIEW OF THE INTERNATIONAL PFC INDUSTRY

Traditionally the production and supply of PFC active ingredients to the US and European markets (as opposed to captive production) has been dominated by Italy and latterly, to a lesser extent, Spain. The production of advanced intermediates has been dominated by the North European countries (Germany, UK and the Netherlands and to a lesser extent France) and Japan. Switzerland has been successful in both sectors, reflecting its unique position in Europe. In the US, many of the major companies have made their own active ingredients, but advanced intermediates were usually sourced from Europe and Japan. The independent, bulk manufacturing sector has been relatively unimportant in the US.

Italy's predominance was a direct result of its privileged product patent laws (product patents were only introduced in 1978, two years later than in Japan). These allowed early development of products and provided the many small companies with several years of cash-flow from these products (by selling in so-called 'free markets'), well before North European companies could legally begin development. Italy did not have and certainly does not possess any special skills in developing fine chemical processes. Indeed, the industry is dominated by individuals having stronger credentials as traders than industrialists.

Although Italy, paradoxically, now has the toughest patent laws (and longest supplementary protection certificates (SPCs), which extend the period of exclusivity) in the EC, its industry continues to thrive. Its commercial strengths have enabled the industry to use Spain, Eastern Europe (especially Slovenia and Hungary), China and India as its sub-contractors. Many US companies, perhaps unknowingly, continue to buy bulk actives produced in certified Italian plants (with type I and II DMFs), which have been sourced from elsewhere.

Japan emerged as an important source of PFCs in the late 1970s, although its high prices generally meant that its customers have usually been multinational pharmaceutical companies, rather than generic producers. Like Italy, however, Japan has been able to maintain the competitiveness of its fine chemical industry through its ability to source advanced intermediates from its Asian neighbours, where costs have been lower.

More recently Taiwan and Korea have emerged as participants, the Taiwanese in particular having benefited from their growing commercial links with mainland China. India and China, which have traditionally maintained a high degree of self-sufficiency, are the latest and undoubtedly the most important Asian players to emerge, since Japan, as major participants in the global PFC business.

CUSTOM SYNTHESIS OF SOPHISTICATED PHARMACEUTICAL FINE CHEMICALS

The manufacture of small amounts of material for initial testing is a specialised endeavour, which is dominated by small entrepreneurial companies. The task involves developing a synthetic route to a (usually) novel compound and preparing up to several hundred grams for the customer. Very often, the supplier receives little technical guidance from the customer (this distinguishes it from contract manufacture, where the customer often supplies the process and technical back-up).

The following generalisations help to characterise this type of fine chemical activity:

- Custom synthesis is best suited to small-scale operations, which are able to react quickly and effectively to the demands of their (generally) larger (and therefore slower) customers.

- In the US, there are many small-scale pharmaceutical producers which have no chemical production and so must seek sub-contractors for clinical trial quantities. There are many more custom synthesis providers for this reason.

- Offering small-scale manufacture as part of the service can lead to much bigger, more lucrative contracts. Medium-sized pharmaceutical fine chemical companies often undertake to carry out custom synthesis on the understanding that, when the new compound is ready for launch, they will receive such a supply contract.

- Many custom synthesis companies tend to fill up their 'pilot facilities' with long-term manufacturing contracts and then cannot accept further contracts until further capital is invested. At this point, companies must decide whether to expand (which involves significant capital investment) or turn business away.

- Many pharmaceutical companies do not accept that they should pay high prices for early trial quantities, since their policy is that those suppliers who have helped in the early days have earned the right to supply at the larger scale once the product is commercialised. This makes it tough for many companies who find the delay in receiving this reward makes such a 'loss-leader' approach unattractive.

- A reasonable price for contract synthesis on non-GLP, non-FDA facilities would be around US$11,000–14,000 per month (to hire a PhD plus technical support); this includes overheads and simple chemicals. US$14,000–25,000 per month appears realistic for GLP, FDA-inspected laboratories (perhaps with ISO 9002 as well).

- Renting out small-scale pilot facilities would be priced at US$700–1,200 per day for non-GMP/FDA operations. A significant premium is obtained if these accreditations are obtained: US$1,600–3,000 per day is a reasonable estimate.

The information for these statistics was mostly gathered from UK companies. European companies tend to charge prices 25–50% higher, at US$1,500–3,000 per day (similar to the prices charged by US companies). A short list of representative companies offering a custom synthesis service to the pharmaceutical industry is presented in Table 6.1.

Table 6.1: Selected small pharmaceutical fine chemicals companies offering custom synthesis/manufacture

Company	Location	Specialities
Carbotek Developmental Laboratories	US	Custom synthesis/pilot plant
Cauldron Process Chemistry	US	Custom synthesis
Casali Institute Pilot Plant	Israel	Small pilot unit, no GMP, FDA approvals
ChemSyn Laboratories	US	GLP custom synthesis/FDA-inspected GMP pilot plant/cytotoxic drugs
Neils Clausen	Denmark	Custom synthesis; offers total package price
Eprova AG	Switzerland	Custom synthesis/pilot plant
High Force Research	UK	GLP custom synthesis/GMP pilot plant
Orpegen GmbH	Germany	Custom synthesis of peptides
Palmer Research	UK	GLP custom synthesis/GMP pilot plant

SUPPLY OF FINE CHEMICAL AND PHARMACEUTICAL INTERMEDIATES

No special requirements are necessary for supply of basic and non-pivotal intermediates for pharmaceutical fine chemical manufacture. These are produced and sold in the same way as intermediates for other industries, although many pharmaceutical chemical buyers like to see better than average raw material, in process and final quality control systems. There is a trend to strengthen the regulatory controls on intermediate production, but this is counteracted by a continuing need for restraining costs.

The vast majority of the business out-sourced by the multinational pharmaceutical industry is for intermediates made in general purpose fine chemical companies. Products fall into two main categories: standard items or custom items.

Standard chemical and fine chemical intermediates

Production and supply of standard compounds to pharmaceutical companies demands little extra development work on the part of the would-be supplier, unless special quality requirements are needed. The choice of company by a potential customer will usually be made on the basis of several factors, including the candidate producer's experience and production capacity in the particular compound, quality standards and price. Standard items are produced for a variety of end-uses and the production capacity will depend upon the major volumetric outlet. This is usually not for pharmaceutical applications, since the demand for these applications is generally relatively low compared to other industries that use intermediates and fine chemicals. Listing the many companies involved in this type of chemical production would

demand too much space. The leading chemical intermediates producers for life science companies (pharmaceuticals and agrochemicals) are listed in Table 6.2, based on their sales turnover. Separating out the life science segments of each company's overall business is a difficult task, but the information provided here appears to represent a reasonable attempt. The fact that pharmaceutical and agrochemical sales are mixed together is appropriate, since a significant proportion of these sales is of intermediates common to both areas of application. It is useful to regroup these leading companies in a different way, in order better to understand their operational and commercial focus.

Table 6.2: World's leading producers of chemical intermediates and fine chemicals for the life science industry

Companies	Locations	1997 sales of chemical intermediates (US$m)
DSM	The Netherlands	995
Clariant	Switzerland	800
Lonza	Switzerland	695
Degussa-Hüls	Germany	670
Bayer	Germany	655
Rhodia	France	480
Eastman	US	410
Reilly Chemicals	US	365
Dow Chemical	US	260
BASF	Germany	250
Cambrex	US	249
Laporte	UK	229
Elf Atochem	France	200
SNPE	France	188
Tessenderlo	Belgium	130
Nippon Soda	Japan	120
OxyChem	US	100
Great Lakes	US	100
Ihara	Japan	83
Avecia (Zeneca)	UK	75
EMS Dottikon	Switzerland	70
Koei Chemical	Japan	70
Borregaard	Norway	65
ChiRex	US	60
BTP	UK	60
Total sales		7,379

Source: Wood McKenzie (1999)

Speciality chemical groups

Most of the larger companies are divisions of chemical companies (D) or have been spun out of larger chemical companies (S). Their total businesses include very significant sales of performance chemicals as well as sales of chemical intermediates for non-life science applications. These companies are:

- DSM (D)
- Clariant (S)
- Degussa-Hüls (S)
- Bayer (D)
- Rhodia (S)
- Eastman (D)
- Dow Chemical (D)
- BASF (D)
- Laporte (D)
- Elf Atochem (D)
- SNPE (D)
- Tessenderlo (D)
- Nippon Soda (D)
- Oxychem (D)
- Avecia (S)
- EMS-Dottikon (D)
- Borregaard (D).

They tend to share common characteristics that mark them out and which affect the way they are able to develop business with the pharmaceutical industry:

- Operate a 'production-push' marketing philosophy, whereby the customer buys what the producer has to offer through its technology strengths. The major European companies illustrate this tendency well.

- The engineering divisions of these companies often possess too much influence over the company culture (particularly strong in divisions, where policy is often controlled by the chemical company culture). This leads to over-spending on new plant, which thereafter becomes an economic albatross around the company's neck.

- Small projects are often not considered seriously, even though they have the potential to grow. 'Big is beautiful' is the basic reaction and high value, low volume business opportunities are hard to drive through the decision making process to a successful conclusion.

Economies of scale in manufacture is a significant advantage in commodity chemicals, but usually have little impact on developing a successful fine chemical or low volume intermediates opportunity.

Independents

Most of the small/medium-sized companies listed (representing only a small sample of the many that exist) are independent companies that specialise in developing and producing fine chemicals. The list grossly under-reports fine chemical companies of this type, which have sales in the region of US$30–150m (Chirex is one that is included). They are not strictly speaking speciality chemicals companies in the true sense of the word, since they lack a performance chemical operation that can generate higher margin business to support the fine chemical and intermediates divisions. More will be said of these fine chemical specialists later in the chapter.

Conglomerates

These are a relatively new phenomenon and generally driven by the need to keep investors in publicly quoted companies happy. It is hard to find merit in these unwieldy groups, other than in those cases in which the financial benefits of older 'cash cow' businesses are intelligently channelled into new growth businesses. Usually the senior managers and their advisors have short-term ambitions that bring neither long- term benefits to the individual operating companies nor the group as a whole.

Others

There are always examples that do not quite fit the general case. Lonza, one of the biggest companies on the list, is one such. It derives much of its income from producing complex fine chemical intermediates and many active ingredients as well. What makes it special? Several factors, of which the most significant are:

- It has enjoyed the patronage of Switzerland's enormously successful life science majors (now united under the names of Novartis and Roche).

- It has been able to pursue its policy of market-led development without undue hindrance from external agencies.

- It has been able to plough back a reasonable percentage of the profits in new business, rather than hand the majority out to shareholders.

- It has maintained a strategy of continuous technical development throughout its history, enabling it to react more successfully to the demands of its customers.

Reilly Chemicals is massively dependent on the income from its production of pyridine for paraquat and is a far weaker player than its ranking suggests. It has, indeed, been held back from greater success by its very conservative management style.

These larger chemical and speciality chemical companies clearly make a major contribution to the production and sale of standard chemical intermediates and some fine chemicals. In Table 6.3 some important ranges of standard items are presented with the leading companies that produce them.

Table 6.3: A selection of medium-sized producers of standard intermediates and fine chemicals

Standard compounds	Companies	Locations
Pyridine derivatives	Koei Chemicals	Japan
	Nepera Inc. (Cambrex)	US
	Reilly Chemicals	US
Diketene derivatives	Clariant GmbH	Germany
	Lonza AG	Switzerland
	Wacker Chemicals	Germany
Chlorinated toluenes	Clariant GmbH	Germany
	Ihara Chemicals	Japan
	Oxychem	US
	Tessenderlo	Belgium
Fluoroaromatics	Allied Chemicals	US
	Avecia PLC	UK
	Miteni	Italy/Japan
	Nippon Shokubai	Japan
	Oxychem	US
	Rhodia	France, UK
Nitriles	DSM (Andeno)	The Netherlands
	Dow	Switzerland
	Lonza	Germany
	Degussa- Hüls	
Nitroparaffins	Angus Chemicals	US
Nitro-aromatics	Dynamit Nobel	Germany
	Hickson & Welch	UK
	Nordic Synthesis (Cambrex)	Sweden/US
	SSF-Dottikon	Switzerland

Custom fine chemicals

The companies at the foot of Table 6.2, with sales under US$100m are representative for a very large group of small/medium-sized producers that focus their activities on providing a service to the global pharmaceutical industry. They have generally established a reputation for solving some of the more difficult chemical problems the pharmaceutical industry sets for its suppliers. Somewhat facetiously grouped under the three-letter acronym, DDD: Difficult, Dangerous or Dirty, these companies fill in gaps between the standard items and the custom compounds that are required for the pharmaceutical industry's never-ending demand for new fine chemicals.

The majority of these smaller companies have been started by their founders' ability to identify a developing requirement for a new type of technology or area of chemistry. Many, of course, fail to achieve success, but the ones that do succeed

provide the basis for the next generation of medium-sized companies. This can occur by organic growth, acquisition or merger. The necessary dynamism required of the fine chemical industry is thus reinforced by these small entrepreneurial operations. This is why the larger companies listed in Table 6.2 are able to retain a successful business, in spite of their structural disadvantages. In Table 6.4, a few typical examples of the competitive basis by which these companies have arisen will help to illustrate this.

Table 6.4: Original specialities of some specialised pharmaceutical fine chemical producers

Company	Location	Technology/chemistry/strategic strengths
Aerojet	US	Azide, diazomethane and other hazardous chemistry
Albany Molecular	US	Multistage syntheses
Andeno	The Netherlands	Chemical resolutions, speed and versatility
Boulder Scientific	US	Grignards, organoborane chemistry
ChemDesign	US	Speed and versatility
ChiroTech	UK	Asymmetric synthesis, biotransformations
Daiso	Japan	Asymmetric synthesis
Expansia SA	France	Phosgenations, diborane, metal hydrides
Fairmount	US	Azides, diazotization, hydrazine chemistry
Fine Organics (now part of Laporte PLC)	UK	Carbon disulphide, nitromethane and thiophosgene chemistry
Hatco Corpn	US	Phosgenations
Lancaster Synthesis	UK	Lab chemicals, custom synthesis
Oxford Asymmetry	UK	Asymmetric synthesis
Phoenix	UK	Chloromethylations, dizaomethane and other hazardous reactions
Polyorganix Inc	US	Purines, pyrimidines
Sterling Organics (now Chirex)	UK	Speed and versatility, use of pharmaceutical parent's underutilised facilities for outsourcing
Sugai Chemicals	Japan	Contract manufacturing
Synthetech Inc	US	Amino acids, biotransformations

SUPPLY OF PHARMACEUTICAL ACTIVE INGREDIENTS

The production of bulk pharmaceutical active ingredients up until the early-mid 1990s had been very much in the hands of several distinct groups of companies:

- The innovative pharmaceutical industry, which manufactured its own bulk drugs in order to defend its proprietary marketing position and (according to the industry representatives) to guarantee continuity of quality.

- Companies licensed to operate bulk drug manufacturing processes by owners of proprietary technology.

- Integrated pharmaceutical companies located in countries where early development of proprietary drugs was possible by virtue of local legal advantages.

- Independent producers of bulk pharmaceuticals which enjoyed patent advantages and were able to supply domestic and foreign markets in which non-licensed formulations were legally available.

Essentially there were the two groups: the major multinationals and their local affiliates/contractors and the 'opposition'. The opposition consisted of integrated pharmaceutical companies located in some parts of the developing world (China, India, Latin America and many of the countries of the former Soviet Union) and bulk pharmaceutical suppliers in Italy and Spain. Table 6.5 presents a short, but representative list of bulk pharmaceutical producers. Note that Chinese companies produce pharmaceutical products as well as bulk drugs and are therefore not listed in Table 6.5.

The two sides were (and in many cases still are) bitter commercial enemies. The multinational companies considered that those pharmaceutical groups that did not recognise product patents were pirates. The non-licensed producers considered themselves to be (in the case of the pharmaceutical manufacturers) patriots that brought affordable drugs to countries that could otherwise ill afford them. The independent bulk producers and (especially) the South American pharmaceutical companies considered themselves lucky to operate under a legal regime that assured them a business that offered easy profits. Among both these two groups there were, of course, unscrupulous individuals and companies that provided extra ammunition for both sides.

Table 6.5: Some of the leading independent producers of bulk pharmaceuticals

Company	Town/country
Farmakon	Czech Republic
Galena	Opava-Komarov/Czech Republic
Egis	Budapest/Hungary
Gedeon Richter	Budapest/Hungary
Cheminor Drugs	Hyderabad/India
Divis Labs	Hyderabad/India
Hetero Drugs	Hyderabad/India

Table 6.5: continued

Company	Town/country
Kopran	Mumbai (Bombay)/India
Lupin	Mumbai (Bombay)/India
Max-India	Delhi/India
Orchid	Chennai (Madras)/India
Sekhsaria	Mumbai (Bombay)/India
Shasun	Chennai (Madras)/India
Wockhardt	Mumbai (Bombay) /India
Angelini	Aprilia/Italy
Antibioticos	Milan/Italy
FIS	Alte di Montecchio Maggiore/Italy
Recordati	Milan/Italy
Zambon	Milan/Italy
LEK	Ljubljana/Slovenia
Krka	Ljubljana/Slovenia
Farmhispania	Barcelona/Spain
Medichem	Barcelona/Spain
Uquifa	Barcelona/Spain
Helsinn	Biasca/Switzerland
Orgamol	Evionnaz/Switzerland
Siegfried	Zofingen/Switzerland

During the 1980s a further complication to this 'them' and 'us' situation arose through government action. Although the creation of the generic industry in certain pharmaceutical markets (most importantly in the US) did not directly involve the founding of any new bulk drug companies, it created new, very profitable demand for independent producers. The US government decided that it needed to create credible competition to the major innovative companies, so that cheaper copies of off-patent drugs could be made available post-patent expiry. The thinking was that, without government assistance, the entry barriers to competition were prohibitively high for competitors. The reason that these entry barriers were high was that satisfying government legislation on the provision of regulatory packages (on toxicology, oncology, efficacy, etc) was so costly that the inventing companies' monopolies were becoming endless. And so another layer of legislation was applied, proving that there is only one way in which a bureaucracy reacts towards its own absurdities: by instituting more layers of bureaucracy! This legislation was passed in 1984 (against bitter opposition from the major pharmaceutical companies) and was named after its proponents, senators Waxman and Hatch. It made the business of launching new, generic copies of a pharmaceutical a highly attractive proposition:

- As long as the new formulation possessed similar bioavailability (in other words, administration of the copy medicine must generate the same concentration of active ingredient at the site of action as the original or branded drug), then no

further proof of efficacy, toxicology, etc. was needed. The new applicant would merely make 'reference' to the original drug data (lodged with the US Food and Drug Administration, the FDA). This saved millions of dollars in development costs for each application.

- An independent supplier of bulk active could be used, so long as the supplier submitted a dossier (a drug master file, DMF) describing its manufacturing operations (a type I DMF) and its manufacturing process (a type II DMF). This ensured that the supply of bulk active could not be withheld, due to the only source (the inventing company or its licensee) refusing to supply it.

A further enhancement to this stimulant to competition was enacted the next year, following a court case between Roche (the Swiss major) and Bolar (a US generic company):

- Development of the generic copy could be undertaken before the patent expires, so long as the material produced was not sold before the patent expired. This ensured that competition to the patented product appeared the day after the patents expired (rather than two to three years later).

The creation of the US generic sector (now valued at nearly a third of the total market, around US$30bn) enabled a new generation of entrepreneurial companies to spring up in the US. Mainly manned by ex-employees of the majors, they set up virtual companies before the term was coined. Their bulk pharmaceutical requirements were sourced almost only from Italy or Spain. (The companies in these countries were already producing the same material for the non-aligned sector of the global industry. They were therefore the logical choice, particularly since their processes were usually identical to the originators and so offered less chance of problems with impurities and physical form.) Specialist firms set up contract tableting and other finished dosage production facilities, which produced and packaged the generic product. The role of the generic companies was to develop and market the copy products. Given the size of the US market and the continuing stream of successful products that have expired since the creation of the US generic market, it is little wonder that the multinational companies have now purchased the independent generic producers (with one or two noteworthy exceptions). The industry still suffers a major shock when the patents on a US product expire, but the loss of revenue is now mainly kept within the industry. Nevertheless, from the perspective of the pharmaceutical fine chemical industry, this initiative has helped to expand the scale of the independent sector quite considerably, as well as creating a whole new sector – bulk pharmaceutical manufacturing – that was much smaller prior to Waxman-Hatch.

Over the past ten years, there have been important changes to the global product patent regime, resulting in an increasing shift of production of both intermediates and active ingredients towards Asia. The favourable situation in Italy and Spain, whereby these countries could openly supply bulk drugs that were still under patent in Europe, was 'rectified' by new patent legislation. In addition, China and India have both acceded to the international patent agreements, albeit with relatively long periods of adjustment (in the case of India, full adherence only begins in 2005). The Italian industry has restructured its operations and is now much more closely integrated with the rest of Europe's fine chemical industry. Spain is still lagging behind, but will eventually conform more closely to the rest of Europe's fine chemical industry.

During this period of transition, the production of bulk pharmaceuticals by independent fine chemical companies in the US and Northern Europe has expanded. Many reasons for this change may be evinced, but the main driver has been the maturation of the global pharmaceutical industry. Pressure to cut costs and changes in government regulations requiring local manufacture has prompted the major innovative companies to close or sell surplus manufacturing capacity. They have then outsourced (bought bulk pharmaceuticals from third party producers) their bulk requirements for non-strategic (older) products or bought from the plants sold to fine chemical companies. In Table 6.6, some examples of bulk pharmaceutical manufacturing acquisitions by fine chemical intermediate producers are presented.

Table 6.6: Selected acquisitions by fine chemical producers of bulk pharmaceutical units

Acquiring company (fine chemical)	Disposing company (pharmaceutical)	Site of bulk pharmaceutical plant
Archimica, UK	Roche	Springfield, IL, US
Catalytica, US	Glaxo Wellcome	Research Triangle, NC, US
Chirex, UK	Glaxo Wellcome	Annan, Scotland
DSM Fine Chemicals, the Netherlands	Bristol-Myers Squibb	Regensburg, Germany
Farmhispania SA	SmithKline Beecham	Zaragosa, Spain
Irotec, Ireland (part of Cambrex, US)	Boehringer Ingelheim	Irish Fher, Cork, Ireland
Laporte	Sanofi, France	Francis, Milan, Italy
Laporte (owns Inspec, the acquirer)	Boots (part of Knoll)	Technochemie, Dossenheim, Germany
Lonza , Switzerland	SmithKline Beecham	Conshohocken, PA, US
PPG, US	Jouveinal, France	SIPSY, Avrille, France
PPG, US	Jouveinal, France	Plaistow Chemicals, Cork, Ireland
Zeeland Chemicals (Cambrex, US)	Searle, US	Chicago, US

There is an increasing trend for US and European pharmaceutical companies to purchase bulk active ingredients from Asia (outside of Japan). Exports from this region started with the export of older commodity products such as aspirin and acetaminophen (paracetamol). More recently, antibiotics such as penicillins and cephalosporins (important for the local Asian markets) and newer actives such as ibuprofen, ranitidine and captopril, became available as the producers improved their performance. The region has now begun to produce even the newest patent-expired bulk drugs. More will be said about Asia in the next section.

CHARACTERISTICS OF MAJOR PRODUCING REGIONS

In the following notes, a brief review of the main PFC producing regions is presented. It is beyond the scope of this report to describe in detail how the pharmaceutical fine chemical industries of the world's major regions have evolved, but it is helpful to understand something of the history and current structure of the industry around the world.

Europe

The first modern pharmaceutical companies were set up in Europe during the 19th century, as described in the introductory chapter. Large-scale production of bulk actives commenced with the extraction of natural products from medicinal herbs. A major stimulus was presented to the development of the modern industry by the discovery and production of penicillin just before World War II. A number of the world's major multinational companies became involved in penicillin production, including Glaxo and Beecham (in the UK) as well as Eli Lilly, Bristol Myers and Pfizer (in the US). From early beginnings, these antibiotic production-based companies first expanded into the production and sale of other antibiotics, then semi-synthetic antibiotics and then into synthetic drugs. Germany and France quickly caught up during their post-war reconstruction and two of the big three German chemical companies, Bayer and Hoechst, rapidly became major forces in the new industry, quickly overtaking the pre-war giants Boehringer Soehne and Merck of Darmstadt. In Switzerland, Sandoz and Geigy, with Roche (which evolved from a nineteenth century medicinal product extraction company), achieved a leading position in the industry for the Swiss industry by bringing skills learned from their chemical manufacturing backgrounds. France's Rhône Poulenc moved into pharmaceuticals on the back of a 1933 UK acquisition: May & Baker, based near London, a company which had made a name for itself by discovering the sulphonamide anti-infective drugs. These companies, together with newer entrants (among them ICI, which came later to pharmaceuticals) maintained a tradition of back-integration and self-reliance. Their chemical manufacturing operations were substantial businesses in their own right and, particularly in the case of the Germans and the Swiss, they generated substantial sales of fine chemicals that were sold to other producers in Europe and elsewhere. Gradually, as the demands on the chemical skills of these groups became ever more complex, smaller independent companies sprang up. These focused on the specialised technologies, and those which demanded greater skills or risks than the usual chemical transformations.

The rise of the US as a major trading power exposed the European companies to new concepts and business practices, such as marketing, in the development of a successful pharmaceutical business. US companies began to influence the way the major European companies were structured and run, particularly in the UK. By the 1960s, the products of these European and US majors were being sold around the world. With the exception of the extraordinary rise of Japan to become the world's second commercial power (and the world's second biggest pharmaceutical market) this situation did not really change, until the end of the 1980s. By that time, many countries in the rest of the world (particularly in Asia) had begun to flex their economic muscles. Their desire to be self sufficient in medicines, once achieved, evolved into a desire to supply export markets.

The European and US multinationals continue to enjoy commercial dominance over the rest of the world in the pharmaceutical industry, but at an increasing cost. Greater concessions are demanded by local governments as a *quid-pro-quo* for allowing the big drug companies to sell into their markets. Development of new pharmaceuticals is now under way in China, Korea and India as well as Japan, where many new products have been discovered during the past 25 years (and they are not all just 'me-too' copies).

Throughout most of this period in Eastern Europe, the dead hand of communism stifled the development of the Czechoslovak and Hungarian pharmaceutical companies which were also formed around the turn of the century (such as Slovakopharma, Gedeon Richter, Chinoin, Alkaloida and Egis). The inventiveness of these groups was severely curtailed by the economic system under which they were governed during the post-war period. After the fall of communism in 1989–90, progress in regenerating these businesses has been hampered by a lack of real help from the West, absence of sufficient capital for investment and a flight of talent.

At the turn of the 20th century, the European pharmaceutical fine chemical industry continues to lead the world. It has had to respond to many threats and has done so by a process of continuous change, more rapidly in some countries than others, but generally quite successfully. The position of those more successful companies that supply the pharmaceutical industry has become stronger as they have given up producing lower priced, commodity products and invested in newer technologies that will be needed for the drugs of the 21st century. Companies that have tried to resist change, have eventually had to suffer catastrophic change as a result. The experiences of major companies such as ICI, Rhône Poulenc and Hoechst have shown that, however large the company, the ultimate fate will be far worse if the necessary business restructuring is put off for too long.

US

Much of what has been said for Europe, also applies to the US, but with several important differences. The chemical industry in the US owes its routes to petrochemicals rather than fine chemicals (with the exception of Eastman Chemicals, which developed an unusual coal-based chemical intermediates business). The natural progression from fine chemicals to pharmaceuticals seen in Europe did not occur in the US, where the production of petrochemicals and chemical intermediates has proved to be a less successful platform for moving into the production of fine chemicals and pharmaceuticals. The US pharmaceutical industry was founded mainly through three major routes:

- The forward integration of pharmacies into manufacture and drug discovery. Eli Lilly and Smith, Kline & French (now absorbed into SmithKline Beecham) represent prominent examples of this route.

- Through the development of fermentation antibiotics: Abbott Laboratories, Pfizer, Squibb and Bristol Myers are examples.

- Development of German companies seized during the two world wars: Sterling Drug (based upon Bayer assets) and Merck (set up by an offshoot of the founders of E. Merck) are examples.

Only one US chemical company has succeeded in setting up a major pharmaceutical operation (Cyanamid), although Marion Laboratories (now part of Aventis) was previously owned by Dow Chemical.

As a result of the differences in US business philosophy and this different industry evolution, the large US pharmaceutical companies have been less interested in back-integration and more responsive to the demands of the market. The US has been overwhelmingly the powerhouse for the generation of new medicines globally since the 1950s, with Europe taking number two position. The opposite has been true for the pharmaceutical fine chemical industry. Even before the creation of the US generic industry, several major US companies outsourced the majority of their bulk pharmaceutical requirements. American Home Products (prior to its acquisition of Cyanamid) and Johnson & Johnson are good examples.

Asia

Japan

There is the main pharmaceutical industry of Asia – in value terms, at least. Its rise was just part of a general increase in prosperity that resulted from the post-war reconstruction of the country. Its characteristics are interesting and the huge size of its market (US$34bn in 1998) in relation to its population (around 130 m) is the result of a peculiarly Japanese healthcare system. Without going into enormous detail, one very important reason for this situation is that Japanese doctors are not paid for their time, but are rewarded mainly by selling pharmaceutical products. Little wonder then that the average Japanese patient leaves the doctor's surgery with five prescriptions! The Japanese government sets prices for new drugs every two years, generally lowering the prices of existing products by a significant margin. This has led the Japanese pharmaceutical industry to introduce new variants on existing active ingredients on a regular basis, so as to maintain the value of their sales. No more clearly can this be seen than the huge range of 'me-too' antibiotic products available in Japan. 'Me-too' products contain active ingredients which differ by non-important changes in structure that nevertheless confer, via patent protection, premium prices.

The supply of active ingredients to the Japanese pharmaceutical industry has been, until very recently, a privilege reserved for the Japanese fine chemical industry. This network of hundreds of small companies usually has larger equity holders that are either one of the banks or giant trading houses (Mitsui, Marubeni, Mitsubishi, Sumitomo, C. Itoh are the biggest ones) or one of the major chemical companies. They enjoy high prices by international standards (as a result of the high prices of drugs in Japan), which has made it difficult for the Japanese to compete directly outside of the country. However, many do supply the multinational pharmaceutical companies for one or a combination of the following reasons:

- Their technical expertise and quality control is high, so that the customer can have confidence in the product and the back-up service.

- Back-to-back supply arrangements between local pharmaceutical companies and international companies, as the result of deals to license products.

China

The Chinese share with the Japanese a cultural pre-disposition to use medicines, and the use of allopathic medicine (as Western medicine is often called in Asia) has grown enormously since the 1950s, from when it was introduced as a complement to the more traditional herbal remedies. Through much of this time, Chinese companies were free to set up and operate the production of Western medicines, without reference to the foreign companies that invented them. Generally, the most successful Western pharmaceuticals have been antibiotics, which still account for more than 50% of the Chinese market by value. Finished dosage prices in China are very low compared with the US, Europe or Japan.

The development and production of pharmaceuticals in China is undertaken in a uniquely inefficient fashion as a result of the economic system that has been set up by the communist regime there. Rather than satisfy national demand for a given product, general pharmaceutical factories in each province produce sufficient materials for their own province. Thus, dozens of small operations produce the same finished product, derived from their own captive production of bulk ingredients. There are thus generally at least 50 companies producing any given drug and sometimes many more. With annual capacities a fraction of what could be reasonably considered viable in the West, China has traditionally operated a very inefficient manufacturing industry. An offshoot of this centrally controlled system is the deliberate over-production of intermediates and ingredients by the factories (at zero cost to them, since materials are supplied by the province against pre-agreed budgets). These surplus fine chemicals have been exported (by third party traders) in order to obtain hard currency, needed to buy materials unavailable in China. In this way, the fine chemical producers in Europe and the US have had to compete with fine chemicals sold at or below cost.

During China's gradual transition to a more capitalist economy, the competition from China in export markets has become considerably tougher, as entrepreneurs (particularly in the Southern provinces around Shanghai) set up large scale manufacturing plants to supply China and export markets. However, in the medium term the number of fine chemical producers in China will be drastically reduced and the industry will become more cost-conscious than has been the case hitherto.

India

The situation there is very different, although this second Asian giant is often lumped with China when people from US and European fine chemical companies complain about the 'Asian threat'. Nevertheless, there are similarities in the structures of the pharmaceutical industries in the two countries. Both countries have a large number of pharmaceutical companies that produce even very new inventions without license from the innovators. Antibiotics and nutritional supplements are important sector, and drug prices are very low compared to the 'West'.

The bigger pharmaceutical companies are back-integrated in the manufacture of bulk actives, although many source intermediates domestically or from abroad, particularly from China. The smaller drug companies source bulk actives from the many smaller fine chemical operations set up to produce fine chemicals for the domestic and overseas markets. Mainly based in the five major fine chemical and pharmaceutical manufacturing regions around Delhi, Hyderabad, Mumbai (Bombay), Ahmedabad and Bangalore, India's thousand-plus companies have built up a formidable industrial strength, particularly since 1985.

Unlike China, India was an imperial colony at the end of the last world war (just) and so the emerging pharmaceutical companies (particularly British companies such as Beecham, Glaxo and later ICI) developed their business in India as part of their international operations. Drugs were priced at international levels, leaving the majority of the Indian population without realistic access to modern therapies. The patent regime and the law was identical to that in Great Britain and so no copy products could be produced at low cost (as was then practiced by *all* other Asian countries, as well as some European countries, such as Italy). Several Indian-owned ('indigenous') companies had been set up even before independence and they eventually (in 1971) persuaded the government of Indhira Ghandi to repeal the country's product patent laws, thus allowing the local companies to produce new drugs at a fraction of the price being asked by the multinationals. ICI's propanolol and Beecham's ampicillin were both specifically named in her speech in Geneva, in which she defied the West with the statement that no government should be able to 'legislate against life'. An interesting parallel now exists in South Africa, where the new government is threatening to repeal product patents in order to gain access to low cost treatment for AIDS (the African pandemic of AIDS is threatening to undermine the future welfare of many countries in the region). Many multinationals (particularly the US-based ones) eventually withdrew from the Indian market, as a result of this action. The Indians have 'called this multinational bluff', however, and have been able to build up an impressive infrastructure to supply both the majority of its own needs and those of an increasing proportion of the Asian, South American and African export markets. Both finished drugs and bulk actives are exported.

Today, the industry has reached a watershed, having accepted the reintroduction of product patents. It is the judgement of the government and its advisers that India has more to gain than to lose by acceding to the West's demands. One third of its people still have no access to modern drugs, but from an Indian point of view, the country's strategy has largely paid off. Most other Asian countries have not developed their own industries and have, as a result, become dependent on multinational companies (that sell at high prices that many of the people cannot afford) or WHO (which can only supply older, cheaper drugs that are often inadequate).

India's pharmaceutical fine chemical industry is still going through a painful re-adjustment to the structural changes that continue to occur as a result of overcapacity and the evolving patent regime. In the medium term, the number of small producers is likely to decrease to perhaps a hundred or so medium-sized companies. The major multinationals (MNCs) are beginning to reassert themselves again, although finished drug prices still remain low by international standards. Glaxo, which never left India, has remained the country's number one pharmaceutical company for the past 15 years. It is generally said that, unlike most other MNCs, Glaxo is considered by the local population to be a local company. Perhaps this is the result of Glaxo India having always been run relatively independently of the parent company.

Technically, India is far stronger than China and Indian chemists have demonstrated the ability to develop efficient chemical processes, in spite of problems with sourcing intermediates. They have achieved this both by commercial means and by developing alternative processes that get around the lack of a critical intermediate. One drawback in the conduct of the country's fine chemical industry is the poor control of proprietary secrets. This has even been actively encouraged by the government, which insists that the results of all government-funded research must be offered on a non-exclusive basis. A much graver problem is that many individuals are willing to divulge processes to competitors when they leave jobs. This happens throughout the

world, of course, with many unscrupulous individuals quite happy to sell their employer's secrets. In India, however, the problem is worse than almost anywhere else, where useful technology is actively developed.

As India prepares for fall product patent protection, the medium-sized bulk pharmaceutical producers have developed business downstream by setting up their own pharmaceutical formulations business (e.g. Cheminor Drugs, Kopran). Smaller companies are either finding major subcontracts or are going out of business.

Rest of the world

Much of the rest of the world derives its pharmaceutical products by importing them directly, or by formulating them using imported active ingredients. From the perspective of this report, these regions are therefore of no great interest.

There are, however, odd exceptions to this general rule, which for the sake of accuracy should, at least, be mentioned.

Korea

In Korea a number of the major conglomerates ('chaebols'), which characterise this country's industrial landscape, have developed pharmaceutical fine chemical development and manufacturing capabilities. Thus LG Chemicals and SK Chemicals have both set up technically competent operations in this area. Smaller players also exist, such as Daesang, which produces antibiotic actives. Nevertheless, these are relatively early days for the country's domestic industry and the majority of the pharmaceuticals consumed in Korea are produced in Japan, China or in the West.

Singapore

Singapore has enticed the major pharmaceutical producers to establish chemical manufacturing operations within this small city-state, by offering generous tax concessions. Based on successful models developed in Puerto Rico and Ireland, the bulk production units installed there cannot be really said to be a fine chemical industry in the true sense of the word. Glaxo Wellcome, SmithKline Beecham and Schering Plough are pharmaceutical companies that have facilities in Singapore. A Japanese fine chemical producer, Kaneka, also makes pharmaceutical intermediates in Singapore.

Taiwan

Although it does have a small fine chemical manufacturing industry, the main role of Taiwan within the international fine chemical industry has been to invest in capital projects in China. The Taiwanese trading companies have helped to build up the infrastructure of the industry around Shanghai, in particular. In return, they have been able to trade Chinese fine chemicals around the world, as well as obtain supplies for Taiwanese pharmaceutical companies.

The countries of the former Soviet Union

Russia's pharmaceutical manufacturing industry is small and depends heavily on imports of fine chemicals and active ingredients from India, China and Eastern Europe (principally from Hungary, Slovenia and the Czech as well as the Slovak republics). There is little sign of an independent local industry emerging at this time.

PROFILES OF TYPICAL INDUSTRY PARTICIPANTS

In the foregoing chapters, mention has been made of a number of basic strategies by which pharmaceutical fine chemical companies can develop their business. It is helpful to present profiles of some of the more successful examples of industry participants in order that the reader can develop a feel for the industry in greater detail. In Table 6.7, a list of fine chemical companies from which the exemplars have been chosen, is given. It excludes most companies that are pharmaceutical company manufacturing divisions and, for this reason, does not include any Chinese companies. Many smaller companies have been omitted from this list, but most of the important ones are included.

Table 6.7: List of major companies that develop and manufacture pharmaceutical fine chemicals (excluding pharmaceutical company chemical manufacturing divisions)

Company	Location of headquarter
ACS Dobfar	Milan, Italy
Aerojet	Sacramento, US
Ajinomoto	Tokyo, Japan
Albany Molecular	Albany, US
Albemarle	Baton Rouge, US
Allied Signal	Morristown, US
American Remedies	Chennai, India
Angelini	Aprilia, Italy
Antibioticos Group	Madrid, Spain
Archimica (BTP)	Manchester, UK
Ascot Group	UK
Avecia	Blackley, UK
Bachem	King of Prussia, US
BASF	Ludwigshafen, Germany
Bayer	Leverkusen, Germany
Bedoukian Research	Danbury, US
Borregaard Synthesis	Sarpsborg, Norway
Calaire	Calais, France
Cambrex Coproration	East Rutherford, US
CarboGen Laboratories	Aarau, Switzerland
Cascade	Reading, UK
Catalytica	California, US
Celgene	Warren, US
Chemagis	Tel Aviv, Israel
ChemDesign Corp.	Fitchburg, US
Chemi	Milan, Italy
Cheminor Drugs	Hyderabad, India
Chemo Iberica	Madrid, Spain

Table 6.7: continued	
Company	**Location of head quarter**
ChemSyn Labs	Kansas, US
Chiral Technologies Inc	Exton, US
ChiRex	Stamford, US
Clariant	Basel, Switzerland
Cognis (Degussa-Hüls)	Frankfurt, Germany
Contract Chemicals	Merseyside, UK
CU Chemie Uetikon	Lahr, Germany
Daicel	Tokyo, Japan
Daiso	Osaka, Japan
Dead Sea Bromine	Israel
Delmar Chemicals	Quebec, Canada
Dextra Labs	Reading, UK
Dow Contract Manufacturing	Midland, US
DSM Fine Chemicals	Heerlen, the Netherlands
Dynamit Nobel	Troisdorf, Germany
Eastman Fine Chemicals	Kingsport, US
Elf-Atochem	Paris, France
EMS-Dottikon	Dottikon, Switzerland
Erregierre	San Paolo d'Argon, Italy
Expansia	Aramon, France
F2 Chemicals	Preston, UK
Fabricolor-Vuos	Semtin, Czech Republic
Farchemia	Treviglio, Italy
Farmhispania	Barcelona, Spain
Finorga	Chasse, France
FIS	Vincenza, Italy
FMC – Lithium Division	Gastonia, US
Hetero Drugs	Hyderabad, India
Hickson & Welch	Castleford, UK
Hodogaya Chemical	Tokyo, Japan
Hokko Chemical	Tokyo, Japan
Hovione	Lisbon, Portugal
ICM	Milan Italy
Ihara Chemical	Shizuoka, Japan
IPCA	Mumbai, India
ISP Fine Chemicals	Charlotte, US
Kaneka	Osaka, Japan
Katwijk Chemie	Katwijik, the Netherlands
Kemira Fine Chemicals	Helsinki, Finland
Kopran	Mumbai, India

Table 6.7: continued	
Company	**Location of headquarter**
Kuraray	Tokyo, Japan
Kyowa Hakko	Tokyo, Japan
Labochim	Milan, Italy
Laporte Fine Chemicals	Teesside, UK
Lonza	Basel, Switzerland
Macfarlan Smith	Edinburgh, Scotland
Mallinckrodt Chemical	US
Miteni	Milan, Italy
Mitsubishi Chemical	Tokyo, Japan
Mitsui Chemical	Tokyo, Japan
Moehs	Barcelona, Spain
Neuland Labs	Hyderabad, India
Orgamol	Evionnaz, Switzerland
Oxford Asymmetry	Oxford, UK
Oxychem	Dallas, US
Pharm-Eco Labs	Lexington, US
Phoenix Chemicals	Merseyside, UK
PPG-SIPSY	Pittsburgh, US
Procos	Cameri, Italy
Quality Chemicals	Jackson, US
Quimica Sintetica	Madrid, Spain
Raschig	Ludwigshafen, Germany
Reilly Chemicals	Indianapolis, US
Rhodia	Paris, France
Sicor de Mexico	Lerma, Mexico
Siegfried	Zoffingham, Switzerland
SNPE	Toulouse, France
Sugai Chemical	Osaka, Japan
Sumitomo Seka	Osaka, Japan
Syngal-Quchem	Belfast, UK
Synthetech	Oregon, US
Tessenderlo Chemie	Brussels, Belgium
Toray Industries	Tokyo, Japan
Torcan Chemical	Ontario, Canada
VIS Farmaceutici	Padova, Italy
Wacker Chemie	Munich, Germany
Wyckoff Chemical	Michigan, US
Zambon Group	Milan, Italy

Business success is generally measured by financial criteria, such as sales or profitability. However, from the perspective of the industry analyst, other factors are also important. A production company's track record in developing new technologies is also important, since this can underpin its performance in the long term. Manufacturing industries are, by their nature, less rapid in delivering cash benefits to their shareholders, but patient investors often look for longer term benefits, such as steady income growth. A sound technological base is vital for sustained success in the development and sale of pharmaceutical fine chemicals. If the reader's interest is in making judgements on suitable suppliers of PFCs, then financial criteria become even less important. Unique skills in developing complex syntheses, coupled with a demonstrable ability in transferring lab processes to the plant would, for example, stand high on the agenda of a pharmaceutical buyer or a marketing representative looking to exploit these skills through his/her organisation.

One final comment is also necessary at this point. Success or failure in the fine chemicals business is fundamentally driven by the people involved in developing, implementing and maintaining the quality of the company's products. This is in contrast to the chemical industry, where the introduction of new technologies is a noteworthy event, the main competitive advantage is created by the scale of a company's capital investments. *All other things being equal*, nothing else really matters.

In the fine chemicals industry, the key skills are much more to do with how the people in the company are able to tailor their skills and resources to meet their customer's needs. Speed of response, ingenuity, access to reliable market information on suppliers, competitors and customers are very important for success. Well-run laboratories, pilot plants and production units are essential, but not crucial, elements for success. This latter point may seem surprising, but the reality is that much spare capacity exists and many companies have developed successful businesses by sub-contracting manufacturing to their more pedestrian competitors (attempts to fill empty capacity as a successful strategy tends to be a much tougher option). Examples of these types of companies will be presented later. The basic success criteria used for the selection of a suitable supplier by a customer are one or a combination of the following:

- Sustained ability to develop and supply new intermediates to the pharmaceutical industry.
- Success in identifying and manufacturing active ingredients to a high standard of quality.
- Ability to develop novel syntheses that can be scaled up and run on a production plant.
- Leading role in introducing new technologies into the industry.
- Continuing sales organic growth, with sustained profitability.
- Reputation for delivering high-quality service at competitive prices.

In selecting representative successful companies to describe in greater detail, it has been necessary to sub-divide the list provided above into companies that have broadly

similar capabilities/ backgrounds. These categories are listed, with typical examples, in Table 6.8.

Table 6.8: Pharmaceutical fine chemical companies sub-types (further divided by relative size of PFC sales within each category)

Sub-type	Large	Medium	Small
All-round	DSM Eastman Lonza Laporte	Archimica Cambrex ChiRex	
Active ingredients	Antibioticos Cheminor Drugs[a] Catalytica Sicor de Mexico	ACS-Dobfar Farmhispania Kopran[a] Macfarlan Smith	Cascade ChemSyn
Custom synthesis	Borregaard Siegfried	Pharm-Eco Omnichem[b] Synthetech	ChiroTech (Ascot) Daiso Oxford Asymmetry
Toll manufacturing	Hickson & Welch ChemDesign Dow Contract Mfg	Calaire Orgamol Sugai Chemicals	Syngal
Raw material focus	Tessenderlo Reilly Chemical SNPE	Oxychem Dead Sea Bromine FMC-Lithco	
Technology focus	Avecia Clariant Rhodia	Ajinomoto Kaneka PPG-SIPSY	Kuraray Phoenix Chemicals

[a] Has also recently developed a formulations business. [b] Owned by Ajinomoto.

The captive chemical development and production divisions of major multinational pharmaceutical companies have been excluded from the final selection, as have the fine chemical groups within large chemical companies. In both cases, these types of operations are generally shielded from the true rigours of the marketplace, although playing a significant role within the overall industry. The operations are less transparent than most independent companies and this makes an assessment of their real fine chemical business more difficult.

The companies profiled in the next few pages are listed in Table 6.9. It is difficult to pick a small representative group from such a diverse mixture of companies, but good examples of the main types of operations are illustrated. After each major profile, companies operating within similar parameters and of similar size are listed in order to help the reader build up a useful introductory impression of the main contours of the fine chemical landscape.

Table 6.9: Pharmaceutical fine chemical companies profiled		
Company	**Location of headquarter**	**Specialisation(s)**
DSM	The Netherlands	Pharmaceutical fine chemicals
Lonza	Switzerland	Broadly-based capabilities
Cambrex	US	Broadly-based capabilities
Kaneka	Japan	Chirally pure pharmaceutical intermediates
PPG-SIPSY	US	Custom synthesis, asymmetric synthesis
Cheminor Drugs	India	Bulk pharmaceuticals
Farmhispania	Spain	Bulk pharmaceuticals
Pharm-Eco	US	Custom synthesis, cGMP units
ChiroTech	UK	Chirally pure pharmaceutical intermediates

DSM fine chemicals

DSM is a large chemical company, based in the Netherlands, whose board decided to move into fine chemicals in the early 1980s. Organic growth, based on its expertise in gas phase chemistry and benzoic acid from toluene technology, eluded the company. It decided to grow by acquisition, which it has since pursued with a great deal of success, achieving a number one sales position in the industry after around 15 years and nine major investments. The most important acquisitions during this period have been (key activities of the acquired company are shown in parentheses): Andeno (custom synthesis and chiral resolutions), Deretil (antibiotic side-chains), Bristol-Myers Squibb plant in Germany (bulk pharmaceuticals), Chemie Linz (chemicals from maleic anhydride, ozonolysis) and Gist Brocades (bulk antibiotics and biotechnology). Andeno, a successful custom synthesis and toll manufacturing specialist based in southern Netherlands, was the bedrock upon which DSM built its fine chemicals business. With the exception of the company's joint ventures in India, DSM's continuing expansion has still not led to new operations outside of Europe. To date this does not appear to have limited its success, although the company maintains an ambition to make a US purchase. The inflated prices asked for US companies is probably the main reason why DSM has still to secure the elusive US plant investment.

With total sales of around US$1.6bn in 1998, of which over US$1.1bn were for products destined for the pharmaceutical industry, DSM Fine Chemicals is the clear fine chemical industry leader in terms of revenue. However, with around half of this figure being for 'anti-infectives' (mainly intermediates for penicillins and cephalosporins), the company's profits have continued to come under pressure, as Indian and Chinese producers take market share and force down prices. Other intermediates (defined as fine and speciality chemicals by DSM) continue to sell well under the terms of long-term contracts, with homochiral intermediates being a major strength.

A summary of DSM Fine Chemical's constituent parts (which retain a semi-autonomous identity), with some of their major products/technologies is listed in Table 6.10.

Table 6.10: Components of DSM Fine Chemicals

Company	Plant locations	Products and technologies
DSM Speciality Organics	Geleen, the Netherlands	HCN, benzaldehyde, benzoic acid
Andeno	Venlo, the Netherlands	D-(-)-phenylglycine, S-AMPA, chiral resolutions, custom synthesis
Holland Sweetener (jv with Tosoh of Japan)	Maastricht, the Netherlands	Aspartame
La Plainea	Geneva, Switzerland	D-(-)-4-hydroxyphenylglycine, erythromycin salts
ACF Chemie	Maarsen, the Netherlands	Iodides (part owns Peruvian mines), quinine
Bristol-Myers Squibb plant	Regensburg, Germany	Bulk and finished pharmaceuticals
Chemferm	Amsterdam, the Netherlands	JV with Gist to develop antibiotics
Chemie Linz	Linz, Austria	Basic intermediates, fine chemicals
Deretil	Barcelona, Spain	Antibiotic side-chains
Gist brocades	Delft, Netherlands	Baking enzymes and antibiotic fine chemicals and enzymes

[a] Sold to Akzo-Nobel in 1998.

DSM Fine Chemicals has the following strengths as a producer of fine chemicals:

- Good range of well-developed technologies, coupled with proven skills in custom synthesis.
- Through the company's chemical operations, the resources and cash to take the longer term view on recovering capital investments.
- Strong position in several key areas of the pharmaceutical fine chemical intermediates business.

DSM Fine Chemicals has grown quickly by acquisition, however, and as with many conglomerates, its parts do not always act 'in concert'. Central decision making can be slow, and it has been the case that poor performing operations have not been dealt with sufficiently quickly.

Companies with similar profiles

From the point of view of the chemical industry, DSM is one of the more successful 'downstream' investment stories, with many other petrochemical majors having fared far worse. Examples of similar, but less successful forays into fine chemicals by major chemical companies include most oil companies (BP, Shell, ENI, Occidental)

and many petrochemical and commodity chemical companies (examples: Atochem, ICI, BASF, Union Carbide).

Lonza AG

Many consider Lonza to be the company to beat in fine chemicals. It has been a top performer in this sector over the past 25 years and has consistently developed its technology and manufacturing base to keep it at the forefront of the industry. The company traces its roots to the manufacture of gunpowder and calcium carbide by the original Lonza, named after the river by which the first plant was built in 1897. Today, it has a huge capital investment in its main R&D and production centre in Visp, located in the picturesque Swiss canton of Valais. After being acquired by Alusuisse in 1974, a strong period of organic growth, coupled with selected acquisitions (in biotechnology and pharmaceutical active ingredient plants), Lonza's sales reached US$1.2bn in 1998. The majority of this turnover is for sales into the pharmaceutical industry, but Lonza also has a strong presence in the supply of chemicals used to make agrochemicals, dyestuffs and polymers. The company has recently been spun out of Alusuisse, following the merger of its parent with two other of the world's major aluminium producers, Alcan and Pechiney. It has announced that it is moving its headquarters from Basel to Zurich.

Lonza combines an unusually broad technology base in chemical intermediates (diketene, hydrogen cyanide, (small scale) phosgenations, hydrogenations up to 100 bar and a variety of oxidations), with a strong capability in custom synthesis. Based in Fair Lawn, New Jersey, US, the US headquarters of Lonza Inc. was the first in a succession of US acquisitions that have enabled the company to operate across the continent.

A number of acquisitions have allowed the company to establish a strong capability in biotechnology, split into Lonza Biologics (based in Slough, UK, making recombinant proteins from mammalian cells and monoclonal antibodies) and Lonza Biotec, based in Visp (Switzerland), Kourim (Czech Republic), Los Angeles (US) and Guangzhou (China), which produces fine chemicals by fermentations and enzyme-catalysed reactions (biotransformations).

Of the larger fine chemical companies, only Lonza has achieved its size mainly by organic growth. It has been aided substantially in this by the special relationship it has enjoyed with the two (once three) Swiss majors, Roche and Novartis (Ciba-Geigy and Sandoz). Lonza has been a major proponent (and supplier) of outsourcing services via special relationships, but these have worked better in Switzerland and Germany than elsewhere, where Lonza's sure but slow approach has not always been what customers required. The company enjoyed 'preferred supplier' status with SmithKline Beecham for a while. This was started following its acquisition of an SB plant in Pennsylvania, US, but more recently the realtionship has become strained. In other companies, such slowness has led to sluggish business performance, but to be fair to Lonza, the company has overcome this disadvantage of size by consistent performance, investments in new technology and a professional approach to marketing (often lacking in the 'technology-push' fine chemical industry).

Eastman Fine Chemicals

Eastman Fine Chemicals, although spawned by a major chemical company, has established a similar approach to developing its business, although its activities in

pharmaceutical fine chemicals are not so well advanced. Its new Hong Kong GMP facility demonstrates the company's commitment to this industry sector and its biotechnology JV, Genecor, highlights its desire to keep abreast of new technologies.

Cambrex Corporation

Established in the mid-1980s, Cambrex is probably the first example of a fine chemical conglomerate set up by investors to exploit the synergies obtained by combining medium sized manufacturers, with relatively poor financial management records, into a single group. Averaging at least one acquisition every year, Cambrex has grown into a (somewhat) sprawling conglomerate of semi-independent companies, that have tight central financial control. More recently, efforts have been made to use the technical and strategic synergies of the group more effectively, but these initiatives have still to bear fruit. By combining the compatible plants under a common capability umbrella, Cambrex has begun the process of integrating the marketing and technology development effort. Three groups have been established, broadly reflecting the target customers: pharmaceuticals, biotechnology and specialty (performance) chemicals. Cambrex's combined sales in 1998 were around US$465m (approximately US$260m of which were sales of fine chemicals for pharmaceutical applications). In Table 6.11, the constituent parts of Cambrex are listed, with locations and specialisations of each company shown. Chiragene was spun out of Celgene and Nordic Synthesis is the name given to the former Nobel Chemicals' fine chemical operations.

Table 6.11: Cambrex Group Companies (1998)

Company	Location(s)	Key technologies/specialisations
BioWhittaker	Maryland, US and Verviers, Belgium	Cell culture and endotoxin detection tests
CasChem	New Jersey, US	Performance chemicals, castor oil
Chiragene Inc	New Jersey, US	Chiral intermediates and bulk actives
Conti BPC	Landen, Belgium	Bulk pharmaceuticals
Cosan Chemical	New Jersey, US	Performance Chemicals
Heico Chemicals	Pennsylvania, US	Organic and inorganic salts, brominations
Humphrey Chemical[a]	Connecticut, US	Performance chemicals for paper making
Irotec	Cork, Ireland	Bulk pharmaceuticals
Nepera Inc.	Harriman, NY, US	Pyridine, picolines and niacinamide, VPC
Nordic Synthesis	Karlskoga, Sweden	Nitrations, cGMP kilo lab, pilot plant
Poietic Technologies	Maryland, US	Human cell culture specialists
Profarmaco	Milan, Italy	Bulk pharmaceuticals
Seal Sands Chemicals	Teesside, UK	Pyridine chemistry, custom synthesis
Salsbury Chemicals	Iowa, US	Animal health and feed chemicals, bulk drugs
Zeeland Chemicals	Zeeland, US	Custom synthesis and toll manufacture

[a] Site recently closed and business transferred to HEICO.

Kaneka

Created by splitting out the spinning division of a larger pre-war company, Kanebo, and renamed Kanegafuchi Spinning Company, Kaneka is now a leading chemical producer, based in Osaka in Japan. Its core competences are the manufacture of PVC and caustic soda, from which it has developed a range of specialist resins, of which MBS is the most well known, and synthetic fibres. These commodities and speciality polymers account for the majority of the company's sales. However, around 20–25% of its income derives from the production and sale of pharmaceutical and nutritional intermediates.

Starting with the establishment of a production unit to produce glutathione, Kaneka's first major success was in developing a novel process for making D-(-)-4-hydroxyphenylglycine (DHPG) using racemic 4-hydroxyphenylhydantoin and a combination of two enzymes (a hydantoinase and a carbamylase) to create the necessary sterochemical purity required for this major antibiotic sidechain (for amoxicillin, originated by (SmithKline) Beecham, but now made by a number of bulk antibiotic producers). Kaneka set up a manufacturing plant for DHPG in Singapore in 1979 and continues to be one of the leading producers of DHPG today.

The company has continually expanded its expertise in the application of enzymes from micro-organisms for the production of fine chemicals catalysts. It now offers a range of commercial intermediates produced in this way. A selection of them is presented in Table 6.12, together with Kaneka's main fermentation products.

Table 6.12: Important homochiral intermediates made by Kaneka

Intermediates made by biotransformations	**Application**
D-(-)-4-Hydroxyphenylglycine	Amoxicillin, cefadroxyl
AL-1, AL-2	Enalapril, lisinopril
(S)-Acetyl-3-mercapto-2-methylpropanoic acid	Captopril
Chiral azetidinone derivatives	Penem/carbapenem antibiotics
(R) & (S)-3-pyrrolidinols	HMG CoA reductase inhibitors
Bulk actives made by fermentations	
Glutathione	
Ergosterol	
Coenzyme Q_{10}	

Kaneka, one of the pioneers in using biotechnology in fine chemical synthesis, has established an enviable reputation for it technological prowess in this field. It has concentrated its efforts on developing many difficult biotransformations, several of which never resulted in commercial sales (usually through the failure of the target drug, but also sometimes because the fruits of Kaneka's pro-active process development were not accepted by the customer that Kaneka had in mind).

A common feature of Japanese fine chemical manufacture is the strong network of small companies that carry out sub-contracts on behalf of the country's larger groups. These include the big trading houses (in the fine chemical industry, Sumitomo Corporation, Mitsubishi Corporation and Mitsui are leading suppliers) and major chemical producers such as Asahi Chemical, Nippon Chemical and Kaneka. By using the capabilities of such specialists, Kaneka has avoided making expensive investments in core technologies, such

as sulphur chemistry, phosgene, fluorine chemistry and many others. There is an interesting parallel here with another company profiled in this chapter, ChiroTech.

PPG-SIPSY

SIPSY was set up in the early 1970s to produce bulk pharmaceuticals for its then owner, Jouveinal, a medium-sized French pharmaceutical company. In order to maximize its return on capital, SIPSY began offering its services to third party customers from 1979–80 onwards. Progress was relatively slow at first, but the company eventually acquired critical mass. It won important contracts to produce pharmaceutical intermediates that included reductions using lithium aluminium hydride. Extending its technology specialisation through a number of acquisitions, it later became known for its expertise in asymmetric synthesis. It bought the rights to the well-known Sharpless titaniun-catalysed olefin epoxidations, as well as Corey's asymmetric borane catalyst for the stereoselective synthesis of homochiral secondary alcohols from prochiral ketones.

By the mid-1990s, the company's sales had reached approximately the equivalent of US$35m. In 1997, Jouveinal sold the company to PPG, the US phosgene specialist, for a reputed US$150m.

PPG's chemical division had made a name for itself in the fine chemical industry as a producer of phosgene-based fine chemicals. One important contract had been the production of N-benzyloxycarbonylaspartic acid, an intermediate in some processes for the manufacture of aspartame. PPG is, at heart, however, a US specialty chemical company.

Together with other large companies of its type, PPG has made a commitment to becoming a major player in the fine chemical industry. Rather than suggest PPG is a special case, it is more appropriate to say a little about the phenomenon of large US 'specialty chemical' companies within the overall industry.

Brief aside on US specialty chemical companies

The business culture in US manufacturing industry has always been very different from that in Europe. The fine chemical industry, as developed by European countries, has not become established in the US in the same way. Although many small custom synthesis companies have set up to supply small volumes of fine chemical intermediates and many toll manufacturing plants have been built to make fine chemicals under contract, very few of these small companies have become medium or large scale players by a process of organic growth. The reasons for these differences are complex and probably not appropriate for exploration within this current review. The facts are that, until the late 1980s, this was the situation. European companies were able to supply a very high proportion of the pharmaceutical industry's intermediate needs.

During the recession of the early 1970s, business development executives within the chemical industry (in particular, large scale petrochemical or other commodity chemical companies) looked at the European fine chemical companies and asked themselves why so few domestic companies were participating in this 'high value-added' business. Many decided that they should be, before giving themselves an opportunity to tackle answering this intriguing question to their satisfaction. Market reports and business entry studies were commissioned from (often poorly qualified) consultants and, subsequently, major investments made in plant and people. The

results have been extremely patchy, with a number of companies 'losing their corporate shirts'. In Table 6.13, a list of US chemical company investments in fine chemicals is presented, together with a brief assessment on their success to date.

Table 6.13: US specialty chemical companies

Company	Acquisitions/divestments	Comments
Albemarle	Hardwicke Chemicals	Sold unit to MTM (now owned by BTP). Lost a useful unit with good synergies and cashflow
Allied Signal	Riedel de Haen	Inefficient producer of fluorine derivatives, bought from Hoechst
Great Lakes Chemicals	QO Chemicals, US	Rump recently sold off
	Associated Octel	'Cash cow' based on lead tetraethyl was still 'giving milk' until business sold
	Ward Blenkinsops, UK	Moribund plant/business run down under Shell Chemicals
	NSC Technologies	Overpriced unit; within two months of purchase, GLC suing Monsanto (seller) for having charged too much
Occidental Chemicals	Hooker Chemicals	Private sale shortly before serious pollution liability exposed
PPG	SIPSY	Good unit, but sold because it was surplus to the needs of parent company. Too early to judge outcome of this US investment

It is striking that many US chemical company investments simply do not thrive under their new owners, leading to leakage of talent, underperformance and eventually, in some cases, divestment. There are some clear reasons for this type of failure:

- *Overly high expectations:* Fine chemical business development is a medium long-term investment, with relatively high risks, some crucial ones being outside the companies' control. This reality sits ill with the fast returns on capital invested that US companies generally expect. Unilateral declarations of unrealistic sales targets only look good to investors; they are hard to fulfil in the real world of fine chemicals.

- *Culture shock:* Chemical companies are run by people used to the dynamics of the chemical industry; building manufacturing plant is crucial for success, generally the bigger, the better. In fine chemicals, the plant is of secondary importance. What counts is the ability of the technical staff to identify and fulfill the needs of the customer for novel chemical intermediates.

- *Prejudice:* Most customers in the US pharmaceutical industry have an in-built belief in the superiority of the European fine chemical industry, and this will often overcome the obvious strategic benefits of sourcing from a domestic company.

- *Flight of talent:* Smart young men and women in the US (and more recently in the UK) have discovered that making a good living and being involved in producing fine chemicals do not usually go together. Studying law, economics or for an MBA makes more sense than studying for a PhD. More recently, the very successful biotechnology, computer and electronics industries have taken much of the technical 'cream', left after the lawyers, finance and business people have been seduced away.

Although these generalisations may seem just that, they actually hold true in very many cases. This is not to say that medium-sized US fine chemical companies cannot become successful; merely that there are greater barriers to success than might be apparent at first glance.

Having established that PPG's acquisition of SIPSY is a higher than usual risk strategy, by virtue of the generally low success rate of such purchases, it does not mean that this one will not become successful in the medium term. The indications are that the management of SIPSY understands US business practice sufficiently well that they will be able to adapt to the new regime. PPG's own senior management has, apparently, also adapted to the dual cultural shocks of collaborating with a European company and with one that develops and makes very small volumes (by PPG standards) of highly sophisticated fine chemicals.

Much is always made of the synergies available through the acquisition of one company by another. What is a little unsettling in the case of PPG-SIPSY is that the new management lost no time in spending a significant amount of money (on top of the acquisition) in building a pilot unit to make phosgene-requiring pharmaceutical intermediates to cGMP standard. Unless the company has a significant project in mind, this bodes badly for the eventual capital overheads that PPG-SIPSY will need to add to every kilogramme of product made.

Cheminor Drugs

Cheminor Drugs operates as an independent business unit within the Dr Reddy Group, which consists of three main companies: Stangen (pharmaceutical formulations), Dr Reddy's Laboratories and Cheminor Drugs. Total reactor capacity for the group is 1.2 m litres. Dr Reddy established his pharmaceutical and bulk drug operations in Hyderabad during the 1970s, having developed a strong link with Russian research institutes. By transferring and developing technologies from the former Soviet Union, Dr Reddy's was able to develop a successful business in bringing newly invented compounds to the Indian market quicker than many other companies. The resources of the nearby Indian Institute of Chemical Technology were an additional benefit to the group.

Over the years, many individuals have left the company in order to set up their own competing plants, creating in Hyderabad a powerhouse of pharmaceutical technology development and manufacture. Although many of these smaller players have not survived into the late 1990s, several have become significant companies in their own right. Examples include Standard Organics, Divi's Laboratories, Shasun Chemicals & Pharmaceuticals and Global Chemicals (formerly Sumitra, now part of Nicholas Piramal's chemical manufacturing operations).

Cheminor Drugs operates three pharmaceutical bulk active plants, the most important of which was formerly called Globe Organics. It is located in Peddadevula Palli and produces a number of bulk drugs, including ranitidine, diltiazem HCl, famotidine and

naproxen. The processes operated by Cheminor are often based upon basic rather than advanced intermediates. This plant is near Tripuram Mandalem in Andhra Pradesh, approximately 150 km South East of Hyderabad and four hours drive by car. The operations were upgraded in 1996, the final product isolation being brought to a high standard, with separate finishing suites being added for each product. As well as operating to cGMP, these plants have been inspected and approved by European and US regulatory auditors.

In 1997, Cheminor Drugs announced that it was setting up a JV with DSM Fine Chemicals to produce pharmaceutical fine chemicals in India. However, the relationship quickly soured and the initiative was a failure. Current annual sales for Cheminor are believed to total the equivalent of approximately US$40m, a high turnover by Indian standards.

Farmhispania

This medium-sized company is headquartered in Barcelona, Spain. It operates two plants, one in Montmelo, a short distance north of Barcelona, and another smaller unit in Zaragosa. The company develops and manufactures bulk pharmaceuticals for the unlicensed and generic pharmaceutical industries. Over the past ten years, it has established a reputation for technical excellence, particularly in the production of the major ACE-inhibitors, captopril, enalapril and lisinopril. It is a typical example of the small bulk drug producers in Italy and Spain, which have had to adapt their style as the advantages of the originally weak domestic patent regime have been destroyed by the effects of European legal and commercial harmonisation.

When acquired by a new management in 1984, like the majority of its peers, the company operated relatively undemanding technologies for producing its fine chemicals. Many processes would involve no more than a simple condensation or salt production step. The pivotal intermediates would be sourced from specialist intermediates producers based in Europe or Asia, allowing the most profitable step to remain in the hands of the bulk pharmaceutical company. This strategy has had to be modified as the company's business has shifted from unlicensed pharmaceutical producers to European and US generic companies. These customers demand far greater transparency, particularly with regard to the process technology being used to make the bulk product. If the production unit uses a process covered by process patents that are still active in the intended market, the product will usually be unacceptable.

Thus 'non-infringing' processes have become essential for sales into the most attractive markets, where margins are still sufficiently high for successful business. Farmhispania has set up a development team that has invented several original routes, which it has patented. With such a technical advantage, even the originating companies have become interested in discussing supply contracts.

Another big change that has taken place at Farmhispania is the relatively high investment that has had to be made in upgrading the production plants, environmental treatment facilities and the quality control laboratories. This is, again, typical of what companies in Spain and Italy have needed to do to survive the changes of the past ten years.

In Table 6.14 a list of the company's most important commercial and developmental products is presented. Financial data is hard to get for private Spanish companies, but

it appears that a sales turnover for the two sites of around US$35m is a reasonable estimate.

Table 6.14: Major commercial and developmental pharmaceutical actives produced by Farmhispania (1998)

Commercial products	Development products
Captopril	Loratidine
Enalapril maleate	Benazepril
Lisinopril	Paroxetine
Metformin	Valaciclovir
Atracurium besylate	

Pharm-Eco

Pharm-Eco is a leading US custom synthesis company, specialising in the provision of early stage pharmaceutical intermediates to innovative pharmaceutical and 'biotech' (emerging pharmaceutical) companies. Sales in 1999 were in the region of US$20m. Pharm-Eco was previously partly owned by SIPSY and was at that time located in California. It grew its original business by developing syntheses and supplying small quantities of pharmaceutical intermediates, especially for the NIH anti-cancer programmes. The company cut its ties with SIPSY in around 1991–93 and moved to its new premises in Lexington and North Andover, Massachusetts, US.

Pharm-Eco has a joint venture with UOP to develop SMB chromatography as a manufacturing operation for separating racemic mixtures of pharmaceutical actives and intermediates. The 50/50 JV is called Universal Pharma Technologies LLC (UPT) and is run by an independent management. Although this SMB technology has taken longer to commercialise than the competing chiral separation technology, preparative HPLC, the economics of running SMB ought to be advantageous once the scale of operation exceeds 5–10 kg. UPT is beginning to make inroads into the market pioneered by its main third party operator of chiral HPLC, Chiral Technologies Inc. of the US (a Daicel subsidiary).

The company has an excellent reputation for the work it does in pharmaceutical fine chemical development, custom synthesis and analytical development. There are around 36 PhDs, organised into many small project groups. The company has endeavoured to build upon its core strengths and reputation in order to develop a new 'one-stop shop', in which it offers 'milligrammes to tons'. It has extensive lab facilities, a kilo lab and a cGMP pilot unit in North Andover (where UPT has its facilities). The company recently acquired a new, 60 acre site (with help from the State of Massachussets) in Devens. The site was previously owned by the US Ministry of Defense.

The new commercial management has made a commitment to double sales within the next year. Achieving this optimistic target has been underpinned by hiring 45 new employees (mainly technical people) and investment in a new '52-lab' site in Devens. It remains to be seen whether such an aggressive expansion will succeed, but the move has certainly created short-term financial difficulties for the company.

This latter problem does illustrate the main conundrum that small companies face when trying to become medium-sized ones: how to fund a major expansion which will only show a return in the medium term.

ChiroTech

In mid-1999, Cambridge-based Chiroscience PLC divided its operations into a pharmaceutical research company (Chiroscence, now combined with CellTech) and a pharmaceutical fine chemical technology development company, ChiroTech, sold to Ascot Holdings. ChiroTech is the core business of earlier companies operating under the names of Chiros, and before that, Enzymatix. The company has made a name for itself by its ability to devise novel syntheses for the preparation of homochiral pharmaceutical fine chemicals.

Chirotech's business activities can be divided into four units:

- A collaborative R&D service, offered to pharmaceutical and drug discovery companies, to solve complex chirality problems.

- Generic single isomer bulk active pharmaceuticals. The objective here is to develop a superior process to an off-patent drug and then find a partner to produce and market it, thus splitting the profits. The prototype has been dexketoprofen, produced in partnership with the Italian pharmaceutical company, Menarini, the enantiopure isomer being produced by a biocatalytic chiral separation of the racemic ester.

- Production of chiral fine chemical intermediates (custom synthesis) using external contractors for the actual manufacturing, e.g. the company uses Mitchell-Cotts as the sub-contractor for the manufacture of the so-called gamma lactam intermediate for GlaxoWellcome's abacavir.

- Novel synthons for sale to pharmaceutical companies interested in production of novel and unique combinatorial libraries. This does not appear to be well thought out and is an example of what is seen as overall poor commercial direction.

The process for making gamma lactam is patented. It uses an enzyme derived from the fungus that caused the annihilation of the English elm (transmitted by a beetle) in Britain during the 1970s. The production of this fine chemical intermediate was developed by Enzymatix as a multi-outlet intermediate for a new generation of nucleoside analogues in the late 1980s. Eventually just one of the six potential drugs was actually launched onto the market: Abacavir. ChiroTech derives over 50% of its income (which was around the equivalent of US$30m in 1998) from this single product. Although it was originally an exclusive supplier, Lonza is now also supplying the intermediate, after many years of effort to devise a competitive route.

There are about 24 scientists in Chirotech with a wide variety of complementary skills, thus enabling them to tackle any problem in chirality. The group has experience to a wide range of chiral technologies and there is a very skilled in house group of analysts with expertise in all forms of chiral chromatography. The scientists are all under 40 with a preponderance of PhDs and the level of skill and intellectual ability is high. The science base is multidisciplinary and includes chemistry in all its aspects: biotransformations, biochemistry, enzymology, molecular biology and fermentation. The company is, however, relatively weak in process development. It

has made a virtue of this weakness by licensing/sub-contracting the technologies it develops, thus avoiding the need to make investments in expensive fine chemical capacity. By luck rather than by good judgement, ChiroTech has taken advantage of the clear lack of 'brains' (original R&D capability) compared to 'brawn' (fine chemical process capacity) in the fine chemical industry.

Since the company's acquisition in August 1999 by a relatively unknown UK holding company (Ascot Holdings, a PLC with a 1998 sales turnover of around US$320m), this happy situation may have changed. Ascot owns several rather low-tech UK fine and performance chemical companies (Chemoxy, Pentagon and Mitchel Cotts) and how it will successfully integrate ChiroTech into this group remains to be seen.

CHAPTER 7: TECHNOLOGY

BRIEF OVERVIEW OF CHEMISTRY INVOLVED IN MAKING MEDICINAL CHEMICALS

In Chapter 3, an introduction to the basic raw materials and standard intermediates used to produce pharmaceutical fine chemicals was presented. In this chapter, the chemistry used to assemble these building blocks will be discussed and a review of some of the more important technologies described.

The first point to make is that the medicinal chemists employed by the pharmaceutical industry develop novel active ingredients in response to the *discoveries* made by them and their colleagues in pharmacology, biochemistry and genetics. In this context, the concept of 'drug design' is somewhat misleading. New pharmaceutical actives are developed using a combination of science and art, with a fair amount of craft thrown in. The object is to identify molecules that are able to effect a change in the chemical interactions present in living organisms. The biochemicals that Nature uses are shuttled around cellular factories according to an apparent 'design' that possesses a degree of sophistication that has resulted from millions of years of trial and error (evolution). Man's attempts to change the outcome of the status quo (be it a malfunction, infection or toxic attack) are actually comparable to opening walnuts with a sledge hammer. The technique produces results, but can hardly be said to be ideal. Collateral damage created by the drug therapy is rectified by the body's own repair mechanisms, which are highly effective and remarkably versatile.

This analogy to drug therapy is slightly less true than it was earlier in this century, but man's degree of ignorance about the workings of the human body remains profound. Nevertheless, over the past fifty years, quite a number of such 'sledge hammers' have been found which do a creditable job. These compounds constitute the basis of the physician's armoury of pharmaceutical substances and many will no doubt survive into the next century.

In order to illustrate the chemistry involved in producing these pharmaceutical fine chemicals, a selection of important pharmaceutical compounds has been made on the basis of their US production volumes and values. Table 7.1 lists these compounds.

Table 7.1: Leading pharmaceutical actives by value and volume	
Top drugs by value	**Top drugs by volume**
Omeprazole	Paracetamol (acetaminophen)
Fluoxetine	Ibuprofen
Erthyropoietin-alpha	Lactulose
Loratidine	Pseudoephedrine
Ethinylestradiol	Amoxicillin
Atoravastatin	Guaphenisin
Sertraline	Sulfamethoxazole
Lansoprazole	Cefalexin
Amlodipine	Iopamidol
Paroxetine	Cholestyramine
Amoxicillin	Penicillin V
Lisinopril	Cimetidine

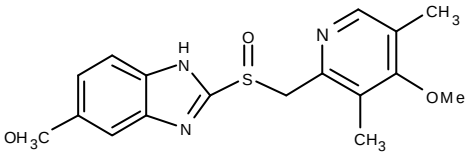
In Figures 7.1 and 7.2, the structures of some of these leading compounds are shown, illustrating their diversity. Drugs that sell in larger volumes tend to be older compounds that have lower specific activities. They also tend to be simpler compounds, often without complex three-dimensional structures. Exceptions, such as lactulose, are based upon cheap fermentation-derived chemicals (lactose, in this case).

Even describing the full range of chemical unit processes used to produce just the small selection of pharmaceutical fine chemicals shown in these figures would require more space than is available for this current review. Nevertheless, it is useful to list the main reactions used to make a selection of the compounds shown in these figures, in order to illustrate the complexity of chemical process technology to general readers. This list is shown in Table 7.2.

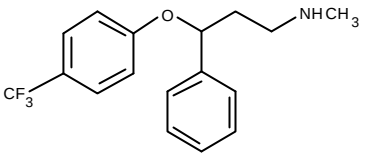
Many excellent reviews on the synthesis of bulk drug actives exist and the interested reader can select titles from the bibliography at the end of the report.

Erthyropoietin, the only biological pharmaceutical in Table 7.1, is manufactured by fermentation, using genetically modified preparations of human cells as the host organism. A number of other very successful new therapies are based upon other 'biological' compounds produced using bio-engineered organisms.

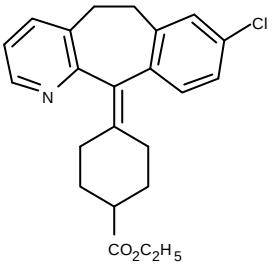
Figure 7.1: Structures of leading pharmaceutical actives (by value)



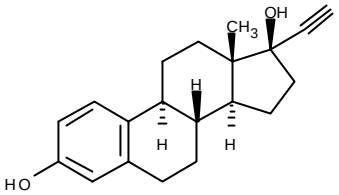
omeprazole
(LOSEC)



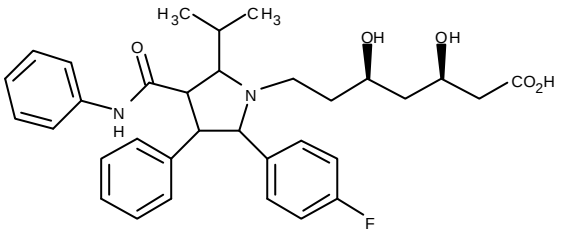
fluoxetine hydrochloride
(PROZAC)



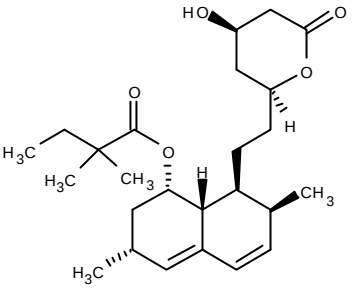
loratidine
(CLARITYN)



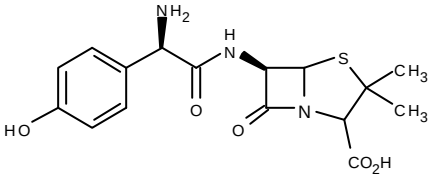
ethyinyl estradiol



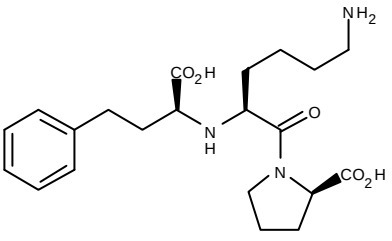
atorvastatin



simvastatin



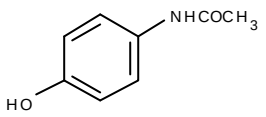
amoxicillin
(penicillin in AUGMENTIN)



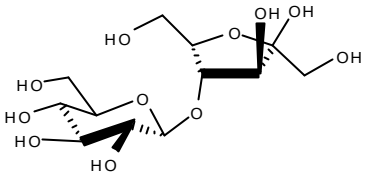
lisinopril
(PRILOSEC)

Source: Brychem

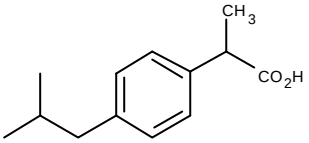
Figure 7.2: Structures of leading pharmaceutical actives (by volume)



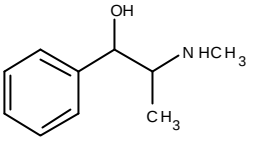
paracetamol
(acetaminophen)



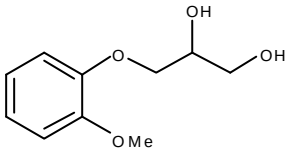
lactulose



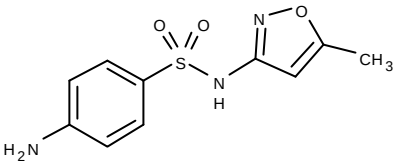
ibuprofen



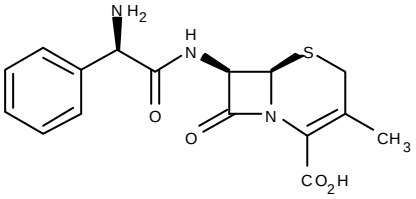
pseudoephedrine



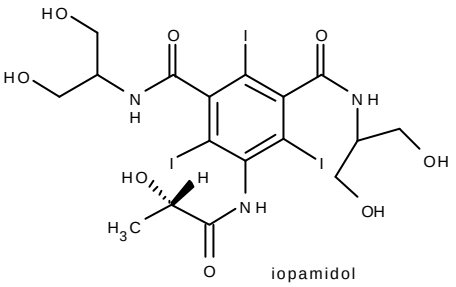
guaifenesin



sulfamethoxazole (SMX)



cefalexin



iopamidol

Source: Brychem

Table 7.2: Reactions used to synthesise selected pharmaceutical active ingredients

Compound	Reactions
Omeprazole	O-methylation, imidazole ring formation using thiourea, nitration, N-oxidation, nucleophilic displacement, N-methylation, S-oxidation
Amoxicillin	Aromatic alkylation, amination, imine formation, amidation (side-chain), fermentation and deamidation (penicillin nucleus)
Lisinopril	Palladium-catalysed carbonylation, hydroxylation of a double-bond, chemical resolution, amidation, N-protection (using trifluoroacetic anhydride), carboxyl activation (using phosgene)
Paracetamol	Partial hydrogenation of nitrobenzene, N-acetylation
Ibuprofen	Aromatic alkylation, HF-catalysed aromatic acetylation, palladium-catalysed carbonylation, alkene hydration
Guaifenesin	Peracid oxidation of phenol, partial N-methylation, nucleophilic displacement on glycidol
Sulfamethoxazole	Sulphonylation of aniline, sulphoamidation
Cefalexin	Aromatic alkylation, amination, imine formation, amidation (side-chain), fermentation, deamidation (penicillin nucleus), acid-catalysed ring expansion

A common theme in fine chemical synthesis is the modification of the basic starting material. This raw material can be obtained, as discussed earlier, from petrochemical stocks, extraction of natural products or complex molecules produce by fermentation. In the following sections, an extended discussion of the standard reactions used to convert these starting materials to the plethora of final pharmaceutical actives is presented. An attempt has also been made to cover some of the more important newer techniques that have become important more recently. These include:

- Creation of stereochemically defined chemicals using asymmetric synthesis, biotransformations and physical separations (loosely called chiral synthesis).
- Use of organometallic chemistry to create carbon-carbon bonds.
- Use of fermentation, with and without recombinant DNA techniques, to produce complex natural products

This section is completed by a review of the newer classes of fine chemicals currently coming through the drug development pipeline.

PROCESS CHEMISTRY

When assembling an organic molecule, it is usually the case that a basic core (raw material) is chosen, which is a standard intermediate. The addition of extra carbon atoms to arrive at the correct carbon skeleton is achieved by joining on one or more

'synthons'. These are one to five carbon molecules that carry reactive groups, enabling them to be added to the growing molecular target. A description of the most important synthons is presented in the next section.

It is intended to highlight the synthetic options available for building up a target molecule. Although many of the following synthons are well established, it is useful to bear in mind their utility when developing new routes. The classification provided below presents a handy source of reference.

C1 synthons

Cyanide is useful for producing aryl and alkyl cyanides and for carrying out Strecker chemistry to produce amino acids and derivatives (note that this can also be done asymmetrically). Catalytic hydrocyanation is a powerful technique, which can also be carried out asymmetrically. The best catalysts are based on nickel.

Formaldehyde is a versatile source of a single carbon. It is used in hydroxymethylations, aminomethylations (Mannich reactions) and in the Prins reaction to make 1,3-diols.

Carbon monoxide can be used to make aromatic aldehydes (Gattermann) and also in the very important hydroformylation and hydrocarboxylation reactions to give a wide variety of aldehydes and carboxylic acids from alkenes. Regio- and enantioselectivity can be controlled by judicious choice of catalyst. Carbon monoxide can also be used in catalysed insertion reactions to give unsymmetrical diaryl ketones.

Phosgene is a versatile C_1 synthon, which is also much used as a reagent for functional group changes (for example: production of acid chlorides).

Despite its inherent hazards, *diazomethane* can be used in a continuous manner to introduce the CH_2 moiety into a molecule. A continuous route to diazomethane (which is safer than the traditional batch process) has been pioneered by Phoenix (UK) and Aerojet (US). Diazomethane has also been made and used by Glaxo Wellcome on a large scale (said to have an 18 metric ton capacity) to make methyl esters of highly sensitive acids and for creating diazine intermediates in corticosteroid production for many years. Schering Plough also has a similar commercial unit.

Bromonitromethane (BNM)/chloroiodomethane. These two reagents have recently been used industrially for the production of cyclopropane rings from the corresponding alkene, as well as epoxides from the corresponding aldehyde. A new generation of quinolone 7-amino side-chains are being made using BNM as the synthon for creating the cyclopropane ring.

1,1-Dichlormethyl Ether is a useful aryl formylating agent produced by SNPE from methyl formate and phosgene. It represents an example of a powerful new synthetic reagent that might be used to simplify current process technologies.

C2 synthons

Acetylene used to be a major chemical raw material prior to the development of the petrochemical industry. It is still a useful C2 synthon and its applications are

promoted by BASF, a company that continues to use it for producing a variety of intermediates as well as some important commodity chemicals.

Oxirane, aziridine, thiirane have been used to effect hydroxyethylations, aminoethylations and mercaptoethylations respectively, but are rather difficult to use. Nevertheless, certain companies have developed an expertise in their production and use. For instance, Nippon Shokubai manufactures cysteamine hydrochloride (for use in the production of cimetidine and ranitidine) using aziridine.

Acetoacetate and malonate are two classic building blocks in this category. Clariant, Wacker and Lonza have built up a range of valuable intermediates based upon this chemistry.

Ketene is the basic feedstock for acetoacetate and the capital expenditure for the construction of the basic plant is a powerful disincentive for would-be competitors. It is a powerful C2 synthon in its own right. Less well known are the *ketene acetals* which can be used in a similar way to ketene itself. They are more expensive, but are easier to produce in small scale equipment.

C3 synthons

Glycidols and derivatives such as *epichlorohydrin propyleneoxide* and *glycerol acetonide*, are versatile C3 synthons, which also find use as homochiral synthons.

Acrylonitrile is used for cyanoethylations and related Michael acceptors such as acrolein and ethyl acrylate. Again it is possible to make and use to good effect chiral versions of these reagents.

C4 synthons

Butadiene and analogues are used in the Diels-Alder reaction. The monoepoxide of butadiene has been recently developed by Eastman as a source of a number of C_4 chemicals such as THF (potentially the cheapest process now available), cyclopropane carboxylic acid and derivatives, and γ-butyrolactones. This intermediate has also been exploited in the asymmetric synthesis of high-value intermediates for the preparation of protease inhibitors.

Diketene and its derivatives (such as 4-chloro-3-ketobutyric acid ethyl ester) are useful 4-carbon synthons. The latter can be reduced asymmetrically in a fermentation process and the resulting 3-hydroxy derivative is a versatile 4-carbon chiral synthon used for the synthesis of a number of different drugs.

Thiophene is a reactive molecule and can be introduced by a number of reactions, for example the Friedel-Crafts acylation. Subsequent reductive desulphurisation results in the net addition of a 4-carbon chain. Of particular utility is formylation to give the aldehyde, followed by a Strecker reaction to give an aminoacid (which could be resolved biocatalytically). Subsequent desulphurisation gives an unnatural aminoacid. This approach is quite general for a whole range of aminoacids and makes thiophene a useful synthon for this type of application.

Furan is a masked 1,4-dicarbonyl moiety and will undergo a variety of downstream reactions which result in the overall addition of a 4-carbon unit. Furans are also active

in Diels Alder reactions and are readily alkylated in the 2-position. This combination of properties makes furan and its derivatives very useful as 4-carbon synthons. A final much overlooked reaction of furans is as a masked carboxylic acid. Subsequent oxidation of the furan produces a carboxylic acid. This interesting approach has been used by Eli Lilly in one of the routes it developed for the preparation of loracarbef.

Other C4 synthons include ã-butyrolactone and malaic anhydride.

C5 synthons

2-Methylfuran has been used as a source of complex substituted cyclopentenones in the synthesis of prostaglandins, pyrethroids and various fragrances.

The key reaction is a mild acid-catalysed rearrangement. Yields can be poor, unless the concentrations of the reactants are kept quite low, but this approach is in use for the production of the prostaglandin intermediate, norprostol and the pyrethroid allethrin.

Functional groups

There are a great number of reagents used to modify functionality and only a few examples of developing areas have been listed below. These are of interest for various reasons, but an important driving force in developed countries is the avoidance of aqueous effluents, so-called 'clean technologies'. Quite often in the past, the development of such technologies has led to cost savings, despite initial doubts about their viability. Other benefits can include modified selectivity and regiospecificity.

- Fluorinations.
- Air oxidations, catalysed by homogeneous metal catalysts.
- Oxidation using hydrogen peroxide.
- Nitrations using nitrogen oxide/ozone mixtures (dinitrogen pentoxide).

As an illustration of the development of fine chemical processing technologies, a short review is given of the improvement in the techniques to introduce fluorine atoms into complex organic compounds.

Fluorine-containing organic compounds

Unlike other halogenated organic compounds, fluorochemicals cannot usually be made in satisfactory yields by direct fluorination. Fluorine is very reactive and when exposed to organic compounds it generally reacts violently and uncontrollably, even at low temperatures, producing mixtures of polyfluorinated products. In order to overcome the limited applicability of fluorine for use in organic synthesis, chemists have developed a number of standard reactions used to introduce fluorine into organic compounds in a more controlled fashion.

Halogen exchange

Reaction of hydrogen fluoride (HF) or potassium fluoride (KF) with labile chloro-compounds (sometimes bromo-compounds) in the presence of a Lewis acid is a useful way to introduce fluorines into methyl groups that are directly or indirectly attached (through an oxygen, nitrogen or sulphur) to aromatic rings. The wide range of trifluoromethylaromatics used for many pharmaceutical intermediates are produced by halogen exchange. An example is p-trifluorophenol (fluoxetine – PROZAC – intermediate), both derived from p-chlorobenzotrichloride.

Halex reaction

Activated chlorine substituents on aromatic rings can be efficiently displaced by nucleophilic substitution using KF in a dipolar aprotic solvent such as DMSO, sulfolane, DMAC or DMF. Fluorinated benzonitriles and nitrobenzene derivatives are the most useful examples of halex technology. 2,6-Difluorobenzamide (a versatile intermediate for a number of herbicides) and p-fluoroaniline are both made using halex reactions.

Balz-Schiemann reaction

Decomposition of a diazonium terafluoroborate (or fluoride) generates fluoroaromatic compounds from the corresponding anilines. This technique is the one used to produce fluorobenzene itself, as well as the fluorotoluenes and 4,4'-difluorobenzophenone (raw material for the high performance polymers, PEEK and PEK, as well as pharmaceuticals).

Direct fluorination

Notwithstanding the comments at the start of this section, it is sometimes possible to use fluorine directly. For instance, 4-fluorobenzonitrile reacts with fluorine to produce 3,4-difluorobenzonitrile and p-chloronitrobenzene reacts to give 3-fluoro-4-chloronitrobenzene (key intermediate for ciprofloxacin) in good yield.

Fluorinations using sources of 'positive fluorine'

There are a number of relatively expensive, selective fluorinating agents that find use in very specialised applications. These mimic fluorine itself, but are much 'tamer' and can be used to replace acidic hydrogens in ketones and vinyl acetates. Chloryl fluoride (ClO_3F), quinuclidinium salts (F-TEDA), pyridinium salts and N-fluorobenzenesulfonimide are examples.

Other fluorination reactions

There are a number of other approaches to inserting fluorine into an organic molecule, which have lesser generality:

- Diaminosulphur trifluoride is used to convert hydroxyls to fluorines in acids, alcohols.

- Difluorochloromethane alkylates phenols, yielding difluoromethoxybenzene derivatives.

- Fluorinated olefins (HCFCs and HFCs) can be used to create more complex alkylated derivatives by Lewis acid additions/substitutions. Certain inorganic fluorides (such as iodine and antimony pentafluoride) can be used to replace other halogens in organic compounds.

In Table 7.3, a summary of the more important fluorinated chemical intermediates and their method of manufacture is presented, together with their (approximate) global production capacities.

Table 7.3: Major fluorinated aromatic intermediates

Compound	Manufacturing process	Approx. global capacity (metric tons)
p-Chlorobenzotrifluoride	Halogen exchange in HF	10,000–15,000
Benzotrifluoride (BTF)	Halogen exchange in HF	10,000
Fluorobenzene	Continuous diazotisation of aniline in HF	5,000
m-Aminobenzotrifluoride	Nitration/reduction of BTF	5,000
o-Fluorotoluene	Diazotisation of o-toluidine	2,500
2-Chloro-5-(trifluoromethyl)pyridine	Halogen exchange in HF	1,000
2,4-Difluoroaniline	Halex reaction	400–600
2,6-Difluorobenzonitrile	Halex reaction	650
2,6-Difluoro-3,4,5-trichloropyridine	Halogen exchange in HF	500
2,3-Dichloro-5-(trifluoromethyl)-pyridine	Halogen exchange in HF	500
4-Fluorophenol	Alkaline hydrolysis of 4-bromofluorobenzene or diazotisation of 4-fluoroaniline	400

CONTROL OF STEREOCHEMISTRY

As indicated previously, a significant number of drugs in development and in the patent literature are homochiral (many also containing the heterocyclic rings indicated above). This trend towards enantiopure drugs is expected to continue. The ‘switch’ of racemic drugs that are already on the market to enantiopure drugs has not been the major success that many companies prophesied, with only very few products having been re-launched to date. The most spectacular flop was (S)-ibuprofen, the almost complete failure of which has depressed interest in the concept as a whole.

The following discussion focuses on enatioselective reactions, but much could also be said about new reagents for diastereoselective reactions, in which two contiguous centres are created.

The successful fine chemical company today needs to have access expertise in chirotechnology. This can be achieved by developing a full spectrum of in-house technologies or by developing a single technology, e.g. asymmetric synthesis, and outsourcing any need arising for the use of other techniques. Chirotechnology is conveniently divided into three main categories, which may themselves be further subdivided.

The chiral pool

This consists of a vast number of naturally occurring enantiopure substances (including amino acids, carbohydrates and terpenes) that are cheap and readily available. It may also include synthetic substances, which are in regular production, for example α-methylbenzylamine, 6-APA and l-menthol.

Exploitation of the chiral pool requires no particular expertise in chirotechnology (other than analysis) since the chirality is built-in. It does, however, require considerable skill, creativity and originality of thought to exploit it to the fullest. For this reason and for reasons of intellectual snobbery it is often overlooked, when in fact it has the potential to offer the optimal economic solution. A number of elegant examples of commercial processes using a chiral pool starting material have been published over the years.

Separation technology

Classic diastereomer resolution

This has a low-tech image but is often the method of choice and is much used industrially. Rapid screening techniques can be evolved to assist in identifying the best resolving system. Some skill and experience in the technique is, nevertheless, an import asset. For good economics, recycling of the unwanted isomer must usually be incorporated into the process. Despite the utility of this approach, however, it is often used when it may not be the best solution simply because many chemists are not familiar with the alternatives.

Racemic conglomerates

These are a special type of racemate which can be separated into the enantiomers simply by fractional crystallisation. It is not straightforward, however, and considerable skill is required to be able to identify and exploit the phenomenon which is in any case relatively rare. Due to its simplicity, it can save a lot of time, energy and cost and does not require recycling of the resolving agent. The phenomenon should always be investigated before embarking on a classic resolution.

Biocatalytic (enzymic) resolution

This technique is based on the kinetic resolution of suitable substrates with hydrolase enzymes such as lipases, esterases and amidases. To exploit the technique to the fullest extent, a company must have expertise in biotransformations, enzymology,

access to a wide range of enzymes from microbial sources (a culture collection), skills in molecular biology, a fermentation capability and biochemical engineering know-how. These broad skills must be fully integrated with good development chemistry capability. Although this technique can often be the method of choice, the cost and time for development remain a substantial barrier to all but the most important fine chemicals.

Nevertheless, as the technology matures more commercial applications will be developed. In the future there will be an opportunity to exploit the vast number of novel enzymes identified in extremophilic organisms coming from such sources as volcanoes and the depths of the ocean. These enzymes are much more robust than many in current use and will lend themselves more readily to everyday use in the development laboratory.

Chiral simulated moving bed chromatography

It has long been the case that chromatographic techniques have been too expensive to operate on an industrial scale, despite the excellence of their performance. UOP has developed this technique to separate chiral mixtures on a significant scale. The technique was originally successfully introduced for the separation of commodity chemicals (for example the xylenes).

The technology has been promoted in cooperation with Chiral Technologies Inc. (Daicel subsidiary), which has pioneered the application of chiral HPLC for kilogramme-scale separations. A French company, Novosep, is also active in this area.

Cost analyses of specific cases appear to demonstrate that the SMB technique could become the method of choice for separations of fine chemicals with a value of > US$250–350/kg, even at production scales of 10-20 metric tons per year.

Membrane separations

Akzo has developed a membrane-based technology which works rather like a kidney dialysis machine, in which, on one side of the membrane there is a racemic solution, and on the other a counter current flow of solutions containing chiral selectors. The separation is essentially continuous but development has been slow and has not been demonstrated at real scale. It does look promising, however, and a watching brief should be kept on this technology.

Gel filtration

Xyrofin, a division of Cultor in Finland, claims to have developed a chromatographic technique whereby ‘chiral holes’ are constructed in a column of a polysaccharide. This has apparently been used to separate aminoacids into pure enantiomers from a racemic mixture. Degussa is reputed to have evaluated it but no details are available.

Chiral separations by distillation

At the present time this technique appears to be only an academic curiosity, but it may have potential in the future. Operationally it is very simple; a racemate is mixed with a suitable pure enantiomer with which one enantiomer in the racemate binds more strongly than the other, the least bound enantiomer is then distilled out. In

principle, it is similar to a classic resolution and although it does not appear to have been scaled up, it may have some limited applications.

Asymmetric synthesis

This is an extremely powerful technique. Unlike separations, only the desired enantiomer is formed, so no recycling of the other enantiomer is necessary. Since the reactions are more specific, there are fewer environmental issues.

The metal ligands (organic compounds that stabilise the metal cations) are just as important as the metals in this technology. It is often not realised that the costly metals are very often the cheaper part of the combination of metal and ligand!

Asymmetric synthesis may be conveniently further subdivided into three sub-categories.

Microbial asymmetric synthesis

This is essentially synonymous with fermentation. Although more difficult to exploit than using isolated hydrolases (described earlier), it is, for a number of reasons, an extremely powerful tool in the hands of those with real expertise in handling enzymes. While the same comments apply as were made earlier there are a number of limitations, for example a given enzyme system will only give one enantiomer of a given pair. If the other is required a new enzyme must be sought. This is not the case with chemocatalysis which is discussed below.

Chiral auxiliaries

This technique is a form of chemical asymmetric synthesis using a 'chiral handle', which is later removed and recycled, to induce chirality in a target molecule. Although it has been much used industrially and even more in academic laboratories, it is generally a cumbersome technique and is only rarely the most effective method. Despite this, it can be a useful tool in the fine chemist's armament and ought not be totally disregarded.

Asymmetric chemocatalysis

This is potentially the most powerful tool of all and will be essential for anyone serious about offering homochiral synthons as a business. This area may be further subdivided into asymmetric hydrogenation of substrates such as prochiral alkenes, imines, ketones, oximes and enamido acids. Also included are asymmetric oxidations, especially to produce epoxides, a major area of current research.

Finally there are asymmetric rearrangements. The latter area is expanding very rapidly and the successful fine chemical company of the future must acquire expertise in this area. In the absence of any existing knowledge, expertise or IPR, then it should be in-licensed or better still obtained by acquisition of an appropriate business. Liaison with a top academic is also a prerequisite in order to keep on top of a rapidly evolving area.

METALS IN ORGANIC CHEMICAL SYNTHESIS

The application of organometallic chemistry is not new in organic synthesis (the Grignard reaction was quickly adopted by industry within a short time of its invention in 1908). In the last decade, however, there have been major strides forward in the use of metals in industrial and academic organic synthesis. In particular, the more exotic metals have been shown to have useful properties, especially in achieving good control of chiral induction. Although much of the following work has involved homogeneous catalysts, heterogeneous catalysis is also of growing importance. The following notes are not intended to be exhaustive, but they do help to demonstrate the diversity of chemistry which is possible using some of these new organometallic reagents. There can be little doubt that fine chemical companies will have to embrace this type of chemistry if they are to provide the compounds needed for the bulk pharmaceuticals of the future.

The importance of complexing ligands in the applications of many organometallic reagents should be stated at the outset. In cases where true catalysis is vital for an economic process, the judicious choice of a suitable ligand is the key to success. Unusual phosphines carrying ferrocenes provide a rich source of ligands that have been shown to endow precious metal catalysts with very high turnover numbers. The problem is that very small variations in structure produce disproportionate changes in properties, so that a specific ligand must often be designed for a specific reaction. Where a large volume product is involved, the necessary research can be worthwhile (Takasago's menthol process is a good example). However, at the moment, the results appear to be hard to predict empirically.

A good review on homogeneous catalysis appeared recently: Organometallic Homogeneous Catalysis – Quo Vadis? (Cornils & Herrmann, Angew Chem Int Ed Engl, *36* (1997) 1048–1067).

In heterogeneous catalysis, the use of more bi-metal catalysts and metal-enzyme complexes is producing interesting new reactions. Such systems allow quite large target molecules to enter the active centre, be modified by one or two metals, before re-escaping. Complex reactions can thus be dovetailed into one efficient step.

Copper

This metal has been used in a number of well-established reactions for a long time; for example the classic Sandmeyer reaction. More recently its use has been greatly expanded and new uses continue to be reported at an increasing rate. Using organocuprates gives many advantages over traditional Grignard and organolithium chemistry, and its range of applications is wider. A similar situation exists for silver chemistry but it is less useful because of its higher price and its thermal and photochemical instability.

Uses include: synthesis of symmetrical and unsymmetrical biaryls, stereoselective coupling of alkenes to afford 1,3-dienes and carboxylation of vinyl copper adducts giving acrylic acids. Organocuprates have also been used in the synthesis of complex terpenes and prostaglandins.

Lanthanides

A great deal of work is being undertaken using lanthanides. A major area for applications is in carbon-carbon bond forming reactions. The problem with these metals is that their economic separation from the natural deposits is difficult, due to their occurrence as complex mixtures of these chemically similar elements.

Nevertheless, they have received a great deal of attention in recent years and continue to do so. Of particular note are *cerium* and *samarium.* The latter has found great use as an oxidant in special circumstances and the latter (in the form of the iodide) has been shown to replace zinc in the Reformatsky reaction, where it gives increased diastereoselectivity.

Scandium

There is also much academic interest (which could be translated into industrial applications within the timeframe considered in this study) in scandium triflate as a Friedel-Crafts catalyst. Some reactions can be carried out in water and in all cases the scandium acts as a true catalyst.

Zirconium

Zirconium is a very cheap metal which is non-toxic and has yet to be properly exploited. Especially useful is the so-called hydrozirconation reaction. The precursor for the reagent is $ZrCl_2(C_5H_5)_2$, that is a zirconocene analogous to the better known ferrocenes. This is converted to $ZrHCl(C_5H_5)_2$. This reagent is much more versatile than the better-known hydroboration reaction and can be used to make a wide variety of molecules that are difficult to produce otherwise. Chirality is another feature which is currently being explored.

Titanium

Besides the classic uses of titanium chemistry, perhaps the best known of the more recent chemistry is the Sharpless epoxidation, which involves using titanium isopropoxide. There is also the less well-known *McMurray* reaction which uses $TiCl_3/LiAlH_4$ to effect the reductive coupling of two carbonyl compounds to give an olefin.

The *Tebbe* reaction, effectively a source of $Cp_2Ti = CH_2$, will react with carbonyl compounds transferring a CH_2 group. It is thus an alternative to the better-known Wittig reaction, but the scope is much greater. For example it will transfer a methylene moiety to esters, amides and lactones – a major advantage. It is also considerably less hazardous than diazomethane, a competing source of 'carbene'.

Enichem's TS1 titanium dioxide heterogeneous catalyst is absorbed on a zeolite and has been shown to effect a range of interesting oxidations, some of them chiral.

Tungsten

The classic use for tungsten is in epoxidations. In the Degussa process for the manufacture of glycidol, tungsten oxides are used as catalysts, for oxidising allyl alcohol. More recently the combination of tungsten hexachloride/butyl lithium has

been used for the deoxygenation of epoxides to alkenes in high yield. This same reagent reacts with aromatic aldehydes to give alkenes via reductive coupling, like the McMurray reaction. The combination of tungsten hexachloride/tetramethyl tin is used for alkene metathesis and unlike most catalysts for this reaction, it is compatible with the presence of ester groups. Finally, tungsten hexafluoride will convert certain hydrazones into carbonyl compounds, a reaction impossible to accomplish otherwise.

Olefin metathesis using tungsten catalysts is another area in which well-known big chemistry technology is being successfully applied in fine cehmicals.

Manganese

The now famous Jacobsen reaction uses a chiral manganese catalyst (derived from a chiral diamine and an aromatic aldehyde) to effect asymmetric epoxidation of unfunctionalised olefins. This reaction exemplifies one of the more recent applications of manganese chemistry. More recently this reaction has been expanded to include kinetic resolution of epoxides, paralleling some enzyme chemistry.

Manganese triacetate, which is readily prepared in situ, will, in the presence of acetic acid, convert alkenes into 5-substituted gamma-lactones. Alkenes will also react with a wide variety of aldehydes and ketones in the presence of this reagent to give branched aldehydes and ketones a potentially vast area of useful chemistry. Mn-III acetylacetonate is probably the most useful reagent for oxidative coupling of phenols and has been used to make galanthamine, an alkaloid found in daffodils, and which is being marketed for the treatment of Alzheimer's disease.

Manganese dioxide is a useful oxidant for the oxidation of allylic, propargylic, benzylic and heterocyclic alcohols to the corresponding aldehydes. It also finds use for the cleavage of 1,2-diols to aldehydes and for the hydration of nitriles to amides and for aromatisation reactions. In situ electrochemical recycling of the manganese is a process improvement that has the potential to reduce dramatically the production of effluents when manganese dioxide is used.

Rhenium

Carbonyl complexes of this metal catalyse chlorination of hydrocarbons in very high yield, e.g. cyclohexane to cyclohexyl chloride. Methyl rhenium oxide is said to be a unique oxidant for some conversions. For example: with hydrogen peroxide it reacts with furan to give 1,4-diones cleanly.

Ruthenium

The now famous Noyori catalysts use ruthenium and rhodium complexes of the chiral ligand BINAP. These catalyse a variety of asymmetric hydrogenations and allylic amine rearrangements. Ruthenium is also an excellent catalyst for hydrogenation of aliphatic carbonyls and some aromatic aldehydes, e.g. furfural to the corresponding alcohol.

RuO_2, under hydrogenation conditions, reduces acids to alcohols. More interestingly, it will reduce an aromatic nitro group to amine in the presence of both double and triple bonds, which remain untouched. Ruthenium trichloride catalyses the Prins reaction and is an excellent oxidant in the presence of N-methylmorpholine oxide for

conversion of alcohols to aldehydes. In the presence of an alcohol alone and an aromatic hydrocarbon such as furan an alkylative coupling will occur to give substituted biaryls.

Ruthenium tetroxide will convert furans into carboxylic acids and is usually generated in situ from the trichloride.

Rhodium

As well as the Noyori catalysts mentioned above there has been a great deal of work on rhodium chemistry in recent years. The trichloride is widely used for isomerisation of alkenes to the most thermodynamically stable isomer. One very useful reaction is in the presence of sodium borohydride, this combination will reduce aromatic rings to the saturated analogue leaving acids, esters and amides untouched.

In the presence of Aliquat 336, rhodium trichloride will reduce alkenes in the presence of a nitro group, the latter being untouched. This is a reversal of the usual order of reactivity.

In the presence of copper II chloride, rhodium trichloride and air will convert alkenes to ketones.

Palladium

The recent chemistry of palladium is vast and only two particularly useful examples are given here to demonstrate the versatility. These reactions are also somewhat under exploited.

The Suzuki reaction involves the coupling of readily available phenyl boronic acid with, for example, a Grignard such as phenyl magnesium bromide to give the biaryl. This reaction is applicable to a wide range of substrates and constitutes one of the best methods of making biaryls, a variety of palladium catalysts is applicable, and the reaction has been used to make combinatorial libraries. In the presence of carbon monoxide unsymmetrical diaryl ketones can be made.

In the Heck reaction phenylboronic acid can be made to react with styrenes or acrylic acids to give stilbenes and cinnamic acids, also mediated by a variety of palladium catalysts.

Conclusion

A number of metals have been highlighted here, but someone, somewhere is developing new chemistry using practically every metal in the periodic table (for instance, chromium and cobalt – for example: Jacobsen's new catalyst – are two metals that could also have been mentioned). Organometallic chemistry is *the* most promising area for rapid advances in industrial chemistry and will revolutionise many well-established processes over the coming 10–15 years.

NEW DEVELOPMENTS

Drug discovery through a mixture of serendipity and mimicking nature is no longer an important strategy amongst leading pharmacologists and medicinal chemists. The success of the rational approach to drug design (particularly the use of the receptor theory for identifying successful commercial products) has been followed-up by the international genome project. With a better understanding of all the genes that define the cellular basis of the human organism, pharmacologists anticipate that new treatments for many of the more intractable diseases (such as cardiovascular disease, cancer, viral infections and autoimmune diseases) will be created.

Thus, current research efforts to find compounds with desirable therapeutic effects are increasingly focused on molecular targets such as receptors and enzymes. This trend is expected to accelerate as the intense research effort in the area of genomics continues. Most of the major companies are involved in this approach to drug discovery, with SmithKline Beecham generally regarded as the leading major multinational player. Many smaller drug discovery companies have also been set up to specialise in developing pharmaceuticals using genomics as the means to new drug discovery.

A review of the drugs currently under development (in the clinic or that have been recently patented) reveals some interesting trends. The drugs, classified by therapeutic areas, that are in clinical trials and in the current patent literature are summarised in Table 7.4.

Table 7.4: Breakdown of drugs in clinical trials and in the patent literature by therapeutic categories

Therapeutic class	Clinical trials (%)	Patents (%)
Central nervous system	12.5	16.8
Cardiovascular	11.3	15.5
Anti-infectives	12.8	13.2
Oncolytic (anticancers)	21.7	11.3
Respiratory	7.9	6.9
Metabolic	5.7	7.5
Antirheumatic	4.2	5.0
Gastro-intestinal agents	6.5	4.6
Endocrine drugs	5.8	4.3
Blood coagulation	3.5	4.9
Renal urological drugs	2.6	3.5
Dermatological drugs	3.3	2.5
Immunological drugs	1.6	2.5
Ophthalmic drugs	0.6	1.4

Of the 1,250 drugs in clinical development, about 20% interact with receptors and 15% are enzyme inhibitors. The remainder fall into an number of miscellaneous categories such as drugs that interact with ion-channels, antibiotics, antivirals and anticancers. A trend becomes apparent when these percentages are compared with novel drugs reported in the patent literature. The corresponding figures for the two big categories are 40% receptors and 25% enzyme targets. This trend towards more drugs based upon receptors and enzyme inhibition is expected to continue, as more information becomes available from the human genome project.

One of the most exciting areas of current medicinal research is the family of enzymes known as *protein kinases*. Approximately 4,000 of these have been identified from the genome project. While some of them, perhaps most, will have no significance, there will be many which will be shown to be implicated in certain disease states (for example: cancer and diabetes). Many major pharmaceutical companies are currently looking at kinases. It seems likely that many of the drugs emanating from this line of research will fall into the class of the *peptidomimetics*. Other new drug candidates will contain novel heterocyclic systems. There will be undoubted opportunities for those companies developing the appropriate technologies to produce these challenging new molecular targets.

Peptidomimetics are essentially tailored enzyme inhibitors, a kind of chemical 'Trojan horse' which are sufficiently similar to the natural peptides to fit into the receptor, but which are sufficiently different that they block the usual response. The outlook for drugs of this class is believed to be very bright. Examples of chemical classes in which peptidomimetics will generate opportunities include:

- Homochiral unnatural aminoacids.
- Novel heterocycles.
- Small non-peptide units.
- Amino alcohols and D-aminoacids.
- Miscellaneous stabilising ring/bridge systems.
- Scaffolds for construction of 'beta turns'.
- Aminoaldehydes and derivatives.
- Aza-peptide sub units.

Of the 1,250 drugs in clinical trials and in the patent literature, many have novel structural features. Processes for these will have to be developed, creating opportunities for the fine chemical industry. Being aware of the types of challenges that medicinal chemists will be setting the independent sector is a key part of the industry's role today.

The majority of these compounds contain novel derivatives of a wide array of *heterocycles* (see Table 7.5). *Chirality* appears to continue to be a very prominent characteristic. A substantial number of the candidates contain *fluorine* (about 5–6%), usually as an aryl fluoride but also as a trifluoromethylaromatic. A list of some of the heterocyclic rings present in the development drugs is presented. In addition to these

general structural features there are more exotic bridged and fused derivatives of the systems already described.

Table 7.5: Heterocyclic systems found in developmental drugs

Azocines	Indoles	Quinoxalines
Azaquinolones	Oxazines	Quinazolines
Azacarbazoles	Octahydroisoquinolines	Quinuclidines
Azetidines	Pyrroles	Thiazoles
Benzisothiazoles	Pyrimidines	Thiadiazoles
Benzodiazepines	Pyridazines	Thiophenes
Benzisoxazoles	Pyridines	Thiazolidines
Benzofurans	Piperazines	Tetrahydrofurans
Benzazepines	Phenothiazines	Indazoles
Chromans	Pyrrolidines	1,2,3 Triazoles
Carbazoles	Piperidines	1,2,4 Triazoles
Dibenzazathiepines	Phthalazines	Tetrazoles
Furans	Pyrazines	Isoxazoles
Imidazoles	Oxadiazoles	Quinolines
Quinolones	Tetrahydroisoquinolines	

Peptides, nucleotides and saccharides

Polymeric and oligomeric biological materials of these three classes are very common. Enzymes, DNA, RNA and sugars constitute very substantial groups of chemical types that are vital to the normal functioning of organisms.

While this group still remains a relatively small sub-set of the armoury of pharmaceutical molecules, continuing pharmacological interest in the smaller chain-length molecules is likely to present the fine chemical industry with new technological challenges within the next 10–15 years. Very brief overviews of the main groups are presented below.

Peptides

Small chain peptides (1–5 aminoacid residues) and oligopeptides (consisting of around 5–20 aminoacids) have been intensively studied, particularly since the discovery of the encephalins and endorphins in the mid-1970s. Much work has been redirected more recently into synthesizing peptide analogues using unusual aminoacids (especially D-aminoacids) and pseudopeptides, where at least some of the amide linkages are replaced by carbon-carbon bonds. These analogues have greater potential as drugs because they are less easily metabolised and can be better tailored to produce a specific biological response.

Although solid state synthesis of the longer oligopeptides is effective in the synthesizing target molecules in the laboratory, solution phase chemistry remains the only generally cost-effective approach.

A number of specialist companies have targeted this type of technology, with Synthetech, Bachem (both in the US) and Cambridge Research Biochemicals (UK) being prominent exponents of these technologies.

A number of polypeptides of chain-lengths greater than 20–30 amino acids (the longer ones are, of course, more commonly called proteins) are important therapeutic agents. They are almost always made by either extracting natural proteins or by fermentation of suitable cellular preparations. A number of the leading biotech products are made by one (or in the case of insulin, both) of these techniques.

Nucleotides

Interest in this area has waned recently, with most effort (and success) being rather directed at blocking nucleotide synthesis (especially in viruses) with small, unnatural nucleosides.

Machines for producing oligonucleotides have been commercially available for some years now, but their use is mainly for the characterisation of naturally occurring products in the research laboratory.

Polysaccharides

Academic interest in polysaccharides has never been higher and new techniques for synthesizing glycoside linkages are being developed by many top research groups. Small start-up companies have also been established to exploit the demand for research quantities of these challenging molecules. In the UK, Dextra Laboratories and Oxford GlycoSystems are two such specialists.

The problem hitherto has been that polysaccharide synthesis has been hampered by the limitations of the available chemistry. Using the new chemical techniques, the full potential of these biomolecules can finally be explored. One useful application is in the delivery of small molecules across biological membranes (by attaching glycosidal 'handles' to existing molecules). An example is morphine glucuronide, which is able to cross the blood-brain barrier effectively.

Although few industrial applications have been yet developed, new pharmaceutical products could be exploiting their unique properties within the next 10–20 years.

CHAPTER 8: CURRENT STATE OF THE INDUSTRY AND OUTLOOK

CAPTIVE PRODUCTION VERSUS OUT-SOURCING

The pharmaceutical industry has traditionally (that is, over the past 40–50 years) seen its role as primarily that of an inventor, manufacturer and seller of finished pharmaceuticals. Given the potential value of a new and successful pharmaceutical, the expectations of people investing in public companies has been for a generous return on their capital. As companies have become bigger, so as to gain access to as many potential patients as possible, the rate of invention of new drugs has decreased and the capital assets and operating costs have increased.

During the past ten years, pressure on the major multinational companies to restructure has increased, so that the expected high profits can be maintained. Failing higher profits, companies have opted for creating significant sales growth by making large acquisitions or agreeing mergers. This produces a year or so of respite, during which the combined companies are restructured. The resulting returns are often as poor, but the capital gains made during the merger help to mollify the investment community.

Among the many ways of reducing fixed and operating costs is for companies to outsource their fine chemical needs. For many years, most US and European drug companies have purchased basic intermediates and solvents from third parties, since it was clearly unnecessary and economically unjustifiable to produce bulk pharmaceuticals from basic intermediates. In entrusting the production of these intermediates to outside producers, the scale of chemical manufacturing capacity could be greatly reduced. The loss of control of proprietary technology and the strategic impact of such decisions was minimal.

As the structure of drug molecules became more complex, suppliers to pharmaceutical companies began to offer more advanced intermediates, the use of which were generally limited to fewer than two to three pharmaceutical actives, often just one. So long as the suppliers were trustworthy, this was not seen as too much of a problem. As the number of suppliers of bulk drugs to countries with weak product patent legislation increased, however, the inventing companies began to develop reasonable fears about loss of sales to suppliers of copy products. The chemicals for these unlicensed products could often only be made from intermediates produced by the originator's suppliers. Basic chemistry was also often supplied by the inventing company to its sub-contractors as part of the overall deal. The decision not to trust external suppliers with more advanced intermediates began to take on a strategic aspect; throttle the supply of intermediates and limit the competition. This complicated the make/buy decision and also led to a two tier pharmaceutical fine chemical industry:

- Trustworthy suppliers locked into exclusive deals;

- Untrustworthy ones having to make do with lower margin business in the supply of lower volumes to unlicensed pharmaceutical companies.

As the pressure on the ever bigger pharmaceutical companies to reduce costs has continued to increase, ways around the drawbacks inherent in outsourcing have been devised:

- Exclusive partnerships in which the sensitive technology transfers are limited to a small carefully selected group of fine chemical suppliers.

- Pressure by US and European governments on countries in the developing world (where most unlicensed sales were taking place) to introduce strong patent legislation. This has been largely successful, with very few countries now still outside the international patent treaty umbrella.

- Increased policing of patent and contractual agreements, so as to detect companies that break their agreements.

The patent legislation enacted around the world by the end of the twentieth century provided protection of exclusive rights and technology IPR at a higher level than ever before. However, the major pharmaceutical companies continue to be reluctant to give up too much of their chemical manufacturing. This is expected to change slowly and the cut of the 'pharmaceutical fine chemical pie' that the third party suppliers is able to achieve will increase. Other factors, less to do with the needs of the multinational innovators, will also hasten this process:

- Increasing maturity of the market, in which older commodity bulk drugs will gain an increasing market share (a much higher proportion of these are made outside the pharmaceutical industry).

- Increase in the number of bigger pharmaceutical fine chemical specialists that work closely with their major pharmaceutical partners, excluding smaller companies from the prime contracts. The risks of selling intermediates 'on the side' will outweigh the benefits of remaining true to the contracts and 'good behaviour' will become simple self-interest.

- Growth of the importance of new, biotech and other pharmaceutical start-ups that simply do not even consider investing in their own chemical manufacturing capacity.

- Continuing sales of surplus chemical manufacturing capacity to independent companies as the result of mergers and takeovers, thus transferring existing business outside the pharmaceutical industry.

The net benefit to the pharmaceutical industry is likely to be that it will increasingly realise that the best fine chemical specialists can produce pharmaceutical intermediates and active ingredients more cheaply and effectively than they themselves are able. As this becomes evermore clear, the pace of change will accelerate. Eventually, it is anticipated that the industry structure will more closely resemble that of the generic industry, where very few companies are back-integrated into chemistry.

Until these changes have taken place, the situation will remain confused and fragmented. Today each major innovator operates a unique system that combines some outsourcing and some own manufacture, with the balance very often determined by chance more than careful analysis. Some examples of this diversity of policy (which are typical and are not meant to be a reflection upon any single company) and the consequent headache it produces in suppliers and customers are useful to consider:

- Monsanto's policy of setting up a group of project champions to see new drug candidates from the lab through to manufacturing, overlaid with Searle's old centralised purchasing organisation, produced an incredible amount of confusion about who was an approved supplier and who was not. Outsourcing of intermediates for celecoxib was a good case in point.

- Some companies, such as Glaxo Wellcome, have a general policy of awarding supplier status for a given intermediate to several producers, whereas others (for example Merck & Co.) may depend upon just one. When companies use multiple sources, administration (sample trials, use testing, plant audits) can become too time-consuming; those relying on a single source can suffer the consequences of accidents, leaving the supply pipe empty (this happened to Merck & Co., when a US supplier's plant was out of commission for several months). Getting the right balance involves many factors, but a good understanding of the relative merits of the fine chemical producers applying to be suppliers is crucial.

- Many European pharmaceutical companies have evolved from within chemical companies. The tradition of captive production in such enterprises is understandable, but has nevertheless led to poor economics. Indeed, the German chemical giant, Hoechst, was broken up largely on the grounds that the interdependence of the various industry groups was holding back the development (and value) of the constituent businesses. The company's fine chemical division was found to be unprofitable upon careful analysis, suggesting outsourcing would have been a better solution all along. Aventis' other partner, Rhône-Poulenc Rorer, has suffered from similar poor ecomomics. Since the separation of Avecia from AstraZeneca, enquiries from its former owner have been found to have increased.

All these examples offer good evidence that captive production is not always the most cost-effective option.

DEVELOPING WORLD, PARTICULARLY INDIA AND CHINA

The companies making pharmaceutical fine chemicals in those parts of the developing world where such an industry exists share a number of characteristics that produce a mixture of fear amongst their competitors and mistrust amongst their potential international customer base. This traditional view is slowly changing, but major pockets of scepticism remain, with continued justification, in many instances.

These PFC industries have been created initially in order to bypass the import of finished pharmaceuticals, where possible. As the experience and skills of the companies involved

increased, these suppliers became bolder and began to export excess production (intermediates and bulk actives) to more developed markets. The prime reason why these sales have developed was the low prices at which the fine chemicals have been offered. The Chinese, in particular, have supplied fine chemicals at such low costs, that many small 'entrepreneurial' companies have been able to 'clean up' sub-standard quality material (usually by carrying out a recrystallisation, a so-called 'benediction') and still save money! No wonder, then, that US, European and Japanese fine chemical producers have complained about unfair Asian competition.

The international pharmaceutical industry has viewed the emergence of these two pharmaceutical giants with an understandable degree of ambivalence. Representing, as they do, huge, barely developed markets for their finished products, these companies have found China, in particular, an irresistible target for developing new business. In spite of the weaker protection of exclusivities than elsewhere, major multinationals have scrambled to get their products onto the Chinese market. The general way to achieve this is by appointing a local joint-venture partner, who usually gets some chemical manufacturing contracts for older products in exchange for allowing the 'Western' partner to gain access to the domestic company's marketing outlets.

India has maintained a greater degree of independence, by virtue of its political stance as a non-aligned country, and its philosophy of self sufficiency (coupled with a useful economic deal with the former Soviet Union). As the world has changed, India too, has relaxed its stance and a succession of governments during the 1990s have opened up the economy to outsiders. Nevertheless, substantial import tariff barriers still exist that allow local producers to compete more effectively in export markets than would otherwise be the case. From the Indian point of view, it is claimed, quite reasonably, that the size and power of 'Western' multinationals must be countered by local measures in order to produce fair competition.

Meanwhile, the volume and value of exports, at very competitive prices, of bulk pharmaceuticals and intermediates from India and China to the US and Europe increases every year.

What are the real reasons for these low prices, which Japanese, European and US companies find so hard to beat? They are many and complex, some financial some fiscal, some structural. The key factors are, however, the following:

- Capital costs and the cost of their amortisation are much lower than in the West.

- Although labour costs are lower, this factor is partly negated by the endemic over-manning found in China and India.

- Exports are often sold on the basis of marginal costs (that is, the surplus production is produced at variable costs only), sometimes with these being zero (has been common in China, where production is centrally funded on a quota basis, a system that can be manipulated by the producer to sell into export markets in order to get foreign exchange for necessary imports of special items).

- Severe over-capacity in both countries creates too much competition that, in turn, drives down prices and margins to levels unacceptable to Western companies. Exporters are therefore used to lower margins and feel able to keep prices low.

The outlook for the future will be that the supply of pharmaceutical fine chemicals from these countries to the West will continue to grow, probably at an accelerating pace. As their market share increases, inward investment by companies in the US, Japan and Europe will begin to reduce the financial impact of this transfer of manufacturing investment. Increased sales of finished pharmaceuticals by Western multinationals will also help to redress the balance.

The net winners will be the Indian and Chinese pharmaceutical industries, which will see their manufacturing industries increase in size, bringing the general prosperity of the people to higher levels. The net losers will be those companies in the West that refuse to adapt to this change and continue to compete head-on with companies from these regions. Those that adapt to this growing reality by buying their own Asian capacity and continuing to develop more sophisticated fine chemical technologies and operations for Western customers will continue to prosper.

PATENTS AND THEIR IMPACT ON THE BALANCE BETWEEN INNOVATION AND MONOPOLY

Patents are legal monopolies granted by states in recognition of the need, by inventors, to obtain a return on the time and money spent carrying out research and development to discover, perfect and market new products. In granting a patent, a national or international patent agency must satisfy itself that the invention is novel, practicable and commercially feasible. Although not enshrined as distinct by patent law, patents covering pharmaceutical fine chemicals fall into three categories:

- *Product patents,* which cover the applications of a defined chemical entity in the treatment of a medical condition.

- *Manufacturing (process) patents,* which cover novel reactions or new combinations of reactions to synthesise a specific group of defined chemical entities.

- *Composition of matter patents,* where novel chemical entities, that have never been described before, can be claimed.

Patent terms used to be granted for many different periods of time (ranging between 7–20 years) until quite recently. Today the normal period of exclusivity is 20 years from the date of filing.

The ability to secure patent protection for its inventions is fundamental to the successful conduct of a modern pharmaceutical company. Without the period of exclusivity in which to enjoy high prices and reduced competition, multinational companies simply could not operate in the way they currently do. It is therefore not surprising that they jealously defend this privilege. They spend millions on lobbying governments, the medical profession and the public in general, and when this is not enough, they threaten to withdraw their products from the marketplaces of recalcitrant countries. Legal departments have become a key group within these companies and many now believe that this profession is more important for success than that of pharmacology and medicinal chemistry!

During the last 40 years, the extension of patent life has been granted on the basis that, without generous periods of exclusivity, drug discovery costs could not be recovered. Ever-escalating average prices for the cost of launching a new pharmaceutical have been quoted (up from US$125m in 1990 to US$450m in 1999). These numbers are as much a reflection of the inefficiency of the huge bureaucratic organisations that multinational drug companies have become, as the need to spend money on research. The much vaunted benefits of scale (that are the advertised reason for the merger mania through which the industry is currently passing) only exacerbate the situation.

The reality that monopoly is always a bad thing is demonstrated throughout the world, with government monopoly being the most obvious and painful example. It leads to the proliferation of individuals who add no value to the running of an organisation and the wasting of time by those who do add value in dealing with them! The successful Roman legions of antiquity were said to be 80-men strong, since this was the optimum number of people with which a single leader (the centurion) could operate. Tightly focussed groups like this can achieve so much more than big, unwieldy groups. Thus, patents have the tendency to maintain undesirable levels of inefficiency leading to poor creativity and waste.

The lack of creativity of large, multinational companies is demonstrated by its increasing need, as the companies get larger, to in-licence new pharmaceutical candidates. The US biotech industry has been created essentially in recognition of this fact. The basis of the industry is founded on a simple model. Research scientists combine with individuals with an appropriate commercial background to develop and commercialise new lead compounds so that they can make a great deal of money by selling the half developed product to a multinational company, once its efficacy and safety has been demonstrated. They are able to work hard and long hours to achieve this, because they are young and energetic. Their efforts are backed by investors who take a higher than average risk in order to win a higher than average reward.

If this view appears to be simplistic or, indeed, erroneous then consider the car industry, where patents are famously not enforced. Is it lacking innovation? Does it find it difficult to generate funds to invest in new products?

In the US, patent term extensions are granted in order to compensate for loss of exclusivity created by regulatory processing. These extensions are designed to provide 20 years of exclusivity for the inventor. In the US patent exclusivity can also be effectively extended by issuing 'continuations', which modify the original submissions, based on new information developed during the period of examination. This has proved to be an effective (although artificial) means of achieving significantly longer periods of exclusivity than elsewhere. In Europe, supplementary protection certificates (SPCs) are granted by government agencies to patent holders in order to prolong exclusive marketing rights in certain cases. The complication of amending the member states' patent legislation was avoided by this means. Where a pharmaceutical company can demonstrate that the patent life remaining at the time of granting marketing approval was insufficient, then such approvals can be obtained. As in the US, delays by EU agencies in granting approval were the main reason for the introduction of this concession.

The debate on the value and morality of patents has become ever greater as the science of genetics has been taken up as a major developmental area for the pharmaceutical industry. With patents now granted on whole micro-organisms, animals and plants, as well as individual genes, many believe the whole area of patents should be reviewed. However,

with such huge sums invested in the pharmaceutical industry and the powerful legal representation it has available, reform is not going to be easy.

GOVERNMENT INTERFERENCE (DIRECT AND INDIRECT) IN THE DEVELOPMENT AND OPERATION OF THE INDUSTRY

One of the prime responsibilities of government is to protect the health of its people. It is therefore not surprising that the pharmaceutical industries of all nations are regulated by their governments to a greater or much greater degree (never lesser). In the pioneering days of the pharmaceutical industry, this level of regulation was relatively light, but as with all self-regulated groups, the situation for the whole was wrecked by the stupidity or greed of the few. Noteworthy examples include:

- Following some highly publicised medical disasters, such as the thalidomide scandal, most countries adopted some form of agency to administer the approval of new drugs.

- Given the freedom created by patent protection, too many companies were unable to control their desire to make enormous profits on their new products. As the price of healthcare increased as a proportion of GDP, most governments introduced some way of controlling new drug costs, since this was relatively easy compared with other methods.

- The creation of the US generic industry, while intended to help control drug prices, by introducing real competition, actually created an industry that was effectively licensed to print money. As profitable as these companies were, some, of course, preferred to cut corners. When this was uncovered (the US generic scandal), more government supervision had to be introduced.

This latter event accelerated the involvement of government inspectors in the supervision of chemical manufacturing and added another layer of unwelcome costs to the pharmaceutical fine chemical industry, both captive and independent.

PROFITABILITY OF THE INDUSTRY – CONSTRAINTS TO GROWTH

The pharmaceutical fine chemical industry does not have any control over the markets in which the ultimate finished products its customers make are sold. It is an industrial business, rather than one which sells its products to a non-technical customer base.

Its pharmaceutical customers have a reasonable idea of the industry's cost base and they try hard to maintain surplus capacity and low prices for themselves, by encouraging fierce competition between its suppliers.

This strategy of 'divide and conquer' has limited the majority of companies to develop negotiating muscle, so that they are able to win better contractual terms. One such example is the common practice of the customer asking the supplier to 'share the risk' on new product development, when all the risk is covered by the high profits to which the pharmaceutical company lays claim!

Although historically, major pharmaceutical companies have generally allowed its suppliers sufficiently good prices to achieve reasonable profits, many have felt they needed to invest too much of their surplus cash in expensive new manufacturing facilities and resources. This has left many European, US and Japanese companies with high overheads that they have been finding difficult to recover from their newly won contracts.

The outlook for the industry is positive, but not rosy. The main reasons for this unexciting prognosis are:

- Pressure on prices, created by continuing overcapacity within the industry.
- New pharmaceutical products not requiring fine chemical facilities (especially biologicals, vaccines, gene therapy, monoclonal antibodies, etc.), but biotechnological investments that can generally only be justified by the pharmaceutical company.
- Steady shift of business from high margin innovative products to low-margin commodity products, as the pharmaceutical industry matures.
- Continuing insistence by customers and regulatory authorities on ever more layers of bureaucratic overheads.

In spite of these drawbacks, there are positive signs, particularly for the medium term. The creation of large pharmaceutical groups over the past ten years has meant that many creative people have left during the reorganisations. In many cases, their talents have been recycled into the creation of new companies (generally referred to as biotech companies by the investment community). This dynamic sector has the potential to generate a significant share of new business for the fine chemical industry as they outsource the production of their new products over the coming years.

RESTRUCTURING OF THE CUSTOMER BASE AND THE FINE CHEMICAL INDUSTRY

As major pharmaceutical companies have looked around for new ways to generate better margins for their insatiable investors, many experiments have been attempted, nearly all of which have been failures. In the early 1990s several adventurous companies (Eli Lilly, SmithKline Beecham and Merck & Co.) invested in managed care companies in the US, effectively moving downstream from their existing business. This idea was an unmitigated disaster and all have now exited.

A far more widespread response was implemented to the simplistic idea of the bioscience company. The theory was that research synergies could be extracted from

agrochemicals and pharmaceuticals operations, leading to much higher hit rates for new compounds and an embarrassment of products in the R&D pipelines.

The reality has been that these combined operations have suffered from low profits and poor innovation (a good example is Novartis, created from Sandoz and Ciba-Geigy, a pre-existing bioscience company created by the merger of Ciba Agrochemicals and Geigy Pharmaceuticals). Novartis is now beginning to be unravelled, as are other leading bioscience companies such as Monsanto (agrochemicals) – Searle (pharmaceuticals), AHP and AstraZeneca. It is hard to understand how senior industry managers were able to believe that an intrinsically low profit business like agrochemicals could be comfortably accommodated within a much more highly profitable pharmaceutical business without serious profit erosion.

The human waste, dislocations and poor efficiency of these experiments has been exacerbated by a whittling down of manufacturing capacity by companies experiencing low profits and the building of new plants by companies with surplus cash.

The investment bankers and advisors who advocated these experiments have recently begun to make inroads into the fine chemical industry. Small/medium-sized companies are regarded as easy prey for building up a portfolio of companies that can be presented as a large fine chemical company, 'fit to compete at the appropriate scale'. At the time of writing this type of activity is continuing to erode the production base of many European countries. The benefits of these loose groupings to the industry (and to its customers) remain to be seen, but early signs are not good. Perhaps the model example is MTM, a company that briefly achieved sales of around US$450m before the speculative bubble burst.

The fact remains that the customer is best served by well-resourced (but not overly big) companies that offer specialist technologies and the ability to deliver a fast and professional response to their needs.

FUTURE DEVELOPMENT OF THE INDUSTRY – OUTLOOK FOR THE US AND EUROPEAN INDUSTRY

The US and European pharmaceutical fine chemical industry faces the new century with the usual combination of problems and opportunities. Solutions to some of the most urgent challenges must be found, if their future is to be secure:

Globalisation

The West must continue to come to terms with the emergence of a strong and technically competent East (Japan, as has become usual over the past twenty-five years, is an honorary member of the 'West').

Consolidation

The creation of bigger companies by putting together smaller ones will continue, since the causes and facile excuses for such mergers will certainly not go away. The

additional overheads and inefficiencies carried by these companies will have to be paid for by greater efforts to develop new profitable business. If they are able to convince their pharmaceutical customers that they merit favoured supplier status, then they will succeed; those that fail may well re-fragment.

Dominance of multinationals as innovators

The 'biotech' model for new drug discovery may well prove to be the most effective way of harnessing the innovative process. This could result in the restructuring of the pharmaceutical industry into something more akin to the global food industry. In this model, the main activity of the finished pharmaceutical company will be to license new products, have them produced by sub-contractors and their key operational activity will be in the sales, distribution and marketing of the dosage forms.

Such a model would further divide the pharmaceutical fine chemical industry into those offering higher volume, lower margin production services (the large companies) from those offering higher margin developmental services (small companies).

APPENDICES

GLOSSARY OF TERMS

Throughout this report, many specialised terms will be used without further definition than appears below.

Biotech companies

These small research companies are funded by shareholders looking for a high return on their investment. The prize is a major new pharmaceutical product that can be licensed to one of the larger marketing companies. Although labelled 'biotech', many companies develop small molecule candidates. Their founders are generally ambitious refugees from the major multinational research-based companies. These companies generally outsource their chemical production, although this potentially interesting benefit to the PFC industry is somewhat diluted by the fact that their licensees often produce the API themselves.

Innovative pharmaceutical company

A pharmaceutical company that discovers and develops novel compounds (NCEs). Given the high development costs of pharmaceutical R&D, these companies need to be substantial enterprises, although there are exceptions: biotech companies and publicly or privately funded research institutes.

Pharmaceutical

Pharmaceutical products, finished products and medicines are all terms used for the formulated mixture of chemical constituents that are given to treat medical conditions.

(Pharmaceutical) active ingredient

The chemical component of a pharmaceutical that confers a therapeutic effect. Also called API (active pharmaceutical ingredient), bulk active, drug, medicinal chemical, raw material (from the perspective of a pharmaceutical producer). When novel, APIs are also termed NCEs (new chemical entities).

Pharmaceutical company

A company that markets formulated (finished dosage) pharmaceutical products.

BIBLIOGRAPHY

The main source of information for this report has been the files and reports written by myself in conducting projects for clients of my specialist consulting company, Brychem. Naturally, only non-confidential information has been reported here, but the majority of industry information that has been obtained has been by direct discussions with pharmaceutical fine chemical companies, their suppliers, agents and their customers. Because a consultant is usually unable to reveal the names of his clients, little more can be said about these sources. However, I would like to make it clear that the contribution made by Brychem's client-base is here gratefully acknowledged.

The following published books, reports, databases, exhibitions and magazines make a useful contribution to all individuals working within the pharmaceutical fine chemical industry. It is not meant to be exhaustive; rather it represents the main secondary sources of published information on the pharmaceutical fine chemical industry used by Brychem.

Books

The Merck Index, published by Merck & Company, Whitehouse Station, New Jersey, US. (This is a valuable resource, listing all major pharmaceutical actives, with brief profiles and the structure of each one).

Magazines (pharmaceuticals)

Scrip, published weekly by PJB, Richmond, Surrey, UK (good for industry news)

Magazines (fine chemicals)

Chemical Marketing Reporter, published weekly by Schnell Publishing, New York, US

Chemical Weekly, published weekly by Sevak Publications, Bombay, India (import/export statistics particularly useful)

Performance Chemicals Europe, published bimonthly by Reed Publishing, Sutton, Surrey, UK

Chimica Oggi, published bimonthly in English by Tekno Scienze srl, Milan, Italy

Pharmaceutical reports

Merrill Lynch and *Lehman Brothers* produce useful reports on the international pharmaceutical industry. These reports present the companies and markets from the perspective of the financial industry and make useful reading for industrialists. Although not freely available, they can generally be obtained by application.

UBS used to produce similar reports on the chemical and the pharmaceutical fine chemical industry, but the analyst group was disbanded in 1998.

Pharmaceutical fine chemical reports and databases

Monographs and Market Reports on Antibiotics: *Chemica* (Caterham, Surrey, UK) publishes an excellent series of well-informed reviews on these topics.

Stanford Research Institute (Menlo Park, California, US) publishes annual reports on the producers of chemicals and fine chemicals in its handbooks, covering Europe, North America, South America, S E Asia and China.

World Chemical Producers Database, published by *Chemical Information Services Inc*, Dallas, Texas, US (useful CD-ROM databases on chemical / fine chemical producers)

B.I.C.3000, published by *Becker Associates*, Paris, France. This is a CD-ROM database that links bulk pharmaceuticals with their intermediates and includes chemical structures, as well as names.

Kilochem, published by *IMS International*, London, UK, produces value and volume estimates for bulk drugs, broken down by producers and countries. The information is derived from the consumption of finished dosage forms. IMS has a monopoly on this type of data and so the price of this information is very high, making the data somewhat exclusive.

The *US Food and Drug Administration* publishes useful data *free* on pharmaceuticals on its web-site. Lists of drug master files lodged by bulk drug and intermediate producers represent a useful resource of data on who makes what.

Pharmaceutical fine chemical exhibitions

CPhI, organised annually by *Miller Freeman* of Amsterdam, Netherlands is probably the most popular industry exhibition. It is certainly the biggest in Europe . Location varies, but has been in Frankfurt, Milan, Paris, London, Turin and will be in Lyon in June 2000. Similar exhibitions are also held in the USA and Asia.

Informex, organised annually by the *US Society of Chemical Manufacturers (SOCMA)* and usually held in New Orleans is the premier exhibition in the US.

Technical literature

The online version of *Chemical Abstracts* (published by the American Chemical Society, US), available through STN, is the most versatile source of primary information on pharmaceuticals and fine chemicals. Access via the Internet makes it much easier to use than previously. Abstracted information published as patents and scientific papers from 1966 is very comprehensive and can be searched by name, formula and sub-structure.

