China – from self-sufficiency to world leadership

China has become increasingly prominent in the production and sale of pharmaceutical fine chemicals over the past decade. Dr Rob Bryant and Jiang Song report on the country's industry structure, its major players and its future development.

According to the government's strategic plan for 1996-2050, China's total drug sales are expected to reach Yuan 700 billion (US$84 billion) by 2010, an average growth rate of just over 16% from 1996. Whether this ambitious growth rate is achieved or not, very few would dispute that China is set to become one of the major pharmaceutical markets in the world.

China's industrial development has accelerated since the reforms of Deng Xiao Ping in the late 1970s and its pharmaceutical industry has been one of its most successful. The use of Western medicines in China is usually said to have begun in 1952, when the antibiotic chloramphenicol was first synthesised and produced domestically. Since that time the country has developed an enormous infrastructure, with over 5,600 registered pharmaceutical companies, of which 3,000 manufacture fine chemical ingredients and intermediates. In fact over 1,500 bulk drugs are currently made in China and sold in 3,500 finished formulations. Given the major advances now taking place in China, it is timely, as the year 2000 approaches, to look at how the industry is developing.

The value of the Chinese pharmaceutical market in 1996 totalled about Yuan 90 billion (US$10.8 billion). In Figure 1, the output of the country's pharmaceutical chemical industry is shown for the period 1991-1996. This includes bulk pharmaceuticals and finished formulations, reflecting the industry's integrated manufacturing structure. The domestic industry supplies around 60% of the market, with the balance coming mainly from imported finished products from producers in the US, Europe and Japan. The sales growth in US$ terms is distorted by the abrupt change in exchange rates in 1994, when the previous dual exchange rate system was scrapped.

The industry is supervised by SPAC, the State Pharmaceutical Administration of China, which is based in Beijing. It supervises over 90% of the country's pharmaceutical companies. These are highly integrated operations. A typical company will be responsible for carrying out product and chemical process development, bulk active and formulation manufacture and sales. Many companies are integrated back into the production of basic chemical raw materials and even process equipment. Of the 5,600 companies registered, the overwhelming majority are very small by Western standards, with just 132 with assets greater than Yuan 40 million (US$4.8 million) and 23 with assets more than Yuan 100 million (US$12 million).

The ten leading pharmaceutical companies in China, by sales, are listed in Figure 2. These figures reflect actual sales, rather than the often quoted output value, which is the nominal worth of the products manufactured at list prices. Many of the companies in this list sell more than their output, because they trade goods as well. Other important producers, not listed in Figure 3, include Hebei, Zhejiang Haimen, Shijiazhuang, Zhejiang Xianju and Tianjin Pharmaceutical Factories.

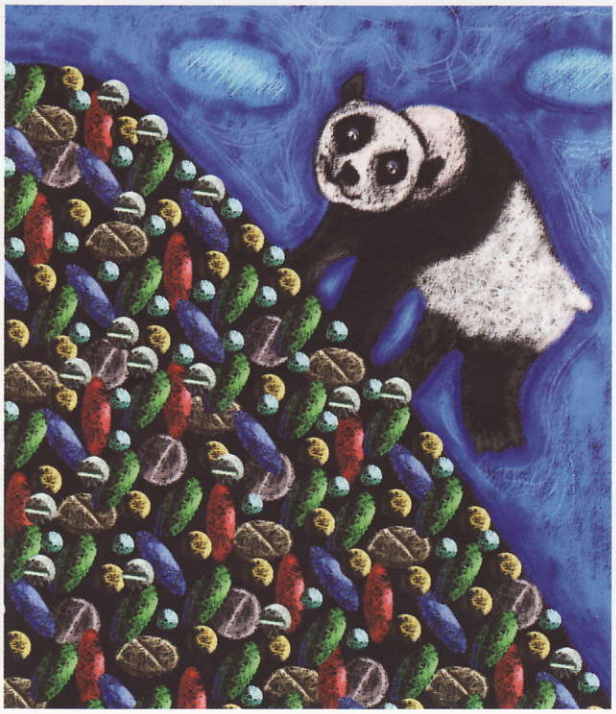

Illustration by Rob Wilcockson

China's determined climb to the top. The country is set to become one of the major pharmaceutical markets in the world, and a leader in the supply of pharmaceutical fine chemical actives and intermediates.

Sales (billion)	Year						
	1991	1992	1993	1994	1995	1996	2000E
Yuan	35	45	53	61	74	86	150
US$	**6.45**	**7.82**	**9.14**	**7.22**	**8.89**	**10.36**	**18.10**
Yuan/US$	5.43	5.75	5.80	8.45	8.32	8.30	8.30

Figure 1: Output of the Chinese pharmaceutical chemical industry from 1991-2000. Source: Beijing Cons Bio-Tech Development Company.

Patents

Until the beginning of 1993, it was not possible to obtain patents for chemical drug substances in China, although the earlier 1985 patent law allowed process patents. Drugs invented outside China between 1.1.87 and 31.12.92 can be granted Administrative Protection for seven and a half years, where earlier protection had not been obtained and the product had not been sold previously in China. This system is only available to countries that have bilateral agreements with China. To date, these partners are the US, the European Community, Switzerland, Japan, Sweden and Norway. By January 1997, 60 foreign applications for administrative protection had been granted under these provisions.

Pharmaceutical factory or company	Location	Sales (1995) Yuan (mill)	US$ (mill)	% net profit
North China	Shijiazhuang, Hebei	2,050	246	16
Shandong Xinhua	Zibo, Shandong	1,243	149	3
Guangzhou Baiyunshan	Guangzhou, Guangdong	1,083	130	6
Northeast General	Shenyang, Liaoning	861	103	6
Harbin	Harbin, Heilongjiang	840	101	7
Zhuhai Livzon Pharmaceutical Group	Zhuhai, Guangdong	821	99	13
Jingjiang Glucose Factory	Jingjiang, Jiangsu	736	88	27
Shanghai Sunve	Shanghai	556	67	6
Shandong Lukang	Jining, Shandong	487	58	10
Sichuan	Chengdu, Sichuan	379	46	7

Figure 2: Leading Chinese pharmaceutical companies by sales in 1995. Source: Beijing Cons Bio-Tech Development Company.

The 1993 Chinese Patent Law grants 20 year patents and is similar to the patent laws of the majority of Western countries. The patent laws of China are supported by the central government agencies, which also try to limit the number of versions of a given active ingredient by granting manufacturing exclusivities of three years to the first company that launches the drug.

Quality assurance and GMP

Poor quality and unreliability of supply are the major issues that concern Western companies when dealing with products made in China. As the industry has become more export oriented, the Ministry of Health (MOH) has responded to such criticisms, promulgating guidelines on good manufacturing practice (GMP) in 1988 and 1992. The MOH then introduced its own GMP certification procedures in 1993, working with a number of leading companies to improve the situation. The cost-burden created severe difficulties and this first programme was a failure. More recently the MOH, in association with SPAC and other ministries, introduced a new certification procedure under the direction of a new agency, the China Certification Committee for Drugs (CCCD). The SPAC has offered an additional incentive to companies that achieve certification, on top of the five year GMP certificate: bulk drugs and preparations will enjoy a 3% premium on the ex-factory prices for the domestic market, respectively. To date, five companies, of which four are foreign joint ventures, have been granted CCCD GMP certificates. Many companies have also applied for foreign certification for some of their products. IMS China Update (jointly published by IMS Pacific and WiCon International) reports that 60 products made by 45 factories have been submitted for approval by the US Food and Drug Administration by the end of 1995.

Technologies

Processes for older products are normally acquired and developed by individual factories, sometimes with the help of foreign technology transfers.

Process technologies for new products are usually developed by Chinese research institutes. Until the early 1980s, most R&D projects were funded by the State (through SPAC, the local administration office or bureau of science and technology) and so the processes were available to factories essentially free of charge. State funding has been reduced over the past 10-15 years and many research institutes have increasingly sought funding from the bigger pharmaceutical factories, on an exclusive basis. The factories are now carrying out much of their own process and product development.

No real protection for technologies existed in China before 1993, especially for pharmaceutical fine chemicals. The process technology was thus free for anyone to operate. This led inevitably to too many producers of popular products (an identical situation exists for similar reasons in India). As in India, cut-throat competition led to a ridiculous downward spiral in prices that did no-one very much good. Recent, traumatic price wars, in which the international competitors were also sucked in, have been fought over penicillin and vitamin C. This has left the industry in an unsatisfactory financial state, with many factories selling their products below cost. India has suffered a similar loss of profitability over the same period.

A newer system of New Drug Certificates has been introduced by the authorities to try to control the proliferation of producers using the same process, but their effectiveness remains to be seen.

Very few foreign joint ventures involve the transfer of processes for making the newer bulk active. Usually these are imported for formulation in China by the pharmaceutical joint venture. This is a major headache for the Chinese authorities, since it limits the local income from the foreign joint ventures.

Price structure

The Chinese authorities have put complex price controls in place. Price calculations depend on SPAC's understanding of the cost of manufacture of the bulk active ingredients and the finished formulations. Understandably, margins on drugs made by many companies are lower than on new products that are made by one or two companies. The system is further complicated, as it is elsewhere, by rebates and commissions given to distributors and customers (particularly high in the case of rebates for hospital pharmacies). In Figure 3 an attempt to show the average build up of a typical pharmaceutical product is presented. It shows that the average list price of a finished pharmaceutical product is generally around 5-7 times the cost of the bulk active. However, these margins can be much less for older, high volume items, such as aspirin, and much higher for newer specialities.

The real costs of production of bulk pharmaceuticals in China are certainly low compared with most other countries, but there are many distortions that allow companies to sell at very much lower prices

Raw material cost of bulk	Cash cost of bulk	Ex factory bulk price	Ex-factory dosage cost	Ex-factory dosage price
0.5	1.0	1.1-1.4	4.4-5.6	4.6-7.6

Figure 3: Price structure of typical Chinese pharmaceutical products (cost of bulk active = 1). Source: Brychem/Beijing Cons Bio-Tech Development Company.

Pharmaceutical factory	Exports (1995)	
	Yuan (mill)	US$ (mill)
North China	488	59
Shanghai Sunve	388	47
Northeast General	386	46
Ganjiang	261	31
Shandong Xinhua	212	25
Fuzhou Antibiotic	200	24
Zhejiang Haimen	189	23
Sichuan	178	21
Southwest Synthetic	161	19
Harbin	157	19

Figure 4: The top ten Chinese pharmaceutical exporters in 1995.
Source: Beijing Cons Bio-Tech Development Company.

than would be justified, if they had to recover all their costs. Government subsidy and financial manipulations by the producers and their agents distort the true economics of these companies, as they do elsewhere in the world. Many Western governments and large multinationals are equally as fond of cross-subsidies and creative accounting as their Eastern counterparts and real progress towards 'fair competition' will only be possible when this type of activity is eliminated.

In the recent past, Chinese pharmaceutical producers have supplied surplus stock via the State trading enterprises at relatively low prices. Over the past 5-10 years, however, many companies have begun trading on their own behalf and have targetted exports as an important source of income. In Figure 4, China's leading exporters of bulk pharmaceuticals are listed, with their export sales for 1995.

Sales of bulk pharmaceuticals for export are very much higher than sales between domestic producers. It is reported that around half the bulk pharmaceutical production in China is made for export. The value of bulk pharmaceutical and finished product exports was estimated at Yuan 11 billion (US$1.33 billion) in 1996.

Sales of pharmaceutical intermediates are also important and, because gross national product and quality assurance issues are less demanding, many companies generate useful income by selling into export markets a proportion of the intermediates produced for their own end products. Major Western pharmaceutical companies, as well as generic producers, have taken advantage of this source of competitively priced intermediates to reduce costs.

Chinese exporters do not generally appoint foreign representative offices, most selling through traders in Beijing, Shanghai, Hong Kong and Taiwan. Direct contacts between domestic companies occur at the two annual Chinese pharmaceutical trade fairs (increasing numbers of foreign traders attend these too). Most foreign contacts are made at the annual international raw material fair in Guangzhou and abroad at exhibitions such as CPhI, PhIUS and PhIA.

Foreign involvement

Pharmaceuticals was one of the first industrial sectors to open up to foreign investors. Since 1980, when the first Sino-foreign pharmaceutical joint venture was set up, direct foreign investments have flowed into the pharmaceutical industry at an increasing rate. By the end of 1995, two in five State-owned pharmaceutical enterprises had received foreign investment. According to statistics, the foreign investment in 1,416 foreign-funded pharmaceutical enterprises was US$1.95 billion (contracted spend), with US$1.27 billion actually invested. Eighteen of the top 20 global pharmaceutical multinationals have entered the Chinese market in this way.

The quality and scale of the inward investments made by foreign companies has disappointed the Chinese authorities, who wish to see much more investment in fine chemical manufacturing capacity. As things stand, however, setting up a joint-venture is a good way to gain access to the Chinese partner's pharmaceutical distribution network. Most companies have invested in joint ventures in order to sell their own products into China, with only a few formulated products being made locally. Importing bulk actives is more profitable because the joint ventures are able to keep finished product prices higher, since local price-setting regulations are based on bulk drug costs. On the other side, poor management control of the production of bulk products by Chinese plants deters many Western companies from setting up local fine chemical manufacturing units. A number of companies have set up successful manufacturing plants, nevertheless, and China will become an increasingly important location for pharmaceutical fine chemical production, as the difficulties on both sides are overcome.

Bulk products

Chinese consumption of bulk pharmaceuticals continues to grow rapidly, with imports constituting a significant share of domestic demand. The leading products by import value are mostly, but not exclusively, antibiotics. Figure 5 lists the import value of leading bulk pharmaceuticals for the domestic market in 1995. Efforts to substitute more of these imports with locally produced bulk actives continue, but in some technologies the industry is unable to produce (or produce enough) products to compete successfully with foreign competition. However, in the case of other products, Chinese producers are major international players. Penicillin GK, ciprofloxacin and norfloxacin, vitamin C, lincomycin, niacinamide and many steroids are just some of the bulk actives for which Chinese companies supply an important share of world demand. Some multinationals have taken advantage of China's low production costs and are exporting bulk actives for their own consumption. Monsanto, Glaxo Wellcome, Hoechst and Pharmacia & Upjohn have well-established primary production operations. More recently, Bristol-Myers Squibb has begun exporting captopril to its own worldwide formulation plants.

Although Chinese companies produce a wide range of bulk pharmaceutical actives, the products do not always meet the high standard required for their sale into the most lucrative export markets. China continues to be viewed as a supplier of low priced older bulk actives and pharmaceutical intermediates, although this is gradually becoming less true. A selection of leading Chinese-made bulk pharmaceutical chemicals is presented in Figure 6. The Figure also shows some of the violent price swings that have affected the market in 1996.

Innovation

Little has been said up to now about innovation in the Chinese pharmaceutical fine chemical industry. There are many excellent chemists, chemical engineers and biotechnologists in China and many have experience of working in overseas research institutes and pharmaceutical R&D groups. The impact of their enterprise is coming to the attention of the international industry and their new companies will benefit from adapting the best methods of East and West to discover ways of producing existing pharmaceutical actives more effectively.

Typical of such companies is Beijing

Bulk pharmaceutical product	1995 imports US$ mill
Cefazolin	87.5
Cefradine	46.8
Cefalexin	26.2
Ampicillin	20.3
Captopril	8.3
Cefoperazone	6.1
Cimetidine	5.1

Figure 5: Import sales of top pharmaceutical products (1995). Source: China Medipharm Insights.

Bulk pharmaceutical product	US$/kg	Change on 1995 (%)
Ciprofloxacin	90-96	-18
Erythromycin	126-130	+28
Hydrocortisone acetate	723	0
Ibuprofen	13.3	-4
Lincomycin (/BOU)	79-81	-32
Naproxen	60	-43
Nifedipine	36	+11
Paracetamol (acetaminophen)	3.3	0
Penicillin G potassium (/BOU)	17-18	-23
Rifampin	117	-1
Vitamin C	6.6	-45

Figure 6: Prices of pharmaceutical actives produced in China in 1996.
Source: China Medipharm Insights.

Unipharm Laboratories which developed an improved process for making azithromycin and has now taken 80% of the Chinese market for this product (Tailite), against competition from the US company, Pfizer. It will soon announce a joint venture to market the bulk active worldwide. The Chinese company also recently entered into a partnership with the Polish company PRI to market its products in China. It has established a US company to develop its business in this leading pharmaceutical market. This is just one example of the many entrepreneurial Chinese groups that will contribute to the success of China's pharmaceutical and pharmaceutical fine chemicals industry over the next 20 years.

In many ways the Chinese pharmaceutical industry still needs to do a great deal to modernise itself. It has a vast number of companies that are making too many duplicate products and active ingredients. The majority of the domestic producers are making old or low cost bulk pharmaceuticals, with the newer products having to be imported because of the lack of local technology or suitable production capacity. The multinational pharmaceutical companies have a significant share of the domestic market and will continue importing the newer, expensive drugs from their own factories in order to maximise their profits. Naturally they will resist China's attempts to retain its self-sufficiency as these new, Western products are introduced.

In spite of these continuing challenges, China has come a long way in the last ten years and there is evidence that the many newer producers that are springing up (particularly in Jiangsu, Zhejiang and Guangdong provinces) will begin to replace the imports of the more expensive drugs. As their adherence to internationally accepted production norms improves, the value of their exports of bulk pharmaceuticals to developed markets will increase. As its domestic market continues to expand, China, like its big Asian neighbour India, will develop a leading position in the supply of fine chemical actives and intermediates to the international pharmaceutical industry. SM

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