

# Adapting to an influx of Western medicine

*South Korean pharmaceutical fine chemical companies find themselves caught between the lower costs of China and India and the financial clout of the multinationals. Dr Rob Bryant looks at recent changes in the country's industry structure and the impact on local production*

Until recently, traditional medicine based on herbal extracts played the predominant role in Korean health-care. Tonics containing such extracts are consumed like soft drinks in the West, and still account for an important part of pharmaceutical spending. In the West, however, they would probably be classified as 'health and sports drinks'.

The rise of the modern South Korean pharma market has been driven by the introduction of anti-infectives and vaccines, which were able to cure or alleviate symptoms that traditional medicine could not. Joint ventures with Western and Japanese companies were set up between 1960 and the mid-1980s, leading to the introduction of modern active pharmaceutical ingredients (APIs) in hospitals and clinics. The Korean partner usually negotiated a manufacturing licence for the API, which led to the establishment of many plants in which semi-synthetic penicillins, cephalosporins and vaccines were produced for both local and Asian markets.

The majority of South Korean pharma

companies became dependent on their international partners for a flow of these new products. And these partnerships enabled big pharma to ensure its intellectual property rights were protected in South Korea. The government enacted product patent legislation in 1987, extended in 1995 to satisfy the demands of TRIPS.

As the market changed, many leading companies began developing their own products in the hope of securing higher rewards. There were also new entrants into the pharma industry. In particular, the large chemical-based 'chaebol' (South Korean conglomerates) began to make significant investments in these 'downstream businesses'. LG (previously Lucky-Goldstar), Samsung, Daesang (formerly Miwon and Sewon) and SK (previously Yukong) are four such examples, each of which set up pharmaceutical, biotechnology and fine chemical groups during the late 1980s to mid-1990s. The results of these investments have been mixed, however, reflecting how hard it is to succeed in this innovative sector. Despite the fact that several companies

have invented and licensed new products to multinationals, few are likely to generate the type of revenues necessary to grow beyond the confines of the local market.

Then came the Asian financial crisis in 1997, which had a major impact on the pharma and fine chemical industries. In particular, the poor competitiveness of local antibiotic fermentation operations was exposed. Since then, pharma companies have increasingly sourced their APIs from cheaper Asian firms, including a number of Chinese-Korean joint ventures. A more recent sea-change in the industry followed the government's introduction of laws controlling the sale of pharmaceuticals. The new system resembles that in Europe, where physicians prescribe medicines, but only pharmacies can sell them. The full impact of this regime on pharmaceutical prices and profitability is yet to be seen.

## South Korean pharma market

With a population of more than 47 million, South Korea spent more than US\$21 billion on healthcare in 1999, according to IMS, and its pharmaceutical sales are generally said to rank tenth highest in the world. However, there is some discrepancy as to what these sales amount to. In 2001 the IMS quoted a figure of US\$4.9 billion while the South Korean industry said it was US\$6 billion. The difference is certainly one of definition with the lower figure probably under-representing the traditional herbal tonic sector. One source suggests this latter business could have totalled as much as US\$2 billion in 2001. Figure 1, which compares Korea's top-selling products in 1995 and 2001, shows that the trend has been for traditional remedies to be displaced in value terms by Western-style products as the industry moves towards the production and sale of the types of pharmaceuticals used in

1995			2001		
Marketer	Brand	Active Ingredient	Marketer	Brand	Active Ingredient
Dong-A	Bacchus-F	Tonic (taurine)	Pfizer Korea	Norvasc	Amlodipine
Il Yang	Wonbi-F	Tonic drink	Dong-A	Bacchus-F	Tonic (taurine)
Janssen Korea	Propulcid	Cisapride	Korean Green Cross	Albumin KGC	Albumin
Kwang Dong	Kwansangantang F	Herbal tonic	Roche Korea	Xenical	Orlistat
Il Dong	Aronamin Gold	Vitamin B complex	Bristol-Myers Squibb	Taxol	Paclitaxel
Cheil Jedang	Hepaxin B	Hepatitis B vaccine	Bayer Korea	Adalat Oros	Nifedipine
Yungjin	Guronsan Vermont	Tonic drink	GlaxoSmithKline	Zeffix	Lamivudine
Janssen Korea	Sporanox	Itraconazole	Janssen Korea	Sporanox	Itraconazole
Chosun Muyak	Solpyo Woowhang	Herbal sedatives	Handok Aventis	Amaryl	Glimepiride
Koren Green Cross	Albumin KGC	Albumin	Il Sung	Augmentin	Amoxicillin-K clavulanate

Figure 1: Top ten South Korean pharmaceutical products, 1995 and 2001.

the US, Europe and Japan. What is also noticeable is the replacement of local companies by multinationals as suppliers of these top-selling drugs.

Greater western penetration of the local market has brought about more widespread western practices. In 1990 the government issued guidelines for the manufacture of finished products and raw materials and, by 1995, more than 75% of the pharma industry had set up some kind of Korean GMP system. Control of the production of raw materials has lagged behind but many companies comply with basic international standards. Since 1995, a number of companies have set up more stringent requirements to secure overseas business and several now comply with US and European standards of GMP. Recently, LG Bio Sciences, Chong Kun Dan (CKD) and Yuhan received US FDA approvals for the GMP manufacture of APIs.

Also since 1995, the patent regime in South Korea has provided the standard protection of novel compounds, products and processes laid down in TRIPS. Prior to this, South Korea had enacted 15-year patents, covering novel compounds, processes and products. In any case, companies have tended to respect product patents more than is the case in other parts

of Asia, since most new products were secured by in-licensing. With a developing innovative capability of its own, South Korea is likely to continue to observe international intellectual property regulations.

The most dramatic recent change in industry regulation came when the Pharmaceutical Affairs Law was published in December 1999. This set out a completely new system for prescribing and dispensing drugs. Previously, patients were able to buy medicines at pharmacies (without a prescription) and pharmacists were allowed to prescribe drugs. Physicians could also prescribe and dispense drugs. The new law introduced a tightly controlled separation of dispensing (by pharmacists) and prescribing (by physicians), as well as allowing some generic substitution for the first time.

## Local industrial strategies

As companies began to adapt to the rapidly evolving market conditions some strategies worked better than others. Those firms that depended on herbal medicines have tended to lose out, although Dong-A has maintained its number one position with a combination of herbal products, in-licensing and its own R&D. Two of the top five companies – Yuhan and Hanmi – have

prospered by developing their own generics brands, whereas Choongwae and Daewoong have based their business on foreign in-licensing.

However, the general trend has been for multinational subsidiaries and joint ventures to gain ground at the expense of local companies, which is likely to continue reducing the business from in-licensed drugs. Figure 2, which charts the changes in the sales of leading pharma companies from 1996-2002, shows the rapidly evolving fortunes of the industry. LG Life Sciences has recently been set up as a separate operating company within the LG Holding Group and its 2003 pharma sales are likely to place it within the top ten pharma companies.

Another obstacle for the home players has been Chinese and Indian competition in the fermentation industry. What Figure 1 fails to show is the importance of anti-infectives, particularly antibiotics made by fermentation, in South Korea over the past 25 years. Production of semi-synthetic penicillins (based on penicillin G imported from China), cephalosporins (from locally produced cephalosporin C) and other antibiotics underpinned the local industry until quite recently, with most plants set up as subsidiaries of pharma companies.

In 1996, all but four of the top 20 locally-

Company	Sales 1996 Won billion	Sales 2001 Won billion	Sales 2002 Won billion*	Notes
Dong-A	255	496	549E	Top-seller in Korea; taurine (Bachus-F). Has active R&D pipeline for own drugs
Chong Kun Dan (CKD)	151	261		Several US fermentation products. Produces mevalonic acid for simvastatin in partnership with Hovione, Portugal
Choongwae	134	242	268E	
Yuhan	153	259	285E	Moved into supplying APIs to US
Hanmi	99	185	230E	Leading generics company in Korea
Daewoong	149	168	111E	Strategic alliance with Eli Lilly
Handok Aventis	95	160E		
Cheil Jedang	116	135		Formerly part of Samsung. Fermentation business
Il Dong	132	130	155E	
Dong-Hwa	169	126		
Boryung	94	110E		
Shinpoong	85	110E		
Il Yang	120	108		Specialises in manufacture of antacids
Chosun Mooyak	118	102		
Kwangdong	117	90E		
Bukwang	–	82	84E	Licensed cevudine to Gilead Biosciences
Yungjin	147	81		Specialises in cephalosporins and penicillins

E = estimates. Exchange rates: 950 Won:US\$ (1996); 1,250 Won:US\$ (2001).

Figure 2: Top South Korean pharma companies (based on 2001 sales).

Sources: Pharmacy in Korea 1997, Daewoo Securities (\*), Dun & Bradstreet, and company websites.

made APIs (by sales value) were fermentation antibiotics and only one was not an anti-infective. But the entry of Chinese, and more recently Indian, producers caused international bulk prices to sink below many companies' production costs. Some, such as Woopyong and Sewon, closed their plants.

### Switching to synthetic APIs

The manufacture of synthetic APIs has begun to emerge as an alternative activity, although it is still a relatively small sector. China became a prime source of cheap raw materials and basic intermediates and many South Korean companies set up trading or manufacturing operations in this booming market.

Production of pharmaceutical intermediates in South Korea is mainly in the hands of three types of companies (see Figure 3 for a list of the leading producers):

- Small- to medium-sized chemical or phar-

maceutical producers that have been able to produce chemicals cost-effectively.

- Groups set up by the chemical-based conglomerates.

- Small independent synthesis laboratories. In general, companies that have developed from the production of basic chemicals (feed-stocks, dyestuffs and electronic chemicals) have stuck to basic intermediates, leaving them vulnerable to low-cost Chinese imports.

When attacking the pharmaceutical fine chemical business, the big conglomerates – such as Samsung, Daesang (formerly Miwon and Sewon), SK, Hansol and LG – have tended to focus on sophisticated intermediates destined for Europe and the US. The fledgling South Korean innovative sector has not developed enough to offer a sufficient supply of business. Starting from their core technology capabilities, these larger companies have developed, in particular, innovative routes to chiral intermedi-

ates for new APIs, a strategy devised to avoid competition with cheaper producers in India and China. Although it has had some success, the drive by big pharma companies to improve their profits has forced them to focus more on costs. These chaebol-based fine chemical producers of intermediates are now passing through a difficult period of re-assessment to find more profitable lines of business. Indeed, both Daesang and Samsung have closed their pharmaceutical operations, although the latter is still looking to re-enter the business.

Smaller fine chemical producers have followed a different strategy in which they supply established intermediates and APIs (loosely called generics) to Korean and export markets. Many small units produce under contract to entrepreneurial companies, many of which were set up to exploit innovative technologies that do not conflict with patented processes. Although such

Company	Notes on fine chemical activities	Products
Daelim Chemical	Chloralkali plant set up in 1970s – moved into biocides, electronic chemicals and pharmaceutical intermediates	2,4-dihydroxyacetophenone, 1-bromo-3,5-dichlorobenzene, 2-phenylpropionic acid, methyl 2-oxopentanoate
Daesang Corporation	Produces fermentation amino acids and nucleosides for pharmaceutical, food and animal nutrition industries	L-phenylalanine, aspartame, L-lysine (plant sold to BASF Korea)
Dong Bang Future Chemical	Makes raw materials for Il Yang Pharmaceuticals	adrenalone, azintamide, felbinac, flurbiprofen, hexaprenaline sulphate, idebenone, ipraflavone, ketoprofen, loxoprofen, mefenamic acid, Taxol
Dongwoo Fine Chem	Wholly owned by Sumitomo Chemical. Has moved from just producing chemicals for electronic materials	Pharmaceutical fine chemicals
Doosan Corporation, Biotech Business Unit	Catalogue company producing sophisticated fatty acid derivatives	omega-fatty acids, phospholipids and prostaglandins
Estechpharma	Has produced mainly formulations, but now also makes APIs. Developed some own products, eg acamprostate for treatment of alcoholism	acamprostate, aceclofenac, acemetacin, afloqualone, albothyl, alibedol, bendazac lysine, carovenine, tiropramide, triflusal, D-penicillamine, levosulpiride, roxatidine acetate, piroxicam, triflusal
Hansol Chemience	APIs, chiral intermediates and other basic chemicals	APIs: clarithromycin, terbinafine HCl and lansoprazole. Intermediates: Chiral epoxides, arene amines and pyrrolidines
Kolon Chemical	Resins and polymer producer that has moved into pharmaceutical intermediates	Lansoprazole
Kyung Dong Pharmaceutical	Founded in 1975. Pharma formulations and APIs	APIs: aceclofenac, cilostazol, difemerine HCl, levofloxacin, nizatidine, rebamipide, tiropramide HCl
LG Bio Sciences (pharma activities)	Discovers and produces pharma products; back-integrated into APIs	APIs (fermentation and synthetic) and intermediates for a wide range of products. Has built a new FDA-approved plant to produce its own fluoroquinolone: Factive (gatifloxacin).
Samchully Pharmaceutical	Produces AZT and nucleosides: acyclovir, doxifluridine, trifluridine, zidovudine, DMT-nucleosides, 2'-deoxynucleosides	Also offers intermediates: 2-deoxy-D-ribose, L-ribose, 2-deoxy-L-ribose. 6-chloroguanine, 2,6-diaminopurine
Samsung Fine Chemicals	In 2002, acquired generic intermediates producer, Handuk Chemicals. Limited range of chiral intermediates based on gamma-hydroxybutyrolactone (HGB)	HGB produced from starch, 3-(S)-hydroxyTHF, ECHB (for atorvastatin). Marketing venture with US-based Synthron was dissolved in 2002
SK Corporation	Intermediates based on a number of technologies, especially continuous hydrogenation. SK Chemical & Energy has a unit in New Jersey, US	Chiral intermediates: butane-1,2,4-triol trimesylate, 3-(S)-hydroxyTHF, ECHB (for atorvastatin), protease inhibitors. SK (Taejon) offers advanced intermediates for benazepril, quetiapine, terbinafine and carvedilol
Yuhan Chemical	Synthetic: levofloxacin, zidovudine, stavudine, ribavirin, ketoprofen, felbinac, mefenamic acid, pyrazinamide, piperacillin sodium, cilostazol, L-carnitine	Fermentation: rifampicin, serratiopeptidase, avermectin (dev). Intermediates: beta-thymidine, 2-deoxyribose, 3-(S)-hydroxy THF, ECHB (for atorvastatin)

Figure 3: A selection of Korean companies producing significant quantities of pharmaceutical fine chemicals.

companies find it difficult to survive, some may well become successful medium-sized businesses in the future.

The recent rapid growth of South Korea's pharma industry is likely to continue to outstrip most Western and many Asian markets. However, local pharma companies have been slow to adjust to an appreciating currency and the increasing cost base of its industry. They will continue to suffer from increased penetration of the local market by US and European products. Local participation will decline.

Companies with the capability to develop novel pharmaceuticals may identify promising candidates but without direct access to international markets, the real benefits of discovery are likely to be given up to multinational licensees. Companies dependent on in-licensing are already effectively subsidiaries of multinationals and, as is now the case with Japan, the major drug groups will formalise this de facto situation when it is politically possible to do so.

Generic pharma companies may have a better outlook, but this depends on the willingness of the government to protect their marketing rights against the multinationals. Companies that produce and sell herbal


remedies and vitamins will come under a different set of regulations and tend to diverge from the prescription drug industry, as is the case elsewhere. This may be the sector where most locally-owned companies continue to thrive.

### Strategic choices

Companies making pharmaceutical fine chemicals will need to focus their efforts on producing APIs or advanced intermediates (under contract or as their own products) either to the innovative or generic pharmaceutical sectors. Those supplying the innovative sector will have to ensure their facilities follow international GMP norms, while those supplying the generic sector (local and export) will need to create original process technologies to differentiate themselves from other Asian competition. Whatever strategy they follow, they will need to find ways to overcome the increasingly high operating and investment costs that prevail in South Korea.

At this stage in the development of South Korea's fine chemical industry it is far from clear how well companies will be able to adapt to the emerging demand for their products. The challenge for the large chemi-

cal companies will be to find the management will to invest in fine chemical subsidiaries during the unprofitable years of business development. Where the pharmaceutical discovery effort comes up with new products, group fine chemical operations may be boosted by receiving internal contracts. Otherwise, the examples of Daesang and Samsung will represent a stark warning.

The manufacturing divisions of pharma companies, such as Hanmi and Yuhan, may also experience problems as they come under pressure to reduce costs to match third party suppliers. The smaller fine chemical specialists will come and go on the back of particular skills in niche technologies or chemical synthesis, with perhaps one or two developing into substantial operations. It is hard to predict the future of such companies, but experience in other developed markets provides some guidance. Development of sales outside South Korea must be a priority if companies are to secure the maximum benefit from their technologies and products. 

**•Dr Rob Bryant runs Brychem, a pharmaceutical fine chemical consultancy based in the UK.**