

## **Market Insight - Israel: land of innovation**

*A leading player in the global generics sector, Israel is also home to a number of innovative, R&D-based pharmaceutical and biotechnology companies. Dr Peter Charlish reports*

The State of Israel was created in 1948 yet the country's pharmaceuticals sector has a much longer history. Teva, Israel's largest and probably best-known pharmaceutical company can trace its origins to 1901, when a small wholesale drug business, Salomon, Levin and Elstein, was founded in Jerusalem to distribute imported medicines. That company has long since been absorbed into Teva, but its name lives on as the shape of Teva's distribution business in Israel.

The impetus to establish local manufacture of pharmaceuticals in Israel came in the 1930s, when the Jewish population in what was then Palestine began a boycott of drugs manufactured in Germany. At the same time, as a result of Nazi persecution, Jewish chemists began to arrive from Germany and other European countries, bringing with them expertise in pharmaceutical manufacturing processes. During the Second World War, small companies set up by these immigrants became the sole source of supply for the local market, as well as for neighbouring countries and for foreign troops stationed in the region.

After the war, the precarious economy of the new state of Israel rendered imported pharmaceuticals beyond the reach of most people, and these newly created companies continued to meet domestic demand. In the 1950s, they began to seek export markets just as the local stock market began to emerge and they were thus able to seek capital for expansion. A period of consolidation followed in the 1960s and 1970s as the larger domestic companies began to acquire smaller pharmaceutical firms. In particular, two firms that merged in 1964, Assia and Zori, first acquired a controlling interest in Teva before the three formally merged in 1976 to create Teva Pharmaceutical Industries Ltd.

By the final decade of the last century the Israeli pharmaceutical industry was firmly established as a major supplier of both generic pharmaceuticals and active pharmaceutical ingredients (APIs), and some Israeli companies began to look overseas not just for export markets but with a view to establishing manufacturing operations outside Israel through M&A activity. This strategy has continued into the current decade. To give an idea of the size of the Israeli pharma sector today, total pharmaceutical production in Israel in 2007 was worth some \$4.5 billion, a 12.5% increase compared with 2006, according to figures from the Manufacturers Association of Israel. Of this total, exports accounted for 80% or \$3.6 billion in 2007, representing some 10% of the country's total exports for that year. The Israeli pharmaceutical industry employs more than 7,000 people and is believed to support more than 20,000 jobs in supporting industries.

### **new drug discovery**

As well as being a major supplier of generics and APIs, the Israeli pharmaceutical

industry is also highly innovative and has a history of new drug discovery. In this respect, the industry benefits from its association with organisations such as the Weizmann Institute of Science in Rehovot, one of the world's leading multidisciplinary research institutions. The Institute carries out research in such diverse areas as ageing, neuroscience, stem cells, vascular biology and cancer, and was responsible for work leading to the development of the interferons, which are used clinically in situations including viral infections, various types of cancer and leukaemia, and multiple sclerosis. The Institute was also responsible for the discovery of copolymer-1 (glatiramer acetate), which has been commercialised by Teva as Copaxone and which is also used in the treatment of multiple sclerosis. Israel has been responsible for the development of innovative treatments for osteoporosis, interstitial cystitis and Parkinson's disease.

The pharmaceutical industry in Israel comes under the control of the Ministry of Health, whose pharmaceutical division is responsible for licensing manufacturers and importers, and inspecting manufacturing premises. The division's powers extend to the manufacture, packaging and control of finished products and APIs, including products destined for both human and veterinary use. The Institute for Standardization and Control of Pharmaceuticals is responsible for ensuring compliance with and enforcement of current Good Manufacturing Practice (cGMP) regulations. The Ministry has applied to become a member of the Pharmaceutical Inspection Convention (PIC).

The Ministry's aim is to inspect every company at least once every two years. Initial inspections of a particular company are carried out in depth, with the level of follow-up required being based on a company's documented compliance profile. Inspections may be announced or unannounced. As a rule, unannounced inspections are made in response to a particular concern with the compliance profile of the company, for example following a complaint, recall, serious deviation, or other GMP concern, although the Institute Director may authorise unannounced inspections at his/her discretion and no justification is required.

### **leading companies**

According to The Scrip 100 (2007/08 edition), Teva was the 18th biggest pharmaceutical company in the world in 2006, with pharmaceutical sales of \$7,821 million, an increase of 65% compared with the previous year. Total sales, which included biogenerics and APIs in addition to generic, branded and proprietary pharmaceuticals, were \$8,408 million in 2006, and rose by 12% to reach \$9,408 million in 2007 - a breakdown of that figure is not yet available.

More than half of Teva's sales are achieved in North America, with Europe accounting for a further 30%. Domestic sales account for a mere 4% of the total. The company has operations in more than 50 countries, with production facilities in North and Latin America, Europe and Israel. Its shares are traded on both the Tel Aviv Stock Exchange and Nasdaq. It has approximately 26,000 employees worldwide.

The first innovative drug brought to market by Teva, and so far the most successful, is Copaxone for the treatment of multiple sclerosis. The product has been approved in almost 50 countries and sales in 2007 were up 21% at \$1,713 million. Almost two-thirds of these sales were achieved in the US, although non-US sales actually grew slightly faster than those in the US. Teva's second product is Azilect (rasagiline mesylate), a monoamine oxidase-B inhibitor that is effective against the principal symptoms of Parkinson's disease when used as monotherapy in early disease, and as an adjunct to levodopa in advanced disease stages. It is also in clinical trials for Alzheimer's disease and cerebral ischemia.

Other products in Teva's portfolio include a hydrofluoroalkane formulation of salbutamol for use in the company's breath-activated Easi-Breathe inhaler, which is marketed in various countries as ProAir, and an injectable formulation of the anticancer drug, paclitaxel (Paxene).

Teva's R&D efforts are focused on therapies for CNS diseases (especially multiple sclerosis), autoimmune diseases and oncology. Two new treatments for multiple sclerosis are currently undergoing Phase III trials. One is an oral formulation of cladribine, an adenosine deaminase-resistant purine analogue, which has fast-track status in the US for use in relapsing multiple sclerosis, while the other is laquinimod, an orally active immunomodulator under licence from the Swedish company, Active Biotech. Other potential products in advanced clinical trials include carlecortemcel-I, a product for haematopoietic reconstruction after chemotherapy in leukaemia and lymphoma patients, being developed in collaboration with another Israeli company, Gamida Cell; an oral formulation of the androgen, dehydroepiandrosterone, licensed from Genelabs; and a sustained-release formulation of octreotide, licensed from the Canadian firm Ambrilia Biopharma, for the treatment of acromegaly. Products for epilepsy, systemic lupus erythematosus, brain cancer and Crohn's disease are at an earlier stage of clinical development.

At the beginning of this year, Teva signed a definitive agreement to acquire Cogenesys, a privately held biopharmaceutical company, for \$400 million in cash. Cogenesys, a closely held spin-off of Human Genome Sciences, has a broad-based biotechnology platform and is focused on the development of peptide- and protein-based medicines. The move is seen as a sign of Teva's intention to be a significant player in the market for generic biotech drugs - which it will need to be to achieve its stated goal of doubling its sales revenues by 2012. Teva has also said that it is exploring alternatives for its animal health business, including possible divestiture, following a strategic review.

### **foreign interest**

Given their expertise in the manufacture of generics and their compliance with the highest international standards, it is not surprising that some Israeli pharmaceutical companies have become attractive to foreign suitors. One such example is Agis Industries, which was acquired by the US OTC medicines manufacturer Perrigo around three years ago. From Perrigo's perspective, the acquisition made a great deal of sense as it brought it a platform for R&D and growth in generic

pharmaceuticals, an established position in APIs, an expanded store-brand OTC product portfolio and an experienced management team.

Agis, subsequently renamed Perrigo Israel Pharmaceuticals Ltd, was a developer of generic pharmaceuticals, APIs, novel dermatological products, and consumer products. It is headquartered in B'nei Brak, Israel, and has manufacturing facilities in Israel, Germany, and the US. It employs more than 1,600 staff.

Chemagis, Perrigo Israel's subsidiary, is Israel's second-largest pharmaceutical company. It develops, produces and markets an extensive line of high-quality APIs and finished dosage forms for the branded and generic pharmaceutical industries. The company specialises in bespoke research and process development of APIs. It has also penetrated the ethical market, particularly the drug delivery systems sector. Perrigo Israel's other main subsidiary is Perrigo Pharmaceuticals, which develops and manufactures generic topical and oral prescription drugs for the US market which are sold under a variety of labels. For the domestic market, Perrigo Israel manufactures prescription products under licence and imports products from major European pharma companies.

If Chemagis/Perrigo Israel is the country's second-largest pharma company, the third largest is probably Taro Pharmaceutical Industries (many Israeli pharma companies are privately owned, so financial information on which to base comparisons is not always available). Taro was founded in 1950 by a group of Israeli pharmacists and US physicians who saw it as a way of promoting the development of a country then only two years old and poor in natural resources but rich in intellectual capital. The word Taro is derived from the Hebrew words for pharmaceutical industry.

Within a few years of its foundation, Taro realised that the political situation in the Middle East made obtaining APIs for its products problematic, and the company set to develop its own manufacturing capability. An equally significant early development was an IPO in the US in 1961, followed in 1982 by a Nasdaq listing. This set the tone for Taro's continued growth, which included the subsequent acquisition of a Canadian manufacturer of topical medicines in 1984. By the 1990s, Taro was committed to a research-based business model, the success of which is reflected in the fact that within 20 years it had gained 50 approvals for prescription medicines in the US (today it has more than 100 ANDA drug approvals in the US). More recently, it has acquired a research facility in the US, a multipurpose research and manufacturing facility in Ireland and, in 2004, a distribution centre in South Brunswick, New Jersey.

Today, Taro boasts a global presence in pharmaceutical manufacturing and a portfolio of prescription medicines that includes anti-arthritis, antibiotics, cardiovascular and CNS products, antifungals and topical steroids, and OTC products in the antifungal, cold/allergy/sinus, female healthcare and haemorrhoid sectors. Its net sales in 2007 were \$313.0 million, generating a net income of approximately \$21.1 million.

However, Taro's expansion came at a price, and by 2007, the company was facing significant liquidity and debt problems. In order to address these issues, the company announced in May 2007 that it had entered a definitive agreement with Sun Pharmaceutical Industries - a specialty pharmaceutical company based in India - for Sun to acquire Taro for \$454 million in cash. The deal involved an immediate injection of \$41 million of working capital, which was followed in August by a further \$18 million. This enabled Taro to meet its scheduled debt repayments for 2007 of approximately \$35 million and left it at year-end with cash and equivalents of \$45 million. This should be sufficient to meet Taro's scheduled 2008 principal and interest repayments of \$42 million: a separate \$28 million credit facility becomes due late in 2008, but the company is confident this debt can be refinanced.

To date the transaction with Sun has not been completed: there has been opposition to the deal from certain shareholders who claimed that the Sun offer was too low and not in the best interests of shareholders, and that other alternatives, such as a rights issue, might be a more appropriate way of dealing with the situation.

### **biotechnology**

Israeli companies are also active in the field of biotechnology, with particular strengths in drug discovery, cell therapy and genetics. A good example is Can-Fite Biopharma, based in Petach Tikva (with a US office in Lexington, Massachusetts). Can-Fite's drug development efforts are built on a proprietary A3 adenosine receptor platform and drug discovery engine.

Studies have shown that the A3 receptor is highly expressed in pathological cells such as inflammatory and tumour cells whereas low expression levels are found in adjacent normal tissues. Specific A3 receptor agonists, such as Can-Fite's candidate CF101, initiate certain signal transduction pathways that lead to inhibition of cell proliferation and apoptosis of the inflammatory and tumour cells. A3 agonists also have an antiviral effect against hepatitis B and C viruses. The company is therefore investigating CF101 and other A3 agonists for the treatment of a number of major human diseases.

Stem cell therapeutics is also an area of considerable activity in Israel. Jerusalem-based Gamida Cell, mentioned earlier, is developing cell therapies based on expanded stem cells for the treatment of such illnesses as haematological malignancies, cardiac disease and neurological disorders. Its first product, which has completed Phase I/II trials, is designed for the treatment of advanced haematological malignancies and is slated to reach the market by 2009. Meanwhile at least two other Israeli biotechs are developing stem cell therapies for Parkinson's disease: Brainstorm Cell Therapeutics, which is located in Petach Tikva, is using autologous bone marrow derived adult stem cells, while Cell Cure Neurosciences, based in Jerusalem, uses human embryonic stem cell technology.

Last summer, the Jerusalem Development Authority launched BioJerusalem, a "one-stop shop" designed to help fuel the economic development of Jerusalem by leveraging the considerable life sciences resources available in the city. Among the

services provided by BioJerusalem are a business coaching programme for bioentrepreneurs and start-ups, a networking framework for industry players in the Jerusalem life sciences sector, information tools and resources for global market competitive analysis in the life and biomedical sciences, and the BioJerusalem Connector, a point of contact to begin building a life sciences venture in Jerusalem. There is a growing start-up sector in Jerusalem: nearly 50% of life sciences companies are less than five years old, and have fewer than seven employees.

### **intellectual property issues**

One issue that has dogged the Israeli pharmaceutical industry in recent years is that of IP protection. At the beginning of 2004, Israel was the only country not to have a system of data exclusivity for pharmaceuticals that was seeking OECD membership, a matter of particular concern to the US that led to negotiations between the Israeli government and the Office of the US Trade Representative (although the dispute predated the negotiations by several years). The Israeli side had proposed that there be five years of marketing exclusivity, meaning that a generic company could refer to an originator's data to support a marketing application for a generic product, but not market it until five years after the original approval. However, the US pressed for five years data exclusivity, which would mean that the generic company could not refer to the originator's data for five years following approval. However, legislation providing for up to five years' marketing exclusivity for new medicines was approved by the Knesset in March 2005.

A related issue is that of patent term extension. The 1998 patent law gave the Israeli patent office the power to grant patent extensions in line with the shortest duration granted in another country, such as the US. However, in 2003, following a number of patent litigation cases, the office changed its policy and began granting extensions for longer periods than in the reference country. This led the Ministry of Justice to introduce an amendment to the legislation to make it clear that patent extensions should be linked to the shortest duration in another country. This was good news to companies like Teva, because otherwise, if a patent extension on a particular product expired in, say, the US, but not in Israel, it would be prevented from exporting a generic version. In fact, it was widely believed that the amendment was introduced as a concession to the generics sector in return for the introduction of marketing exclusivity.

Despite extensive efforts by Israel and the US to bridge their differences on IP issues, the outcome fell "significantly short" of responding to US concerns, and the US elevated Israel to its 301 Priority Watch List, citing additional concerns about problems experienced by US biotech firms operating in Israel. As of 2007, Israel remained on the List, despite the US' acknowledgement that steps taken by Israel to preclude reliance on data generated to obtain marketing approval for exports represented "a positive step towards addressing the United States' concerns on this issue". In February of this year, the Israeli government issued a rebuttal of the concerns raised by the US (and in particular by PhRMA), in a submission to the US Trade Representative, but as yet there seems to be no resolution to the dispute.

**more than generics**

As well as playing a major role in the international generics sector, Israel is home to a number of innovative, R&D-based companies, both large and small. Among the factors in its success is the presence of several world-class research institutions, including the Hebrew University of Jerusalem, the Technion-Israel Institute of Technology and the Weizmann Institute of Sciences; a number of experienced technology transfer organisations; a highly educated workforce; and the entrepreneurial and risk-taking attitude characteristic of Israeli population. Although a member of the World Trade Organization, Israel is not yet a member of the OECD, but this objective should be within its grasp once outstanding IP issues have been resolved.

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