The chemistry of APIs

Guy Villax, the second generation CEO of **Hovione**, has a powerful insight into the state of the industry. Andrew Warmington met him at the company's main site near Lisbon

The Second World War and its aftermath sent millions of people to unlikely places. Portugal, a neutral country, was the setting for three exiled Hungarians - one of them the son of Hungary's last pre-Communist head of state, Admiral Horthy - to found a firm producing antibiotic active ingredients in the late 1950s. It took its name from their surnames: **Ho**rthy, **V**illax and **O**nody. The other two founders sold out their interest to Ivan Villax within two years but Hovione carried on under the same name and in the Villax family's majority ownership. Guy Villax, Ivan's son, is now the CEO and his daughter Sofia heads up communications, while Ivan Villax himself is still actively involved.

For many years, the company was little more than an R&D laboratory in the family basement, mainly researching semi-synthetic tetracycline antibiotics and anti-inflammatory corticosteroids. Much of the early income derived from royalties from fermentation processes which Hovione licensed out to, among others, National Fermentation of South Africa in 1962 and ICI in 1966. The processes were also used at Fermentfarma, an API fermentation plant in Milan that was also founded by Hungarians. They took a 25% share in Hovione, while Ivan Villax became technical director of Fermentfarma in 1961.

When Rachelle Laboratories of the US bought Fermentfarma in 1967, the proceeds were used to build Hovione's first plant at Loures, a small town just to the north of Lisbon, in 1969. This helped to drive further growth in the 1970s, particularly in Japan where Hovione found good business for its corticosteroids based on betamethasone and its derivatives and manufactured by means of a complex 16-step process.

The main Hovione site is on the outskirts of Loures in Portugal

Expansion in the '80s and '90s

Following a first successful FDA inspection in 1982, the company launched doxycycline, a semi-synthetic antibiotic, in the US. Despite intense competition, it still claims a 75% market share for doxycline in the US. The 1980s also saw expansion into the US generics market and other products, such as minocycline. During the 1990s, the company expanded into custom synthesis, both exclusively and for multiple customers, and into contrast media agents. The Loures site has grown and now has 18 numbered buildings; Building 18 was commissioned in October 2001.

"If you look at the history of Hovione, you will see that we spend our lives looking for difficult things to do. If it is easy to do, then there is a lot of competition and you are producing a cheap commodity," says Guy Villax. The company's products now cover most types of drugs, including inhalers and terminally sterilised injectable products, and those for the treatment of conditions including HIV (it has been involved in developing four HIV projects in the clinical phases since 1994), cancer, respiratory disorders and Alzheimer's disease. In 2000-1, Hovione was the world's largest independent supplier of API protease inhibitor.

Hovione has become a global player, with facilities on three continents and sales patterns to match. Turnover was just over €80 million in 2001, of which 55% was in North America, 25% in Europe, 12% in Japan and 8% elsewhere. World-wide, production capacity is now over 500 m^3 - double the figure for 1995 - and there are some 600 staff. These included (in 2001) 205 in production, 101 in QA, QC and regulatory affairs, 77 in engineering and plant design and 70 in process chemistry development.

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The company can now carry out all known chemical reactions at industrial scale, though it chooses not to work with cyanide, phosgene, beta-lactams, penicillins or cephalosporins. According to the company's US marketing director Paula Weissberger, who showcased Hovione at Informex, the company regards itself as a generalist capable of carrying out any chemistry necessary for a particular API, but its areas of strongest expertise are:

- High-pressure (up to 100 bar) hydrogenation, to which Hovione has dedicated a laboratory and which has led to the development of a proprietary line of regiospecific and stereospecific catalysts
- Safe handling of anhydrous hydrofluoride (HF), a vital but highly corrosive material for the synthesis of complex, multi-step APIs
- Low-temperature (down to -90°C) reactions, using highly pyrophoric organometallic reagents, such as alkyl lithium, lithium aluminium hydride and Grignard reagents
- Injectable grade API production, which is carried out in seven clean rooms in batch sizes up to 1,250 kg

The company has been investing heavily in recent years, aided by a loan from the European Investment Bank. The budget for the years 2001-3 is about €63 million, of which over one third has been spent on the new technology transfer centre (TTC) in the US. The current wave of

investments and expansions reflect the company's core technologies and global status.

In June 2001, Hovione started up a dedicated 220 m^2 unit for the synthesis of corticosteroids and similar compounds (excluding steroids with hormonal activity) under cGMP conditions for oral, topical, inhalation and injectable administration. This is carried out in the original Building 1 at Loures, which has been fully renovated and went through an FDA pre-approval inspection that month, for which no Form 483 was issued.

Global presence

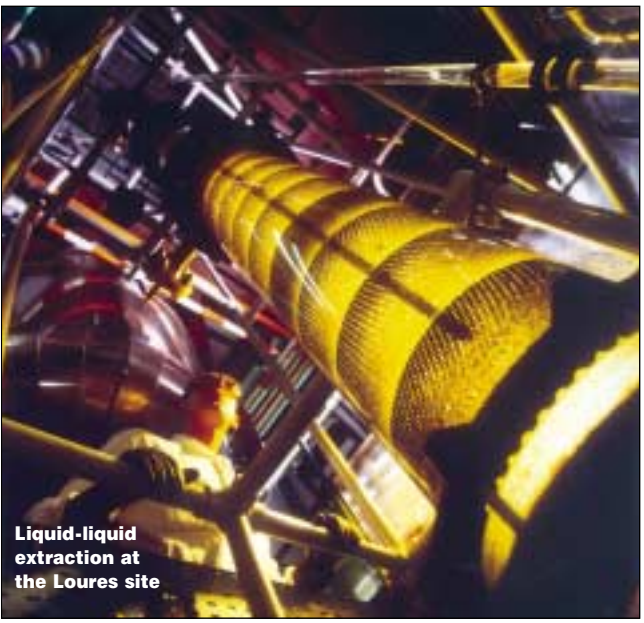
The new unit produces APIs for INDs, NDAs and commercial compounds in batches of 1-100 kg, while filtration, drying, milling, sieving, micronisation and packaging all take place in three separate Class 10,000 clean rooms. It also features controlled personnel and materials access, tri-clamped lines to transport the crystallised reaction mixture to the clean rooms and closed-circuit charging of the solids through a high containment solids transfer valve in order to prevent the product from coming into contact with the outside.

Process equipment in the unit includes glass-lined and stainless steel vessels of up to 7,500 litres, monoplate filters and static bed dryers. Later this year, the company is also scheduled to break ground for its new 1,360 m^2 pilot plant at Loures. This will be capable of handling highly active compounds and will feature a Class 10,000 clean room, kilo labs and reactors from 90 to 5,000 litres, including Hastelloy reactors that work down to -100˚C.

Also in 2001, Hovione completed a €16 million expansion at a site in Taipa, in the former Portuguese colony of Macau. This was the location of its first move into manufacturing abroad in 1986. It added a production facility, BK2A, which duplicates the original factory, on a newly acquired parcel of land.

This consists of two symmetric and fully automated four-level manufacturing lines with a reactor volume of 40 m^3, bringing the site's total volume to 100 m^3. Start-up took place in November 2001. A new block has also been added for the engineering and expansion project teams and construction started on another building in March.

The Macau plant does not specifically serve the Asian market. Hovione spread there in part because customers prefer not to depend too much on one plant and in part to source raw materials from China. However - and quite apart from the limited space for expansion at Loures, which abuts the outskirts of the town on one side and a hill on the other - the company says that further manu-



Liquid-liquid extraction at the Loures site

State of independence

Despite the company's growth and development, Guy Villax is proud to state that Hovione's strategy has remained unchanged in 40 years. It is, always has been and will remain a privately owned producer of APIs, and serves no other industries. During that time, its work has, of course, changed hugely as it has reacted to or anticipated changes in the market. Hovione formerly made and licensed out new molecules when this made economic sense in the 1960s and 1970s, and did likewise with generic drugs in the 1980s. The focus on high-value, complex APIs naturally became sharper in the 1990s as competition from China and India emerged.

"We have never tried to be uniquely specialised in one area or the lowest cost producer - and what is the point of being the lowest cost producer anyway? This is a very atomised industry. Nothing in pharmaceuticals is produced at levels much more than 100 tonnes/year and 95% of the 4,000 APIs in the world are worth less than €2 million/year. As long as that is the case, there will be a place for companies like us," Villax says. "To be in this market at all, you must be a generalist, able to tackle any kind of chemistry. Customers come to you because you are fast, capable and ready to do anything".

He adds: "There are plenty of other companies who have capabilities like ours, but that does not mean that market products have arisen as a result. Track record is what matters and that is something you can't buy. It is the same in custom manufacturing - we have been doing it for ten years, but we are still newcomers compared to the likes of Lonza. Unless companies like them make huge mistakes - which they won't - our only chance of getting onto Big Pharma's preferred supplier lists is through technology niches or if their business grows".

Villax is also a vociferous critic of some of the trends within the industry and openly sceptical of some of the trends within it - not least the siren voices from within some of the big companies that say that independents will be squeezed out. He emphasises that Hovione will not be sold or merged until the customers say the same things. "At the moment, they are saying quite the opposite - that they like working with us because we are small and can make decisions quickly", he adds.

"You can broadly divide the business into the small companies that are totally focused and independent and the giants, who generally try to supply everything from the basic chemicals to the building blocks, the intermediates and the APIs. The jury is still out but the smaller companies have a lot to offer that the large companies cannot, like their readiness to innovate, to seize opportunities and to invest in order to differentiate themselves. And they think in terms of service and solutions rather than manufacturing, budgets and filling the vessels to meet quarterly targets".

In recent years, there has been a trend for those chemical companies that are trying to move away from commodities to seek to

Guy Vilax (right) succeeded his father Ivan (left) as CEO of Hovione

acquire the ability to deliver a full service in pharmaceutical intermediates. To this end, many have invested: Clariant bought Archimica with BTP, Rhodia acquired Chirex and DSM got Catalytica, for example. The snag, Villax observes, is the ability of multi-billion dollar corporations to manage and add service to products worth less then €2 million/year. Moreover, some are now suffering the consequences of paying too much through over-optimism about future growth. As a result, the current wave is one of consolidations and plant closures.

One of the main burdens for Hovione is the regulatory regime at both EU and national level. "As well as IPPC, SPC, the White Paper and the other regulations asphyxiating the fine chemicals industry, regulatory bodies in countries like Spain, Portugal and Italy are inadequately staffed and take too long to respond to company submissions. One added reason for building the TTC in the US is that, even when we only want to create 20 kg of a product in Europe we still have to do toxicity studies, when 90% of the projects die in development anyway," says Villax.

He continues: "Europe is the historic heart of the fine chemicals and APIs businesses, yet at the moment about 2,600 new chemicals come out of the US every year and less than 1,000 out of Europe, because of over-regulation. The situation is crazy. With one hand the EU is giving its biotechnology sector incentives and tax breaks to help it catch up with the US, while with the other it is effectively trying to kill its jewel in the crown, the fine chemicals industry which provides Europe with hundreds of thousands of jobs".

Biotechnology, Villax observes, is largely a Wall Street term and most of the firms that use the term do not make 'biotech' products. He divides these firms into three groups of roughly equal size: those making large molecules, those involved in highly innovative processes like peptides and oligonucleotides and those that make small molecules. Hovione wants to supply fine chemicals to companies like the latter, not least because, technologically, they are a world apart from fine chemicals and will never make them in their own right.

facturing expansion is likely to be here because the culture and capabilities are the same as at Loures and China does not suffer from the expensive and complex regulatory regime that Europe imposes. Portugal's cession of Macau to China in 1997 has not impacted the business in any way, Villax adds.

Perhaps the most significant development in the long term will be the new TTC, which is located at East Windsor, near Princeton, New Jersey. Occupancy is scheduled for the second half of this year. The TTC has a GMP kilo lab and a pilot plant, including a Class 100,000 clean room, which will prepare APIs in small quantities to support pre-clinical and early phase clinical development prior to transferring production to Hovione's full-scale plants. It also has Hastelloy and glass-lined reactors ranging in size from 50 to 800 litres, two dryers of 200 and 240 litres capacity and three Hastelloy monoplate filters of 0.25-0.5 m^2.

Capacity for expansion

At first the site will house 26 people, but it has the capacity to expand to 45. The TTC will conduct process R&D and give US customers process development and scale-up services, QA, QC and regulatory support, as the European and Asian facilities do. It will also house the US headquarters, with a sales and marketing operation and a distribution centre for existing commercial products. In all, the TTC represents an investment of over €20 million. The philosophy behind the decision to build the TTC was a simple one of proximity to customers. Since the 1980s, more than half of Hovione's sales have been to the US and New Jersey is at the heart of the US industry, both for Big Pharma and start-up companies.

"We wanted to do more than have an office. We wanted to do the chemistry and show customers how we work. The methods and standards will be exactly the same as at Loures and Macau and many of the people have had prior experience at one of the other centres before," says Villax. "It is not enough just to buy a company in the US. When you buy a company, you buy its culture and you simply can't get seamless technology transfer that way. The new centre will greatly accelerate technology transfer from the kilo lab to the pilot plant and on to the factory, and will also facilitate technology transfer from the customer to us."

Hovione currently has four of its own products under development. Two corticosteroids - fluticasone propionate and halobetasol propionate - have both been through pilot-scale production and were due to undergo process validation in the first half of 2002, with a cholesterol-lowering API, simvastatin, to follow in the third quarter. Tibolone, a hormone, is some way behind and there are three more pipeline products: bicalutamide, tamsulosin and finasteride. These will eventually join a product list that runs to nine corticosteroids, six antibiotics, two contrast media and one top-selling veterinary ingredient, Iveremectrin.

Inside the main plant at Loures

Anthrax challenge

The anthrax scares and the consequent boom in demand for anthrax antiobiotics in late 2001 also brought a challenge. Hovione's doxycycline is one of only two approved treatments and, as a generic, is five times cheaper than Bayer's Cipro brand of ciprofloxacin, which remains under patent. The company immediately ramped up its production schedule towards meeting the US's estimated stockpile needs of 30 tonnes - enough to treat 46 million people for four weeks. (This was not the first time that this happened, incidentally - Hovione had to supply about 8 tonnes to the US Army prior to the Gulf War).

"In the last quarter of 2001, we shipped more of this product than in the previous 18 months combined. This sounds like good business but it was not really," says Villax. "We had to reorganise our production schedule and produce in a less cost-efficient way. Obviously we were not about to put our prices up in such a situation and sales of this product are likely to be very low this year".

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Custom synthesis and generics

Bill Heggie, vice-president of Process Chemistry at Hovione, says that his division is divided into three groups, with responsibilities at different stages: Laboratory, Scale-up/Industrialisation and Process R&D. The two main end-use businesses, generics and custom synthesis, each account for about 50% of sales. These each have separate groups working on them, though there is some cross-over in terms of experience.

Generally, generic drugs customers do not bring processes in with them and Hovione does all the process development from a literature search to developing a suitable method. In custom synthesis, many customers have already developed their process as far as the laboratory or pilot scale and want Hovione to scale it up for them, though in some instances it has go back to improve the chemistry. Whilst many details are confidential, Heggie adds that the company has significant projects where its major strengths lie - formerly in steroids and now increasingly in semi-synthetic antibiotics, that is tetracyclines and erythromycine derivatives.

"Our project portfolio is well balanced between pharmaceuticals majors, generics producers and biotech start-ups, which is good because we don't want to rely too much on one type of customer," he says. "The biotech companies have matured over the past ten years and have proved some of their concepts on the market. Now they are becoming a significant part of the customer base. In many ways, they are good to work with because we tend to have longer-term projects and more regular contact with them than is the case with Big Pharma".