A new era dawns at Louvain

One of the pioneering sites in HPAIs changed hands last year. Andrew Warmington visited **Minakem High Potent** in Belgium

It was one of the earliest sites to make high potency APIs (HPAIs) and Minakem was already seeking to expand into the field. It was also quite close to two of Minakem's existing API sites, so acquiring the Ajinomoto OmniChem facility near the ultra-modern university town of Louvain-la-Neuve, south of Brussels, was too good an opportunity to miss.

The deal was completed in June 2015 and the newly constituted Minakem High Potent (MHP) is now one of six businesses belonging to Minafin, a global fine chemicals group which had sales of €136 million last year and sites in Europe and North America, and which now employs about 500 people. Pharma still accounts for 70% of Minafin's turnover, with the rest being technical additives (18%), cosmetics and food additives (7%) and agrochemicals (5%). Its other business units are:

- Minakem itself, based at the two main sites in northern France at Beuvry-la-Forêt , formerly known as SEAC, which Minafin owner Frédéric Gauchet acquired in 2004, and the former AstraZeneca site in Dunkerque, which was acquired in 2009
- Pennakem, based in Memphis, Tennessee, and acquired in 2008, which specialises in furan and furfural products
- Pressure Chemical, a Pittsburgh-based CMO, which was acquired in 2013
- Minasolve, which has marketed capabilities for the cosmetics and food additives markets from Beuvry-la-Forêt since 2009
- Minascent, which has just been established to manage the Leuna site near Leipzig in Germany, itself acquired in 2006, reflecting Leuna's increasing focus on non-pharma business and sulfur and selenium chemistry

Dr Stefan Peterli, formerly with Siegfried, Lonza, Chemie Uetikon and Senn Chemicals among others, was brought in as CEO of MHP in October 2015. The acquisition, he stresses, refers only to the HPAI facility and related amino acid blending that Minakem continues to carry out on behalf of Ajinomoto, which remains active at the site in other fields. Some 100 people transferred over.

Reactor filling using glove box with alpha beta port

"Ajinomoto was looking to divest and we had geographical proximity and a common language," Peterli says. "Minakem had spent some time looking to get into high potency and there were a lot of enquiries from clients. As it stood, we could do all but the last few stages at our main site, so the choice was either to invest there or acquire. It has always been Mr Gauchet's policy to acquire complementary technologies into the group."

Two new joint ventures have since been formed between MHP and firms with related capabilities. Aami Services is a blender of amino acid ingredients for third parties and Ajinomoto, while Mikamed, with financial investor Lafimed and Tunisian formulation manufacturing firm MédiS, will manufacture cytotoxic, steroid and oncology drugs based on HPAIs supplied by MHP.

This alliance will enable both parties to make generic oncological finished dosage forms for the European, Middle East and African markets, with an initial focus on the Middle East and North Africa. Initial low-dosage galenic formulation projects are currently being studied.

With Louvain-la-Neuve on board and also including Leuna, Minakem now has a network of four FDA-approved sites for large volume or niche APIs and repeat or one-shot production. Beuvry-la-Forêt and Dunkerque are also approved by France's ANSM.

In all, the four sites have 400 m^3 of reactor volume and can carry out organic synthesis at up to 20 steps in volumes from grams to 300 tonnes. They hold nine CEPs, 17 DMFs and have considerable experience in filing, as well as regulatory documentation and alternative raw material sourcing. Key areas of chemical expertise include process improvement, impurity elimination, production cycle reduction, injectable grades for oncology and high containment.

The other sites, particularly Dunkerque, are much larger than Louvain-la-Neuve and produce on a much higher tonnage scale. Back integration into them, according to sales director Dr Claudio Salvagnini, makes Minakem a much more attractive proposition, particularly for small and medium-sized pharma companies seeking a single-source supplier.

"The key gain here is that Minakem can make starting materials and intermediates, GMP and non-GMP. We can do the last and most potent stages here, normally between two and five of them, and non-potent materials can come in from elsewhere at various stages, depending on the toxic moiety. We see this as a good differentiator," Salvagnini says.

Louvain-la-Neuve is a multi-purpose plant with over 40 years' experience in HPAI production since it began producing 'vinca' alkaloids in 1972. It has a containment system down to OEB Class 5 and associated R&D, analytical development, manufacturing, QA, QC and warehouse and storage areas. OmniChem continued to invest there throughout its ownership, adding a high-containment R&D lab in 1998, a Class 5 handling facility and microbiological QC lab in 2007 and a high-containment QC lab in 2010.

In fact, Salvagnini says, Louvain-la-Neuve under OmniChem – it was acquired by Ajinomoto in 1989 – was the high containment site in the pioneering days: all of the SOPs and protocols were developed there that are used in its other sites and elsewhere in the industry. Minakem continues to use the same containment system.

Peterli – Many clients enquired into high potency

Working in a HAPI class 5 small scale production laboratory in a glove box connected to a laminar flow hood

The site can operate at capacities from 100 grams to hundreds of kilos and at all stages from development to commercial. "We can isolate batches of 75-100 kg so we can improve continuously in terms of capacity. We also have multiple sizes of isolation equipment, so we can accommodate batches of 25, 50 or 100 kg and different phases of development, all within the same site," he adds.

Key manufacturing assets begin with four multi-purpose, high-containment manufacturing trains with glass-lined, stainless steel and Hastelloy equipment ranging from 50 to 1,600 litres, plus small-scale (2-20 litre) glass vessels. Glove box isolators are equipped with alpha beta rapid transfer ports. Bulk HPAIs can be freeze-dried in batches of up to 1.1 kg. Notable chemistries include hydrogenation, oxidation and the handling of hazardous compounds.

Other key CMO activities there include: process optimisation and scale-up, analytical method development and validation; regulatory support for filings, full supply chain management; and, continuous improvement for COGS reduction. Customers, Salvagnini says, have stayed with the site since the acquisition, recognising its competence and skills from production to QA and project management.

Now MHP aims to build on those relationships, while also repositioning itself in the HPAI market, where Minakem was not hitherto known as a player. Ultimately it hopes to be market leader but the immediate vision in HPAIs is to become: a global reference for HPAI development and manufacture; a European market leader in generic controlled substances – US DEA Regulations on Schedule II substances dictate that it cannot, as a European manufacturer, enter the US market for some products; and, the market leader in vinca alkaloid-based oncological HPAIs.

Narcotics capabilities date at Louvain-la-Neuve back to when the Belgopia production unit was set up to make controlled substances in 1981. The site still has a licence to make them and MHP is now gearing up to address the opiates market with products made using optimised technology and new raw material sources based on extracts of *Papaver somniferum.*

Vinca alkaloids are produced in tiny quantities, usually not exceeding a few kg/year. Manufacturing starts from a crude extract of *Vinca rosea,* which is purified and chemically derivatised to obtain vinorelbine, vinblastine, vincristine and vindesine.

As is the case for most HPAI facilities, oncology is still the driving force for the growth of the site, followed by pain treatment. Business, says Peterli, is "as expected" – while some of it is in for classic high potency products, including cytotoxics and cytostatics, some anaesthetics are handled under HPAI conditions due to their exceptionally low dosage, in the microgram range. The customer base covers most countries in Western Europe and North America, plus Japan, Australia, Brazil, India, Israel and even Vietnam.

Five of the top ten Big Pharma companies have commercial products made here but it also deals with many small and medium-sized pharma companies and biotechs picking up opportunities with molecules dropped by Big Pharma. Another interesting areas is antibody-drug conjugates, which typically use even higher toxic payloads and so require Class 6 containment. MHP is now studying a project to invest in this technology, due to client demand.

"We are also looking at preparative HPLC and solid state under containment, which is of interest to a number of clients," Peterli says. A small preparative HPLC line will come onstream in October and MHP is planning to invest with a client on a larger scale using this technology, which could also be used internally to replace another, more traditional purification technique.

Solid state, he adds, is a key competence at Beuvry-la-Forêt. Minakem has a laboratory there which is currently being adapted to handle Class 5 compounds.

"Now we are seeking to get ourselves better known in this field world-wide," Peterli concludes. "We are attending the relevant events in Boston and Basel and are putting our name out there."

"It is a strong market with good growth potential but the barriers to entry are high. In fact, one of the key challenges is getting the people who can run the reactions and the engineers who can set up a high potency plant. We consider it a strategic advantage to have retained the highly trained key personnel while going through the transition."

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