

---

## Fine Chemical Producers Strive to Meet Demand for High-Potency APIs

### A Potent Combination

By Feliza Mirasol

Growing demand for HPAPIs drives investment in this high-tech market. How are companies differentiating their offerings?

DOUBLE-DIGIT growth rates for highly potent active pharmaceutical ingredients (HPAPIs) is spurring leading players in the market to invest in capacity. And companies are seeking differentiation from competitors through specialized technologies and demonstrated experience.

Compounds classified as highly potent are effective in treating diseases at low doses, but also pose an exposure risk to healthy people. Implementation of appropriate safety systems requires significant investment.

The potential market size for many of these specialized drugs is also smaller, and the risks associated with development are greater. As a result, many pharmaceutical companies are increasingly outsourcing HPAPI production to custom manufacturers.

The growth in demand for HPAPIs is estimated to be nearly double that for non-potent compounds. Most of the drugs on the market currently classified as potent are cancer therapies.

In 2007, oncology drugs accounted for 6.2% of the global pharmaceutical market, according to global consultancy IMS Health. By 2012, IMS expects the value of the oncology market to be \$75bn-80bn (€55bn-58bn).

"Longer life expectancy and the ability to detect diseases at early stages are going to increase the demand for cancer drugs, which in turn will result in an increase for HPAPIs," says Olivier Dapremont, director of process technologies business development for US-based AMPAC Fine Chemicals (AFC).

In addition to cancer therapies, there is a growing interest in the development of HPAPIs for treatment of chronic heart disease, musculoskeletal problems, central nervous system diseases and many others.

### COST REDUCTION AND EFFICACY

"Cost reduction is a key driver. Pharma companies are always looking to reduce the amount of API needed in a drug. The way to do that is by increasing the potency," notes David Feldker, vice president of US-based fine chemical firm SAFC.

"The evolution of the 'targeted therapy' approach is also leading to APIs with multi-targeted modes of action to improve both efficacy and duration of response," adds Rhona McIntyre, commercial director for Switzerland-based fine chemical firm CARBOGEN AMCIS. "This approach is heralding a return to small molecules with greater potency at lower dosage."

With so many positive drivers for growth, most custom manufacturers of HPAPIs believe the market will remain strong even through the economic downturn. Feldker expects the

growth rate to decline somewhat in the near term as customers slow down or drop some projects.

Smaller, emerging clients are being affected most noticeably. "These companies are slowing their programs as they try to conserve cash while the credit markets recoup," explains Eric Neuffer, vice president for sales and business development in North America for US-based fine chemical firm Cambrex. Mid-sized and small biotech companies will be hardest hit in the first half of 2009.

## TECHNOLOGY AS THE DIFFERENTIATOR

Even with the expected reduction in growth rate, custom manufacturers continue to move forward with expansion plans. Competition will increase, but there still remain very few companies manufacturing HPAPIs on a commercial scale.

"Capacity really means a whole lot more than cubic meters of kettles," stresses Dr. Stephen Munk, president and CEO of Ash Stevens. "Customers need suppliers that meet timelines and specifications. Along with pots and pans, any investment has to include an ability to deliver."

Producing HPAPIs requires much more than assets, agrees Dr. Laurent Ducry, R&D leader for antibody-drug conjugates with Switzerland-based fine chemical firm Lonza. "Skilled specialists are an absolute necessity. Therefore the top players should continue to have plenty of opportunities," he says.

Those suppliers with good infrastructure, systems, services and a range of technologies will thrive in the market. CARBOGEN AMCIS, in conjunction with owner India-based Dishman Pharmaceuticals & Chemicals, offers broad chemistry capabilities for both potent and non-potent products, enabling customers to balance their requirements for speed, scale and costs without the need for additional technology transfer, according to McIntyre.

The company also has extensive experience in the conjugation of potent compounds to different targeting systems, including antibodies, peptides and polymers. "We believe this capability places us amongst a select group of service providers," McIntyre says. CARBOGEN AMCIS' micronization and milling capability is a further differentiator, as oral dosage forms become more prevalent.

The company has added a dedicated lab to its HPAPI facilities in Bubendorf, Switzerland and is considering additional technologies for the site. Its \$15m-18m high-potent production facility in Bayla, India comprised of four cells with three vessels in each (up to 2,500 liters), will be operational in mid-2009. This site will also include development laboratories for highly potent compounds.

## CAPACITY BOOST

Conjugation capabilities have been a focus for SAFC as well. The company commissioned a new production facility in St. Louis, Missouri, US, in September 2008 for production of such substances in development quantities, with possible expansion to commercial scale.

Further biological capabilities are being added through SAFC's \$29m investment in production capability for HPAPIs derived from bacteria and fungi in Israel. This plant will be operational in 2009, along with two commercial suites for production of viral vaccines that are being added at its Carlsbad, California, US, facility at a cost of \$12m.

SAFC isn't neglecting traditional small-molecule chemistry, though. The company recently invested \$4.5m in a cGMP pilot plant and kilo lab at its Madison, Wisconsin, US, site, and has broken ground on a \$30m greenfield project for commercial-scale production of HPAPIs, which is expected to be completed by the end of 2009. This plant will include reactors up to 4,000 liters.

"We believe that our ability to provide production of highly potent compounds from lab through to true commercial scale is undoubtedly a key differentiator for us," asserts Feldker. "These investments in greater capacity and expanded biologics capabilities reflect our commitment to the HPAPI sector. And we will continue to make investments in differentiating technologies that will propel SAFC forward into a leadership role."

Cambrex also stresses the importance of large-scale HPAPI production capabilities. "The HPAPI sector will see an increase in reactor scale to meet higher volume programs in the short term. Having commercial-scale equipment in place now will provide a significant advantage," says Neuffer. The company currently has reactors up to 2,000 liters for HPAPI production.

In May 2008, Cambrex expanded small-scale cGMP capacity at its Charles City, Iowa, US, site. The new High Potency Development Center includes chemical and analytical development laboratories.

"With these new facilities, we are now better equipped to fully service our HPAPI client programs from development through commercial scale," Neuffer says. In addition, Cambrex is offering high potency micronization services, as there is little competition in the US market.

Ducry, too, emphasizes Lonza's ability to produce highly potent compounds in the lab, in small and large reactor trains. The company started cGMP production in 2008 in a new 40,000 liter facility for the production of HPAPIs.

Expansions of laboratory, mid, and large-scale HPAPI facilities are planned in 2009 to cover all development phases. "Combined with our broad production capabilities, our special technologies, experienced personnel and know-how regarding the handling of hazardous chemicals differentiate us from our competition," Ducry asserts.

Lonza has also built small-scale and large-scale cGMP facilities for the production of antibody-drug conjugates. Further expansions are planned for 2009 and 2010.

For Ash Stevens, the differentiator is a proven ability to deliver. "We are different because we have a complete package: equipment, a deep understanding of chemistry, and a proven system including regulatory compliance," says Munk.

In 2008, the company added contained processing equipment and commissioned a new process safety laboratory. It is currently installing additional LC-MS instrumentation and

will be adding additional reaction vessels, including the capability to conduct hydrogenation chemistry, in 2009.

AFC has invested in continuous processing capabilities to address the need for large scale HPAPI manufacture. Its "zone reactor" technology produces a few kg/hr continuously in equipment with a very small footprint.

"Continuous processing is perfectly suited for large-scale production of HPAPIs. It will provide a higher level of containment at a much lower cost than batch processes," Dapremont says.

A new kilo facility containing a zone reactor will be operational in February. The company is also expanding its existing kilo-scale HPAPI facility in 2009 and is planning to add a new HPAPI line (50-200 gal reactors) in 2010. AFC's 6 x 75mm simulated moving bed (SMB), solely used for chromatographic separation/ purification of HPAPIs, is another differentiator for the company.

Other companies active in the HPAPI sector have also made investments. France's Novasep expanded HPAPI capacity at its Le Mans, France location, adding both a kilo lab and capacity for production of late clinical and early commercial phase quantities. India-based NPIL Pharma began operating its sixth production suite for highly potent compounds in Scotland early in 2008. US-based AMRI finished a new cGMP HPAPI development lab suite at its plant in Albany, New York. Aesica announced that it will double HPAPI capacity at its Queenborough, UK plant in 2009. Almac has said that it plans to increase capacity for HPAPIs. The company has experienced increased demand for radiolabeled compounds.

By: Feliza Mirasol  
+1 713 525 2653