Expanding R&D capabilities with new technologies

Investments in SMB technology for chiral separations, exploitation of energetic chemistry expertise, and development of high-potency API capabilities are driving the rapidly-expanding chemistry R&D business of Ampac Fine Chemicals.

In November 2005, American Pacific, a speciality chemical company specialising in energetic products, acquired the former Aerojet Fine Chemicals business, now known as Ampac Fine Chemicals (AFC). The company is now a leading manufacturer of active pharmaceutical ingredients and registered intermediates under cGMP guidelines for the pharmaceutical industry. Through its recent technology investments, AFC has developed special emphasis on high-potency compounds, energetic and nucleoside chemistries, and chiral separations, manufacturing products from kilogram to multi-tonne scale at its facilities near Sacramento, California, USA.

"AFC leverages more than 50 years of experience as a manufacturer of energetic materials for the US Department of Defense (DOD)," says company President, Dr Aslam Malik. "This heritage has allowed us to develop expertise in safely and reliably developing and scaling up processes that involve hazardous or toxic chemistry. Consequently, we have a very strong team of experienced chemists and engineers and special know-how for conducting cGMP production of energetic and potent chemicals for the pharmaceutical industry. A logical extension of our expertise in chemistry and engineering was demonstrated by the addition of our third technology platform, simulated moving bed chromatography (SMB) in 1997.

"Use of energetic chemistry and chromatography at the early stages of drug development allows chemists to produce, in most cases, higher-quality products in a short period of time. Also, these technologies provide product in high yields and are readily scaleable, thus saving valuable development time.

"Finally, confidentiality is very important in the pharma industry and with our DOD heritage, we have the mindset and the culture required to maintain complete confidentiality for our customers," he says.

The 5x1000mm SMB unit installed in 2006 is the largest of the 6 units installed at AFC to provide separation services from gram to multi-tonne quantities.

Most of the company's existing products are FDA-approved, on the market, and growing in sales. Over recent years, its customers have brought to market a number of products that address treatment of diseases in anti-viral, cancer, and central nervous system therapeutic areas.

"Our strategy is to maintain leadership positions in each of the three major technology platforms we offer to our customers for cGMP manufacturing of intermediates and APIs," says Malik. "Our three major technology platforms are energetic chemistry, HPAIs, and continuous chromatography (SMB). We maintain our leadership by focusing on innovation and by recruiting highly-qualified chemists and engineers. We believe that the expertise offered by AFC in these three major technologies provide our company with the unique abilities needed to compete successfully with other custom chemical companies."

Strong focus on chiral chemistry

Malik observes that a large percentage (>70 per cent) of new chemical entities (NCEs) currently in development are chiral, and says that this area is growing significantly as molecules become more complex with multiple chiral centres.

"One of AFC's areas of expertise is chiral separation of racemic mixtures by SMB. SMB is a non-destructive technique and provides access to both enantiomers, which is typically required for early drug development work. In addition, scale-up of SMB separations is linear and the technique is a seamless solution (eg high throughput, low solvent consumption, low cost, a reliable robust process, high product recovery, etc) for commercial-scale production, thus reducing drug development time," says Dr Olivier Dapremont, Director of chromatographic separations.

"AFC provides SMB separation services for all phases of drug development. We have six SMB units to support separations ranging from gram to multi-tonne scale. We also have a highly experienced team of chromatographers, chemists and engineers that can take a process developed at gram scale (eg on our 8-10mm lab-scale SMB unit) to 200-300 kg scale (eg on our 8-200 mm pilot-scale SMB unit) in a matter of just a few weeks. This is a good example of how AFC can bring added value to customers," says Dapremont.

High Containment serves a growing market

Malik explains how the company's expertise in cytotoxic and high containment is derived from its experience in developing safe and reliable processes for highly toxic chemicals:

"Our containment strategy is based on three levels of controls. The first level is process development. At this level, processes are developed to minimise product handling, resulting in

High-containment capabilities at Ampac Fine Chemicals.

minimum opportunities for exposure to our staff and the environment. At the second level, we design and implement engineering controls to further minimise exposure. Finally, we employ personal protective equipment (PPE) as the last level of protection. Since the toxicity of most compounds in early-stage drug development is not known, it is critical that the processes are developed by incorporating the principles described above. Also, this leads to processes that are suitable for scale-up and, consequently, a reduction in development time.

"AFC provides HPAI production capabilities for drugs that are in Phase I and later stages of drug development. AFC offers three totally independent manufacturing facilities with reactors ranging from 20 to 200 gallons that contain all of the supporting equipment needed for producing highly-potent compounds. We also have high-containment laboratories for QC testing and R&D work. In 2007, we will produce nearly two tonnes of HPAIs," he says.

Hazardous and energetic chemistries support drug discovery and development

"Energetic chemistries offer a wide diversity of reactions that are scalable, reliable and clean. The high energy associated with this type of chemistry allows us to conduct reactions that are highly stereo- and regioselective. This, in turn, provides clean reaction mixtures that are easier to purify and, as a result, increases the overall efficiency of the process," says Malik.

"Very often these chemistries are used in early development work, but are then replaced with traditional syntheses as the drug matures. We encourage our customers to use energetic chemistry at the early development stage and, when the quantities increase, turn to experts in this field, such as AFC, for scale-up and commercial production.

"At AFC, we develop energetic processes that can be safely and reliably scaled up to commercial scale (1,500-2,000 gallon scale). We have three production lines, one pilot plant and three remote R&D bays for developing and producing energetic materials.

"We conduct tests in-house to help ensure that all chemicals, intermediates and processes are fully characterised to allow proper equipment selection and operating procedure development: we perform hazard analyses for all new chemical operations; and we perform critical reviews of all new processes prior to start-up.

"AFC also has a rich history in development of continuous processes. We are building on our heritage and are offering our expertise and experience in this area to our customers," he says.

An evolving business in process research and custom chemicals

"AFC is a custom manufacturing organisation focused on cGMP production of intermediates and APIs. We maintain our focus on our expertise and experience in three major technology areas and our ability to safely and reliably scale up chemical processes. The majority of our business is commercial production of regulatory-approved APIs and intermediates. However, a growing percentage of our business involves various projects in Phase I and the earlier phases of clinical trials. We specialise in development of commercially viable processes, in particular, processes that utilise AFC's core technologies in one of the steps. Consequently, we bring the most value to our customers when the process is still in development and improvements and changes in the synthesis route and design are still possible," says Richard Beatty, VP product management.

Currently, the production of regulatory-approved intermediates and APIs represents the majority of AFC's business. Over the next few years, the company plans to substantially increase its R&D/Process Engineering group and the percentage of revenues derived from early drug development projects.

"We will continue to maintain our focus on our select customers," says Beatty. "We have substantially broadened our customer base over the past two years and will continue to do so to support our growth. However, providing high-quality service to our customers has been and remains our primary focus.

"It is clear that this market is evolving at a fast pace. The competition from Asia is moving faster than anyone predicted and we anticipate that many customers will outsource early steps of the chemistry to this part of the world. The custom chemical business is still very diversified and we believe that consolidations will continue over the next few years in order to streamline costs and improve manufacturing capabilities," he says.

"AFC is focused on providing world-class service and unique technologies to our pharma customers. In addition, due to our DOD heritage, we have the capability for maintaining complete confidentiality. However, we believe in an open communication service model with our customers and each customer has full access to all of the data, documentation and improvements related to their process. Our approach to project management, coupled with our process development and engineering capabilities, allow us to provide our customers with the best overall solution," concludes Malik. sp²

FURTHER INFORMATION

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