Outsourcing: The Dust Has Now Settled

By Guy Villax, CEO, Hovione

The dust has now settled after the exciting but turbulent times two years ago that saw the chemical giants snapping up pharmaceutical Fine Chemical specialists for hundreds of millions. Almost $3 billion were invested in three deals alone.

The drivers for outsourcing of APIs remain unchanged, yet the business model adopted by the various players seems to fall clearly into two very different types, with different offerings and different strategies. Yet for all exclusive manufacturing of NCE APIs remains a roller coaster: Approvals carry high rewards; product cancellations and withdrawals mean significant disappointments.

The notable new entrants are the integrated chemical giants that have acquired or invested in GMP businesses (some of the businesses that got acquired were great brands: Archimica, Carbogen, Chirex, Finorga, Raylo, Torcan…). Their original strategy was to bet on size and enter a high-margin, non-cyclical business that had synergies with their existing businesses. Some articles emphasized that the acquisition of API capabilities was strategically aimed at giving them total control over the key building blocks, which could be sourced internally.

On the other hand, the traditional players have remained independent and have taken no part in the M&A frenzy (FIS, Hovione, Lonza, Omnichem, Orgamol, Siegfried). In fact, they all probably see M&A as a strength-diluting exercise, as it debilitates one of their strongest assets; namely, their company culture. Their growth, which has been consistently in double digits for the past 10 years, remains purely organic.

The Independents strongly disagree with the assumptions that formed the strategies of the new entrants:

- Why should size matter?
  - when most APIs are only a few tens of tons
  - when there is a trend to more highly-active compounds
  - when an API producer should be a generalist—able to do all technologies—and not the lowest-cost technology specialist
  - when the early phase clinical materials require service, service, and more service, which traditionally is not a characteristic of large, multi-site companies
- Backward integrating only adds to an already risky business, whereas the Independents have the whole world—including India and China—to source low cost raw materials.
- Buying sites from large Pharma with supply agreements often resulted in:
  - a low-margin business,
  - a single-customer dependence,
  - an old plant, which was often not multi-purpose and certainly not designed for quick change-over and evolving compliance standards.

Furthermore, with their expansion into the API business, the chemical giants risk antagonizing their traditional customers who now could perceive them as competitors and no longer as supplier/partners. As an example, Hovione would prefer to discuss its new catalyst needs with Engelhard rather than Degussa or Johnson Matthey, who are now perceived to be competitors.

Neither the analysts, the board members, nor the shareholders considered any of these matters, but management thought they saw opportunities for making a difference in their shareholder value and the stock market supported them wholeheartedly.

In our view, the winning model appears to be a company big enough to:

- have the critical mass that will support the diversified portfolio necessary to mitigate risk
- support a large process chemistry group able to develop several dozen simultaneous projects
- have the depth and breadth of know-how and technology that is necessary to support multiple process validation campaigns per year
- assure long-term capacity.

and yet small enough to:

- take decisions and communicate them quickly
- provide extreme levels of service, flexibility and transparency

We believe the entrepreneurial, single-minded company without share-price concerns or peripheral activities to serve as distractions is likely to be a step ahead of the competition.

The constant need for large amounts of capital investment, the many years that projects take to mature from development phase to commercial scale, and the inherent risk of each project make our business unfriendly to the stock market. Therefore, it should be no surprise that the key players have a reference shareholder able to look at the longer-term: whether it be Ajinomoto, a family, or a foundation.

Over the last 12 months Hovione's normal growth has been further enhanced by:

- Satisfied customers who bring us repeat business
- Projects that have moved beyond validation to commercial phase

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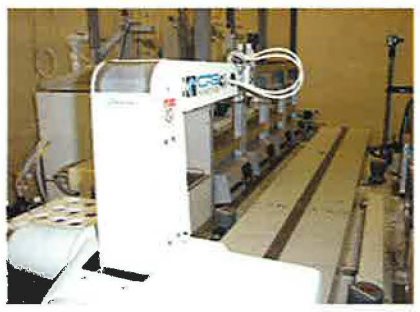
Sumitomo Chemical Catalysts Improve Yield, Regiospecificity

Sumitomo Chemical's novel proprietary catalyst technology is in the forefront of novel synthesis of customized racemic and chiral Cyclopropane carboxylates. Employing proprietary novel catalysts, Sumitomo Chemical has simultaneously achieved significant yield improvements and enhanced regiospecificity in the synthesis of Cyclopropane carboxylates.

Chrysanthemic acid is a well-known cyclopropane carboxylic acid derivative occurring in natural pyrethroids such as Allethrin. Such intermediates are important in the Life Science industry in the synthesis of drugs as well as crop science chemicals.

Industrial synthesis is conducted by either the addition of a copper carbenoid species, prepared from a diazoacetate, to an alkene, or by addition of an alpha-halo ester to an alkene. Other synthetic approaches have involved the employment of Dimeric rhodium carboxylates such as rhodium acetate ($Rh_2(OAc)_4$) , which have been extensively used as extremely mild catalysts for decomposition of diazo compounds but are known to have limitations in the synthesis of cyclopropane carboxylic acids.

In the course of Sumitomo Chemical's research to find more effective catalysts, a new Rhodium catalyst, Dimeric Rhodium triphenylacetate, ($Rh_2(OCOCPh)$), has been discovered, which has a very high reactivity, and gives higher yields of cyclopropane carboxylic acids compared with rhodium acetate catalysts. This catalyst enables higher yield attainment for products than is achieved with conventional catalysts, even when high yields have been difficult to achieve with substrates such as mono substituted alkenes. The addition of diazoacetates to alkenes goes smoothly when employing alpha, beta unsaturated esters. Good results have never so far been reported in the reaction of such substrates with copper or rhodium carbenoids.



Despite a history of successful asymmetric synthesis of cyclopropane derivatives by chemocatalysis, where Sumitomo Chemical has itself been to the forefront of such technology, the company has now developed novel procedures employing optical resolution and biocatalysis for the economic synthesis of cyclopropane carboxylates. This has involved the use of proprietary enzymes and optical resolving agents (chiral acids & amines), supported by robotics and analytical science to rapidly identify the most economic catalyst system.

Industrial activity ranges from Kilo Laboratory, through pilot to commercial manufacturing scale. The core of such processes is novelty in catalyst design. ❊

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- Customers with projects in Phase III who are looking for a more reliable long-term supplier

Our experience indicates that Phase III projects change suppliers because:

- They want a stable supplier for the long term, "one that does not shop itself around constantly"
- They want assurance of capacity and of compliance and are fed up with "getting a different color batch every time"
- They want to be in-the-loop and not be the last ones to know of problems or of process changes

The key buying factors for our customers seem to include: a company capable of developing robust processes based on sound science that delivers "right-first time, every time"—shareholders who are committed for the long-term, and a track-record of rock-solid delivery as well as open and honest communications.

Some European companies have continued to invest at a time when others are trying to sell. Orgamol is building a new pilot plant and synthesis unit in Switzerland; Siegfried has innovated dramatically in the GMP design of its own new facility; Rohner has started up a new cGMP multipurpose plant.

Hovione has just commissioned its new Technology Transfer Center in New Jersey (USA). This is an investment in a green-field site with kilo-lab and pilot-plant facilities within a short drive of the largest cluster of API customers in the World.

In the past few years exclusive manufacturing as an industry has been the object of far too much interest, and too many bets were placed with exaggerated expectations—and most are not pleased with their investments. The business, however, exists, and the market continues to grow; but it is just not as simple as many companies expected it to be. Fines for non-compliance of GMP that have reached a record half billion dollars, and FDA's most recent initiative, "Pharmaceutical cGMPs for the 21st Century," are but two indications that the scope for differentiation has increased yet again; and that the role of a professional independent manufacturer of APIs has never been more relevant. ❊