Big interest in small molecules

Venture capital isn't the only source of funding for small molecule start-ups, says Dr Rob Bryant. There is a compelling case for investment from the larger fine chemical companies, although the concept is still regarded as novel by many industry players

A straw poll would probably show that around a third of companies in the emerging pharmaceutical sector are developing low molecular weight chemical compounds, the same number are involved in diagnostics and the final third are developing new biologics. Within the small molecule sector, there are some businesses developing new molecular entities, others looking at candidates dropped from earlier R&D pipelines, and a growing number of specialists that have moved into investigating novel delivery systems and their minor variants, such as salts, esters and polymorphs, because this minimises risk and the eventual payback time.

Much like the earlier generation of biotech companies, the majority of enterprises that have chosen to develop small molecules continue to seek equity investment from two main sources:

- Venture capitalists, at varying early stages of development, prior to an initial public offering (IPO); or
- Major pharma companies, usually at a later stage, when proof of concept in the clinic has been demonstrated.

However, there may also be alternative sources of capital that could be more attractive to this sub-sector of the biotech industry including fine chemical companies, API producers, both independent and captive, generics companies and regional pharma firms.

A fresh look at investments

It is relatively easy to set out a compelling case for the larger enterprises – those with sales of around US$100 million or more – within the fine chemicals sector to make selective investments in small molecule developers. Given the industry's low profitability and recent contraction in their sales performance, the major pharmaceutical fine chemical (PFC) players, at least those with a reasonable cash position, really ought to be taking a fresh look at how to make more profitable investments than those seen in the past five to seven years. With a portfolio of ten to 15 well-chosen investments of US$15–20 million each, the potential for success could be high. And, unlike venture capitalists, fine chemical producers could view such investments as long-term, allowing the selected emerging pharma companies to concentrate on developing new products, rather than continually seeking fresh injections of short-term funding. The capital investments could also be partially paid for by the revenue generated from contracts to undertake chemical development and manufacture.

Discussions with a number of fine chemical companies suggest that less risky arrangements, such as the supply of chemical services and APIs in exchange for eventual manufacturing contracts and/or royalties, are already being made. These deals avoid the need for raising cash, which makes them attractive. They can also secure a stronger position for fine chemical companies when the developer seeks to license its new product to big pharma.

Fine chemical companies have the resources to make sound judgements on suitable investments, provide chemical development support and good manufacturing practice (GMP) all

the way to launch. They also have the expertise to assist in negotiating marketing deals with pharma companies for successful products. Commercial and development people in the fine chemical industry are used to working alongside pharmaceutical research groups and PFC managers are much less likely to interfere with the autonomy and creative environment that is rightly sought by emerging pharma companies.

This said, some of the bigger European PFC companies would need to improve their management systems to offer the type of support needed for successful collaborations. Another potential problem, pointed out by a UK biotech, is that the eventual new product package might be less attractive than usual to big pharma. Profits, for example, may be lower because of 'stacked royalties' and demand for control of manufacturing by the vendor.

It does appear that several companies have already begun to make such investments. Two of the larger fine chemical companies are believed to have groups looking into emerging pharma start-ups as investment opportunities. However, despite the fact that many of the major European pharma companies evolved from fine chemical or chemical companies – Roche, Novartis, Bayer, Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis to name a few – the concept continues to be seen as 'novel' by the majority of the industry's players.

API producers as investors?

As for captive API producers, many chemical manufacturing divisions of multinational pharma companies are even more experienced in developing manufacturing processes for new drugs. Often they take early-stage processes right through to production. The majority have a great deal of spare capacity – 20–30% utilisation rates appear to be typical – which could, in principle, be used for third party manufacture. A number of such units, including Sterling Organics (now Rhodia) and SIPSY (now PPG-SIPSY), have developed successful contract manufacturing businesses in the past. Extending the concept by offering to invest in an emerging pharma company might appear to make sense.

However, there seem to be several reasons why this sector would be unlikely to offer significant hope of development. Convincing senior pharmaceutical management to support the idea would be difficult, and the activity would also clash with companies' in-licensing groups. In addition, such operations tend to have higher costs than independents and would be less competitive.

A comment made by a senior manager of a group of API plants is also rather compelling – they tend to be run by rather risk-averse individuals, which is clearly a good thing for the dependable supply of uniform quality APIs. But because investing in drug development is an inherently risky enterprise, this is probably a serious argument against seeking investment from this industry sub-group.

Independent specialists in the manufacture of APIs – mainly, but by no means exclusively, for generics firms – might also fulfil a number of criteria needed to qualify as investors in the emerging pharma industry. Indeed many have forward-integrated into producing finished formulations over the past five years and taking the next step forward might seem a viable option.

In all likelihood, the main reason why this would probably not be so attractive in general is that the majority of such companies are usually rather specialised and lack both the skills and manpower to set up a well-qualified investment group. Nevertheless, some might well be in a position to make investments, possibly in partnership with their generic pharmaceutical partners (see below).

Another potential source of capital is regional pharma. Companies in this category include integrated Asian pharma firms in countries like India, Korea and China, as well as medium-sized European companies. As part of their overall strategy to develop a greater global presence and to secure higher value-added products, some of these companies have already set up drug research programmes, albeit usually focussed on 'me-too' drugs.

Investing in pharma start-ups, many of which have developed truly original candidates, might represent a useful expansion in these companies' development plans. The successful emergence of the innovative industry in Japan offers a useful model of what can be achieved, although in this case, the investments have usually been limited to Japanese pharmaceutical development groups.

In the generics sector, meanwhile, Teva Pharmaceuticals Industries' launch of its own novel pharmaceutical, Copaxone, is evidence that the basic idea of generics firms investing in small molecules is already being put into practice. However, as a fully back-integrated company, Teva is not a typical example. The normal model for this sector, especially in the US, has been based on minimal capital investment, with APIs and formulations outsourced while product development, registration and sales remain the key functions retained in-house. Many companies have been attracted to developing variants on existing products, although novel formulations tend to be more popular because their development is less risky. In Europe, companies such as Schwarz Pharma have begun to develop novel products and this strategy could include investing in emerging pharma companies.

Science over presentation

The merits of seeking alternative sources of funding can easily be seen when compared with the existing approach to attracting and maintaining investment. It has to be said that seeking equity investment from venture capitalists and big pharma has its limitations, as the best-pitched packages are often favoured over business cases put forward by individuals with good scientific, but weak presentation skills. It is undoubtedly the case that a number of good ideas must have been dropped for the wrong reasons. However, a new group of investors with stronger scientific qualifications and more modest financial objectives might prove to be better at identifying and developing some of the next generation of small molecule-based pharmaceutical products.

It seems there is a realistic opportunity for those fine chemical companies with investment funds to make a real contribution to the support of pharmaceutical research by small, independent development companies. The bigger companies could even have a real chance to transform themselves into pharma firms in their own right, with the improved profits and sales that the resulting products can bring. Certainly, in the current climate of low margins, decreasing sales and chronic under-utilisation of expensive manufacturing capacity, such an investment must make more sense than continuing current policies.

If such additional activities help secure a sounder future for the European fine chemical industry, then this will be an additional benefit. Although the majority of the international drug companies have not yet realised it, the contract manufacturing and custom synthesis industry in Europe could effectively disappear by the time its outsourcing managers realise that Asia does not offer the full range of services that it has come to accept as its right.

Dr Rob Bryant is director of Brychem, a pharmaceutical fine chemical consultancy based in the UK.