Contemporary R&D – a virtual reality

In the current climate of R&D with advanced technologies providing ever more leads through genomics, combinatorial chemistry and high-throughput screening (HTS), there is now a gap between the early-stage assay hits and clinical trial candidates that have been developed to proof-of-principle stage. Coupled with the pressures on R&D budgets and a need for flexible resourcing to accommodate the changing demands throughout product development, a new breed of virtual company has emerged that fills the niche. One such company, Arachnova (Cambridge, UK), has recently been founded by David Cavalla (CEO) and Robert Gristwood (Research Director), both of whom have gained many years experience within major pharmaceutical companies. I had the pleasure to meet with David and discuss the role of the virtual company in drug discovery.

David, what are the big operational differences between pharmaceutical companies operating in the late 1990s versus those operating ten years ago?

I think the industry is very different from what it was in the early 1990s and certainly in the 1980s. These differences are primarily down to out-sourcing and the ways in which the industry is vastly more complicated and multivariate now. It is still composed of large multinational companies, but in addition the importance of other companies acting as service providers has increased dramatically. Such companies vary from the contract research organizations (CROs), which provide developmental activities through to the biotechnology sector, which operates in a more complicated fashion. But ultimately the differences are all down to the relationship between multiple companies in a client–server relationship.

There has been a proliferation of virtual companies, first in the USA and more recently in Europe, and particularly in Cambridge. Do you believe that this trend will continue?

The short answer is yes, I think this trend will very much continue. But the kind of companies that have arisen and operate in a virtual sense are often very small. There are some exceptions – probably Vanguard Medica (Guildford, UK) is one of the largest virtual companies – but there are also many other very small companies, some with only a handful of people. This doesn't mean that they are unimportant – there are several lessons that can be learnt from their strategy of operation, which will mean that this type of outfit will continue to grow in importance in the future.

Born in the USA

As to the geographical location of these companies, there are perhaps some interesting contributing factors. Firstly, the USA was where biotechnology arose, with the likes of Amgen (Boulder, CO, USA) and Genentech (South San Francisco, CA, USA); it has also been a place where venture capital has been relatively easy to obtain; and lastly, it is also a country where entrepreneurialism is almost in the blood, particularly on the West Coast, which possesses a kind of 'frontier spirit'. Some people have commented that entrepreneurial ventures often originate around academic centres and one can see that to a certain extent around the Bay Area in San Francisco, around Los Angeles and Boston. If that factor is important, then that could possibly explain the number of companies in Cambridge, UK.

Surely this will mean that a radical reshaping of the industry is required. How do you foresee the overall R&D structure in the year 2010?

It would take a brave man to be categorical about that, however, there are certain trends that I foresee continuing, at least for the medium term. Certainly multinational pharmaceutical companies will continue to exist, but the merger trend will continue, so that there will be fewer larger companies. The reasons why they will merge are primarily based around the need for them to have a greater global impact. Their global registration and marketing activities are one of the key strategies for their continued success.

A second trend will be a consolidation in the technology provider type of operation, such as companies that have arisen out of single technologies like genomics, combinatorial chemistry and HTS. There is increasing evidence now that these companies, although offering a very useful service, may have their business advantage eroded over time as the technology becomes more widely available. Hence, what they have to offer becomes more of a commodity rather than something intrinsically valuable.

Towards virtuality

I also believe there will be an increased trend towards virtuality. Thus, there will be even greater reliance on out-sourcing. So the type of structure adopted within the pharmaceutical industry in the year 2010 may well become similar to the more traditional and mature industries of automotive manufacture and construction. Bear in mind, however,

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that the industry in some ways is quite resistant to change because its products are patented and protected for many years after they have been invented.

Also, there is another key factor, which is relatively less well appreciated; the reasons why a company succeeds or fails in the pharmaceutical industry is not just based on their operational strategy or competence, but a major factor can be serendipity. It can often be quite difficult for a company that has a successful product to see the real reasons why that arose and to acknowledge that serendipity played a fair part in the success.

Recent years have seen increasing commercial awareness of the value of academic research, initially on behalf of the big companies but, more recently, by academia itself. Do you think this means major changes in outlook for academics?

Yes, but this question cannot be separated from the wider question of the extent to which government or public money should be put into academic research. At the more extreme end, some people advocate that very little public money should be put into academic research. This will mean a major change in outlook for some academics; however, those who are involved in particular areas of research with great practical and commercial importance may well find it is easier to attract funds from industry.

Another side to this is that the trend itself can, in some academics' minds, lead them to over value the worth of their research. The processes involved in research and development are quite different, and commercializing an academic invention is often a more complicated task than arriving at the actual invention itself.

How can academics approach this alien environment when they already have a hefty workload of their own core activities?

I would suggest that everybody is working extremely hard these days, so I don't think that the pressures on academics are radically more severe than those in the pharmaceutical industry. Anyone involved in the pharmaceutical industry will have realized that these days it is not sufficient to be smart or hard working, one has to be smart and hard working. Similarly, the days of the ivory tower mentality within academia are fortunately receding.

Which elements of pharmaceutical R&D lend themselves most readily to virtual integration?

Of course the ability to perform anything virtually depends upon the availability of providers; in drug development there are a profusion of providers in the form of the CROs. However, it is also true that sales and marketing activities are accomplished extensively by contract. For example, Innovex operates as a contract sales provider and has the largest sales force in the UK.

The availability of providers to perform elements of drug discovery is relatively less well developed than drug development, but this is a situation that is changing quite radically. It is changing because more organizations are offering the component parts of drug discovery (i.e. combinatorial chemistry, HTS or genomics) and also these providers are becoming more accepting of a purely contractual type of relationship, rather than the type of relationship that typified early combinatorial chemistry or genomics collaborations, which were based upon intellectual property transfers and assigning fees, milestones, royalties and so on.

The large companies remain large; for example, Glaxo Wellcome (Stevenage, UK) and SmithKline Beecham (Harlow, UK). Why do you think they haven't proceeded further along the route to virtuality?

I don't think it is true that large companies haven't considered virtuality. Roche for instance has it own subsidiary called Protodigm (Hemel Hempstead, UK), which is a virtual organization, and SmithKline Beecham has recently spun-out AdProTech (Royston, UK), which also has elements of virtuality.

Forging ahead

One must bear in mind that until the late 1980s the idea of out-sourcing was relatively poorly developed, so the large pharmaceutical companies have moved a long way in a relatively short space of time. Even companies like Glaxo Wellcome are now thinking strongly about how to trial some aspects of virtuality in their business strategy. Probably most of the large companies have considered virtuality and many of them will implement it as a component of a varied business strategy and they will see how it goes.

The virtual company can clearly use its resources in a very efficient manner, but by definition it has to rely on the resources of only a few core individuals to drive the business forward. Do you think this makes them weaker than their more traditional counterparts?

Clearly, where you have very few individuals in an organization it would be a great loss if someone of key importance left. However, I think one needs to construct a type of reward within the virtual organization that gives such individuals the best opportunities and prospects of staying. The short answer is that virtual companies are more subject to the problem of key individuals leaving, but overall, for reasons I will come to, I don't think they are weaker organizations.

One can imagine that with interfacing so many different entities, a virtual company could become bound up in time-consuming contractual and IP matters. How can this be minimized?

What one has to attempt to arrange is the use of collaborating bodies in a purely contractual fashion rather than in a fashion that involves exchange of intellectual property – this is certainly the way that we intend to work at

Arachnova (see Fig. 1). The more one can operate contractually, the faster and easier the negotiations will be and, consequently, the greater the flexibility will be. When I was working at Napp Research Centre (Cambridge, UK), we conducted a virtual research programme to develop a PDE4 inhibitor into Phase I. This was conducted in an entirely contractual form and it had tremendous advantages in terms of flexibility and speed of operation. It was, in fact, during this time when I first had the idea of setting up a virtual company.

From a personal viewpoint, you have left the security of an existing company to be at the cutting edge of virtual R&D, how certain can you be that this will be a success and how do you feel about this as a personal challenge?

One of the major reasons for my founding Arachnova is because it is a personal challenge. One cannot be certain of anything being a success in life, but I can guarantee that if I hadn't tried it, it wouldn't have succeeded. Virtuality has a great deal to offer to the future strategy of pharmaceutical R&D and I think that there are four reasons for this.

First, the virtual strategy offers a greater degree of flexibility, which is very important in the product innovation process within the pharmaceutical industry. This process is prone to variable levels of resource demand throughout discovery and development of a new chemical entity. Bringing on board the right level and the right type of resources at the right time is a complex management problem. Being able to operate this by a virtual strategy offers great advantages in terms of flexibility.

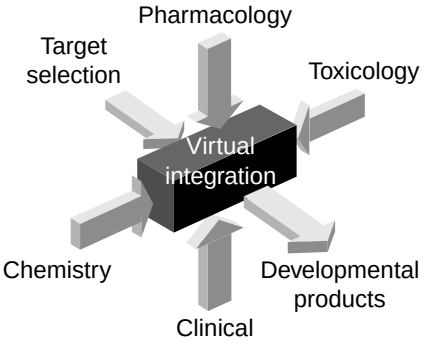

Figure 1. *Virtual integration at Arachnova involves taking selected compounds at or beyond the 'hit' stage and implementing the analysis, evaluation and development of these through contractual collaborators. Such compounds, when carried through into human trials, become substantially enhanced in value and can be either returned to their originator or out-licensed on.*

The second point is that operating virtually allows one to gain access to the best technology worldwide, which is of particular relevance, currently, as drug discovery technology is advancing very rapidly and technologies such as combinatorial chemistry, HTS and genomics technology are becoming increasingly integral to the early part of the product innovation pipeline. Being able to gain access to the best facilities alleviates one from the problem of having to be an expert in all areas – if one can't be an expert in all areas then why be an expert in any?

The third reason why I think virtuality will be successful is evidenced by the history of the development of a new treatment for periodontitis by a virtual company called Collagenex (Wayne, PA, USA). The company took a compound on from Johnson & Johnson based on some work that had been carried out at the State University of New York and took it through to an NDA for a total cost of $6.2 million. It was managed by a team of fewer than half a dozen people and, therefore, it represents a paradigm shift in the costs and resources that are thought to be necessary to develop new pharmaceutical products.

The fourth advantage of virtuality is based on the cost advantage that I previously alluded to: the consequence is that products that address relatively small markets can become profitable enterprises. Rather than having to concentrate only on products of worldwide importance with huge market potential, one can consider products that have a niche application.

Summary

The four advantages of virtual R&D are:

- Flexibility
- Access to the best technology
- Cheaper discovery and development processes leading to advantages relative to one's competitors
- Access to niche markets, which expands the whole pharmaceutical market

For further information see David's recent book entitled *Modern Strategy for Preclinical Pharmaceutical R&D*, published by John Wiley & Sons (1997). £45.00 (ix + 218 pages)
ISBN 0 471 97117 0.

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