Virtual drug development

Nowadays, it would seem that there is no aspect of drug development that cannot be "virtualised" - with varying degrees of success.

Dr John Hutchison, Vernalis

The layman might be forgiven for associating the term "virtual" with computer-based technologies, as in "virtual reality". Whilst this interpretation of the word has some relevance to pharmaceutical R&D (particularly in research), in the context of drug development the term "virtual" has come to describe a management philosophy rather than a new technology. Nonetheless, sophisticated computer-modelling techniques are making inroads into the process of R&D, so this is where we will begin.

Virtual discovery and pre-clinical development

... virtual techniques are marching further and further down the screening cascade

The benefits of using "in silico" techniques for compound screening in the drug discovery process are well established. The power of modelling arises from the ability to produce dynamic images of putative drugs and binding sites in a three-dimensional form, whilst also factoring other influences such as surface charge. Huge numbers of compounds contained within electronic libraries can be screened for binding potential without the bothersome task of actually making them. This has greatly increased the speed and efficiency with which leads for conventional medicinal chemistry can be identified. This process is truly virtual in every sense of the word.

Beyond drug discovery, academic groups and others are also using virtual modelling techniques to recreate biological functions, including models of enzymatic reactions, cellular responses and organ function. In the same way that receptor modelling might simulate the binding characteristics of a molecule, it is hoped that these techniques will predict functional and other outcomes. Consequently, virtual techniques are marching further and further down the screening cascade.

Two companies have made models available which can simulate a drug's metabolism and predict pharmacokinetics - namely the Camitro Corporation and Navicyte, both based in California. Simulations Plus Inc offers a product which is believed to predict drug absorption from the gastrointestinal tract, and a collaboration between scientists in the US, UK and New Zealand has resulted in the creation of a virtual heart. It is claimed that this cardiac model can simulate certain pathological states and may be of value in predicting drug responsiveness in patients. Entelos PhysioLabs is also into commercialising disease models, having created simulations of asthma, obesity and HIV, which they claim will reduce the failure rate in pharmaceutical R&D. Finally, the Physiome project (responsible for the virtual heart) aims to create an entire virtual human body. Time will tell how predictive and useful these models turn out to be, but it is clear that virtual technology - as it is understood by the man on the street - will impact certain aspects of drug development and possibly improve our decision-making in the early stages of a potential drug's life.

Virtual development

As indicated, "virtual development" embodies a rather different concept and owes little to silicon valley. In the context of drug development, the

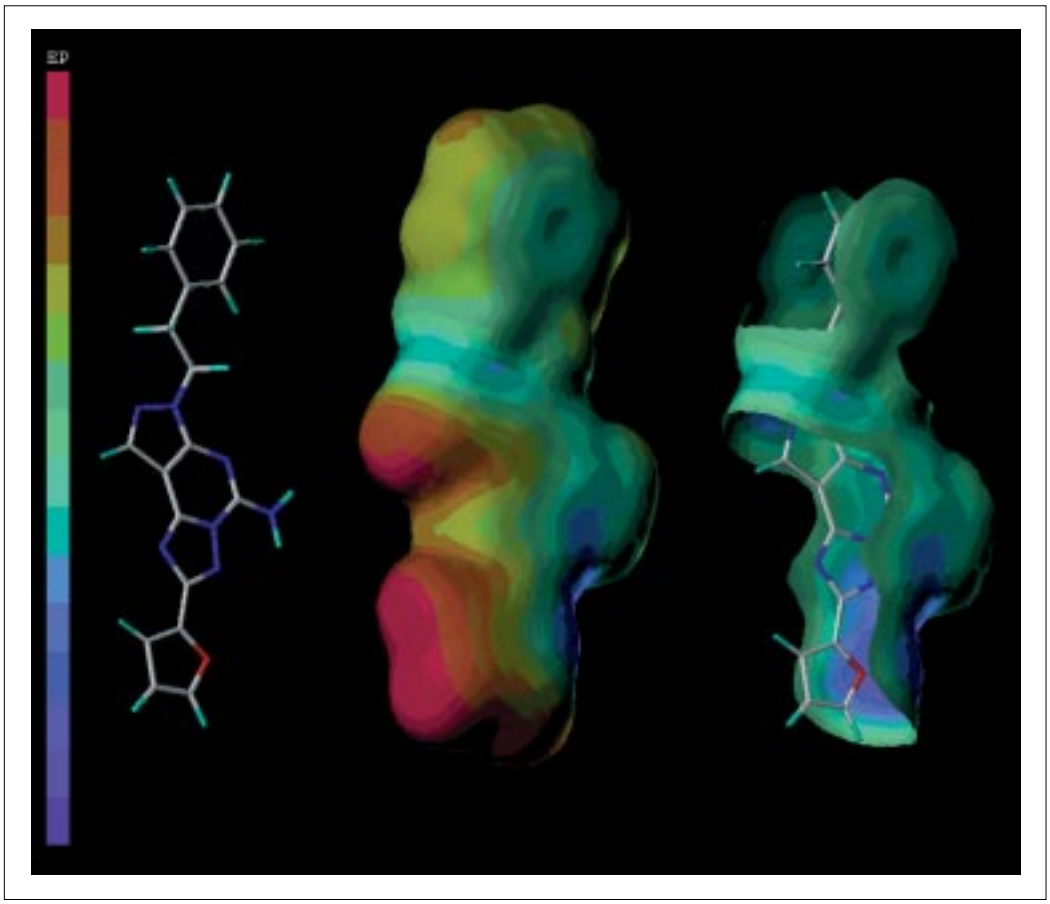

Figure 1. Three-dimensional representation of electrostatic surface potential (charge) of a potential drug.

term "virtual" relates to the way the process is directed and managed, relying as it does on outsourcing. The choice of the word "virtual" to define this way of working is a bit misleading but, emerging as it did in the early 1990s, was probably influenced as much by fashion as anything else.

In the past, established pharmaceutical companies conducted most - if not all - of their drug development in-house. Consequently, each required the capability and infrastructure to support all aspects of development including chemical development and primary manufacturing, analytical and bioanalytical chemistry, toxicology, pharmaceutics and secondary manufacturing, clinical development, regulatory affairs - and an array of support functions plus a management structure to control it all. Some large companies still operate exclusively in this way, although for most the trend is to use outsourcing to even out peaks and troughs. It is clear, therefore, that to set up a fully staffed "in-house" development group from scratch requires a huge investment, hundreds of staff and years of operation to become effective. This is clearly never going to be a realistic prospect for a start-up company (although apparently it hasn't stopped one or two from trying). Therefore, if small companies are to engage in drug development, a different approach is required.

Companies adopting a "virtual" approach work on the principle that operational tasks can be contracted outside the company, whilst the strategic and project management functions are retained within. This shortens the line of command and provides a clearer delineation of responsibility. In this pared-down environment, executive decisions may not be any more correct but at least they stand a better chance of being understood, acted upon and not constantly

recycled through impenetrable layers of middle managers. All the evidence points to a shortening of development time and cost. The extent to which tasks are delegated outside varies between companies, but the outsourcing principle underlies the virtual development concept. To be effective, the "in-house team" has to be experienced (functional head level in many cases) and the skill-base has to cover the full range of disciplines engaged in development.

Factors influencing the growth of virtual development

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In the last decade or so, a number of forces have conspired to change the face of the pharmaceutical industry. R&D expenditure has increased whilst pricing and other regulations have squeezed profitability, resulting in a wave of mergers, acquisitions and consolidations - a wave which continues with ever-larger players. This process has had the effect, not surprisingly, of releasing experienced and talented industry personnel into the marketplace. Some have moved into contract research organisations (CROs), which initially sprang up in considerable numbers. Many of the early CROs were focused on the provision of contract clinical research, but the market soon expanded to include other services such as contract synthesis, analytical and preclinical functions, and in some cases sales and marketing.

Currently, there are few skills within the industry that are not available in the contract sector. At the same time, entrepreneurial research and development start-up companies were formed in larger numbers, often based on ideas or technologies licensed from industry or from academic institutions. A symbiotic relationship between early-stage pharma companies and contract organisations emerged - and thrives today with a number of operational alliances. Hence in the 1990s, the environment was right for small (in some cases very small) companies to take on development programmes which in the past would have been the sole province of the pharmaceutical majors. To get some idea of the diversity of the virtual approach and philosophy, it is worth looking at some examples - although the following does not purport to be an exhaustive list which would be beyond the scope of this feature.

Virtual development companies

Many adolescent biopharmaceutical companies (that is, those now in their teens and beyond) have been through the virtual stage (in some cases before the term was coined) and now - by virtue of organic growth and consolidation - more resemble conventional pharmaceutical companies. Celltech Medeva and its subsumed companies would fall into this category. In the US, Genentech and Biogen have also developed from small-scale beginnings into fully integrated pharma operations.

Looking at the more recent UK start-ups, Vanguard Medica (now Vernalis) was one of the first to identify itself as a "virtual development" company, and for some time the phrase "Vanguard Model" was used as a descriptor. Two new chemical entities (NCEs) have been approved in the last year or so, having been through the virtual development process - the anaesthetic chirocaine from Chiroscience (now part of Celltech Medeva) and frovatriptan from Vernalis. Consequently, the model is validated to the extent that it has delivered products and, in both cases, has done so more speedily than the industry average. However, as market conditions and investor sentiment have changed during this decade, it is now unusual to find small companies willing or able to undertake a full development through to registration. More often, small companies will undertake the earlier stages (to so-called proof of principle in early patient studies, Phase IIa) and thenceforth seek partners for the more expensive later stages. Cambridge Antibody Technology (CAT) is an example which has achieved success with its antibody-based platform technologies, and has a number of antibody products in development. Its development effort is directed at the early stages (that is, up to Phase II), whilst the more expensive Phase III studies are conducted in collaboration with partners. Whilst this is perhaps the norm, there are some opportunities to take certain compounds all the way through, particularly for niche indications - as will be discussed later.

Big pharma has experimented with the idea of virtual development, as evidenced by Hoffman-La Roche's creation of Protodigm in 1996. Protodigm employed only nine staff, representing one of the leanest of the virtual organisations, and demonstrated the cost-effectiveness of the virtual principle during its life by improving development times and reducing costs by approximately 25 per cent compared with industry standards. Protodigm now exists as an independent company, Fulcrum Pharma Developments, offering drug development services on a contract basis. It has recently announced an agreement with Xenova, another biopharmaceutical player, to develop products in oncology.

More recent entrants onto the virtual development scene in the UK include Arachnova Ltd, which specialises in identifying and developing new therapeutic uses for existing products, and DevCo, which licenses-in CNS projects from other pharmaceutical companies. Larger pharma companies may release compounds for development outside if they no longer fall within their therapeutic focus, and occasionally merger activity can release products or candidate

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drugs where there is duplication. Where the originator company wishes to retain downstream rights to its compounds, an alliance with a virtual company can provide an "off balance sheet" vehicle which permits projects to be continued without impacting the originator's profit and loss account. The collaborative approach, which involves cost- and risk-sharing, is attractive to many small cap investors who are more sensitised to the natural attrition of compounds during development now than they were ten years ago.

Not surprisingly, the US has not been backward in coming forward with virtual approaches to drug development. The more established biotechnology companies have gone beyond the point at which they could be considered virtual. Of the more recent players, the Medicines Company (founded in 1996) is unusual in that it takes compounds at a later stage of development. Based near Boston, the company specialises in late-stage development and commercialisation; it has one cardiovascular product (bivalirudin) in the registration process and a number of others in the later stages. The company has 61 employees worldwide and has entered into a strategic alliance with the service provider, Quintiles, which acts as a partner for both the development and commercialisation of products. The company clearly has global aspirations having opened offices in the UK and New Zealand.

New entrants are still joining the virtual company parade - a recent example being the aptly named Virtual Drug Development Company. This group intends to concentrate on early stage clinical research in cancer, and hopes to make use of the various regulatory mechanisms in the US to fast-track drugs destined for serious and life-threatening disease indications. The company has formed a variety of alliances, including one with the aforementioned Fulcrum, presumably to exert leverage on development opportunities on both sides of the Atlantic. It is likely that further collaborations along these lines will emerge as smaller players seek to find synergies.

Investment in areas of high unmet medical need is attractive to a number of smaller companies, even if the eventual market (defined by patient population) is relatively small. Legislation in the US permits fast-tracking during the development of drugs for serious or life-

Figure 2. The Virtual Development Organisation.

threatening conditions, and Orphan Drug legislation now in place in Europe as well as the US provides assistance and incentives for companies to develop drugs for rare diseases. These conditions very often fall below the radar screen of the pharmaceutical majors, but provide an interesting opportunity for the smaller players. By way of example, Cephalon, an established US biotechnology player, has built a successful business out of developing a treatment for narcolepsy, a rare sleep disorder.

The prospects for virtual development in the future

The pharmaceutical industry is constantly evolving, but it seems that the virtual approach to development will survive so long as there are start-ups wishing to conduct drug development, and it is quite likely that the pharmaceutical majors will continue to pursue more aggressive outsourcing policies and hence virtualise some aspects of their operations. No doubt economics, rather than anything else, will drive the move in this direction but the savings are plain. The smaller "drug development" boutiques cannot afford to stand still either, and the challenge that faces them all is how to secure a supply of quality drug development candidates. One solution, and indeed the route followed by Vernalis, is to acquire a drug discovery operation to create an integrated R&D function. I am sure that a variety of strategies will be played out with varying degrees of success, but one thing can be assured - the sector will never be dull.

Dr John Hutchison was awarded a PhD in physiology by the University of Liverpool in 1980, and subsequently studied clinical medicine at he University of Leicester. After four years in hospital medicine, he joined the pharmaceutical industry working in the department of clinical pharmacology at Fisons. Over the next ten years he held a number of posts in drug development within Fisons and Astra, eventually heading up Astra's experimental medicine function. Since then, he has managed development operations in two small companies, firstly Cerebrus and more recently Vernalis. Dr Hutchison is a Member of the Royal Society of Physicians (London) and a Fellow of the Faculty of Pharmaceutical Medicine.

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