Figure 1
Transgenics: pro-nuclear micro-injection techniques

Harnessing the CRO intellect

There is no question that pharmaceutical companies are qualified to perform their own discovery and preclinical research. However, to fully exploit the new technologies in the early research phases, to maximise drug leads, and to minimise costs, would the outsourcing to a fully integrated service partner that can provide operational excellence make better commercial sense?

By Ian Lennox and Dr Nigel Brown

Big pharma is big financial news. Highly publicised sales of blockbusters like Viagra and Prilosec have investors, who might have previously disregarded healthcare, rubbing their hands together in anticipation of the next launch. And loud cries are heard if a product introduction is met with less than record-breaking numbers. It is clear that patient and healthcare provider needs are running neck and neck with those of Wall Street. Everyone is watching big pharma, and the expectations are high.

Rapid consolidation within the pharmaceutical industry has continued undiminished over the past five years. Ironically, increased pressure from the financial community to deliver continued growth in earnings (a key driver for consolidation) is a stressor unaided by mergers. While mergers provide cost reduction, they have little beneficial impact on the pharma industry's *raison d'être* – the development and introduction of new chemical entities to the commercial marketplace and to patients around the world. Regardless of their new partnerships, pharmaceutical companies are still facing the need to grow pipelines at an unprecedented rate in order to fulfill revenue demands.

With uncanny serendipity, an explosion of new technologies in drug discovery promises to deliver this very thing (see sidebar for a brief overview). Functional genomics, proteomics, transgenics – if one could properly assemble and apply these technologies, it could radically reduce the time needed to identify a target and bring it to market.

The science that's shaking up pharma

The science of discovery is fundamentally different from other stages of research. Unregulated, the goal-oriented atmosphere appeals to risk-takers and lovers of high science and high technology. This creates a markedly different environment from the meticulous, highly regulated later phases. The culture is dynamic.

Thus, each new breakthrough generates tremendous excitement. Because the reasons for drug failure have remained fairly consistent – poor biopharmaceutical properties (metabolism, pharmacokinetics, etc), toxicity, and lack of efficacy – potential new methods for the early weeding of compounds have enormous value. Here are a few of the top-line issues and new technologies.

Genomics

The Human Genome Project has thrust genomics into the limelight and excitement is great. (One enthusiast proclaimed that, based on the genome project, we would see the end of most major diseases in the next 30 years[1].) The technology is fascinating but still somewhat removed from practical application. To make an analogy, the DNA sequencing conducted to date has helped develop a crude dictionary of the human genetic language, but there isn't enough information yet to make a sentence. Some amazing applications have been developed, but the bulk of the value is yet to come.

Functional genomics is the study of gene function and its relationship to disease pathways. It is a way of biochemically characterising a disease, typically through expression of protein profiles. Pharmacogenomics is the use of genotyping to anticipate drug action in particular patients. Its application has important implications for the pharmaceutical industry, as it could significantly refine the recruitment process for clinical trials and enhance the statistical power of trials in certain populations.

Transgenics

High-quality human models are essential to discovery, as the use of human subjects is impossible. A poor human model in discovery can mean a failed drug in Phase III – $250 million later. It is a foundation of research.

There are several ways to mimic the action of drugs in humans. One is tissue extraction, the study of human tissue cultured in a test tube. Another is animal models. Mice, for example, are genetically similar to humans, but the small genetic variances cause significant physiological differences. Thus the quandary: do you use animals because they are close to humans, but subject yourself to the risk? Transgenics is offering a new approach.

Transgenics allows the injection of human genes into animals, essentially creating a humanised mouse, expressing humanised proteins that can then be studied. An added benefit is the shorter maturity onset in a mouse – considerably shorter than in humans – so results are seen more quickly.

Proteomics

If genomics is the dictionary, proteomics is the encyclopedia. Proteomics is the study of proteins expressed by active genes; it can help reveal the way an encoded protein behaves and link certain behaviours to disease.

A recent article on proteomics underscores the key benefit. "Understanding protein structure and protein structural properties will allow pharmaceutical companies to make better choices of candidate compounds before tens of millions of dollars are spent on clinical trials."[4]

The new discovery technologies are without doubt both exciting and unprecedented. In the past century, 300 fundamentally different biological molecules were introduced to combat human disease. If we are able to fully exploit the information generated in the postgenomics era, this number could increase 10-fold or more[1]. This is exciting news indeed for pharma companies which, in order to maintain their current growth in future years, are going to have to quadruple their productivity[2].

Yet caution is required. In the past, no one has been able to translate similar technological advances into faster processes. Despite astonishing developments in science, the average length of time for drug discovery and development is essentially unchanged, and, if anything, substantially more expensive.

So an important question remains: Will the pharmaceutical industry be able to capitalise on the new technologies and enhance the drug development process? And if they cannot, is there someone else who can help them?

Exploiting the potential of new technologies

Let us explore that question for a moment. What type of company can best exploit the potential of these new data? First, based on the sheer mass of data generated by these new technologies, it should be one comfortable with managing enormous amounts of information. Second, it requires a company that performs enough volume to justify significant investment in new technology platforms. It should also be a company within an industry that is highly comfortable with the adoption of new technology. Third, it should be a company with solid in-house scientific expertise – in particular, an organisation that offers a multidisciplinary research environment where synergistic processes are available and encouraged.

Based on these criteria, an obvious candidate leaps to mind. A good choice – though not the only – is the contract research organisation.

This is not, in any way, to minimise the importance of the pharmaceutical companies themselves in the drug discovery and development process. It is simply an acknowledgment that the industry is changing and that those changes indicate a need for a shift in business practices.

The relationship between CROs and the pharmaceutical industry has not always been smooth. However, increasing evidence points to the fact that deeper partnerships may be the ideal approach to the substantial challenges facing the discovery and development of new drugs.

Figure 2
Team-based laboratory procedure

The changing role of the CRO

In the past 20 years, the CRO has become a dramatically different institution. Early CROs were generally limited in geographic scope and scientific expertise. Essentially, they were the equivalent of a corner-store operation, offering specific skills to fulfill a particular niche. Then, as the outsourcing needs of pharmaceutical companies grew, CROs consolidated and their scope, and capabilities expanded. Today, a number of global research organisations exist that are capable of taking a compound from its earliest stages through clinical trials.

But then again, so can most pharma companies. What can a CRO bring to the drug discovery and development process that is so unique?

Let us return to our criteria. First, there is the management of data. Few would dispute the fact that this is a core competency of a CRO, an organisation built around the efficient compilation and distribution of information. The investment in appropriate technology is significant, and the staff is highly trained in data management. In addition, the CRO itself is a more compact organisation. In comparison to a newly-merged pharma company with multiple locations and a vast geographical spread, there are simply fewer places for data to get lost.

Second, there is the issue of investment in new technology itself. Traditionally, pharma companies have not been quick to adopt new technologies. But more importantly, it would be difficult to justify investment in new platforms (which are expensive, require highly specialised personnel, and have a tendency to age quickly), based on the amount of anticipated volume. CROs perform dramatically more volume in early discovery and preclinical research; ideally, their costs should be proportionately lower and their processes inherently more efficient. This is a fundamental business practice: economy of scale.

Finally, there is the nature of the research environment. Intuitively, we understand that, particularly in early development stages, a multidisciplinary approach is the most effective and efficient. The ability to leverage diverse scientific and therapeutic expertise is critical and will only become more important with the advent of new technologies. For

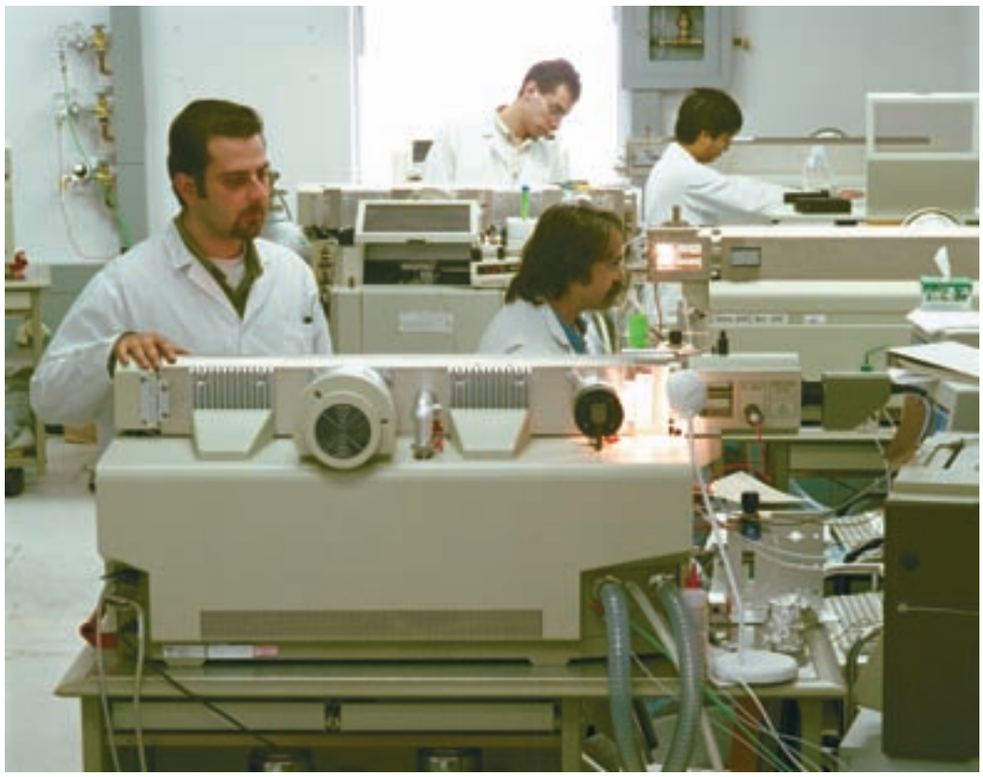

Figure 3
Analytical discovery – quantitative and qualitative approaches

example, in order to develop a high-quality disease model, it may be necessary to merge genomics technology with traditional *in vitro*, *in vivo*, and analytical assays. With a well-staffed, co-operative team, that is possible.

Furthermore, outsourcing to some extent will always exist in the pharma industry. Pharmaceutical companies simply do not have the resources to perform all the necessary research steps in-house – thus, the need for the creation of CROs. And it is difficult to create a synergistic research environment when projects may be distributed between two, three or even more outsourcing firms.

Lastly, the corporate divisions of a pharmaceutical company may not always lend themselves to a team-oriented atmosphere. Competition exists in a way that may not in a CRO. There is a tendency for work to leave a specific division, go upward for review, then return to a different division – one that may be competing with the first for capital funding.

Learning from Detroit

There is no question that pharmaceutical companies are qualified to perform their own discovery and preclinical research. After all, they have been doing exactly that since aspirin was introduced in 1899. However, outsourcing to a fully integrated service provider may be a better business practice.

In some ways, the issue compares to the automotive industry. Traditionally, the core competency has been engineering; a company was defined by the people who built its engines. Today, automotive companies have migrated from that – they outsource. They outsource not because those skills have low value, but because they are not proprietary. Why not outsource to someone who has invested in the latest technology, who is servicing seven other automotive firms, and who consistently pushes the knowledge envelope?

The point is clear. Pharmaceutical companies should move upstream, into the waters where their abilities are unmatched: capital allocation, the selection of therapeutic target areas, strategic implementation of late-stage clinical trials, global commercialisation and marketing. To fully exploit the new technologies in the early research phases, to maximise drug leads, and to minimise costs, perhaps they should find a partner.

But which CRO?

An important point requires clarification: not all CROs can, or even desire to, fulfill this role of research partner. As the CRO industry has

changed, and mergers and acquisitions have created new companies, individual CRO core competencies have diversified. Though the main players are few (the top 15 CROs account for 70% of the market[3]), their strengths are diverse.

Many new technologies primarily impact discovery and preclinical success. Therefore, CROs that focus on late-stage clinical research (Phase II and beyond) would not necessarily be interested in the staffing and technological investments necessary to expand their discovery and preclinical services. A more natural segue might be into information technology. Likewise, for CROs with a weighted investment in contract manufacturing, an attempt to capitalise on the new platforms would be as costly and complex as for the pharma companies themselves.

In addition, any CRO lacking a commitment to superior customer service would be ill-suited for a partnership of this kind. A responsive, proactive, highly organised management group and staff are required to implement a venture this complex and this dependent on trust and co-operation.

However, the CRO that has already made the investment in staff, in relevant proprietary technologies, and in the strategic application of those resources, stands well prepared to provide the pharma companies with an outstanding partner. Today, a fully integrated CRO has the potential to move compounds through discovery and preclinical quickly, and at a lower cost, precisely because they have the capabilities readily available. There is no need to tap multiple sources; the process has been centralised, streamlined, and the benefits are clear.

Here and now

Today, the concept of a pharmaceutical company and a CRO in a collaborative, long-term relationship is still primarily a concept. In practice, it is rare. Most outsourcing remains *a la carte*. However, the industry has changed many times in its short history and is in flux right now. Years ago, outsourcing began essentially as overflow control. Reliance grew until, at this point in time, pharma companies have deliberately eliminated certain in-house research services and are outsourcing them entirely.

Scientific and technological expertise is another key reason to choose an outside service provider. Pharma companies will go to a CRO in order to utilise technologies it cannot access internally. Outsourcing such as this – beyond operational, yet not fully strategic – nevertheless indicates a substantial movement toward a more collaborative relationship with CROs.

The fundamental logic of full strategic outsourcing will not go unrecognised long. Already, at the most successful pharmaceutical companies, the change is under way. Once the new technologies begin to bear fruit, resulting in increases in productivity and decreases in cost, the shift will be inevitable.

More to come

Pharmacogenomics, nanotechnology, In Silico screening – such breakthroughs and new sciences are coming at an astonishing rate. As more technologies are introduced, the issue at hand will continue to grow.

Today, however, the questions remain unanswered: Will the pharmaceutical industry be able to translate the recent breakthroughs into improved productivity? How significant a role will CROs play in that process? Which technology will be key in accelerating the drug discovery and development process?

The answers are coming soon. DDW

Ian Lennox *is President and CEO of MDS Pharma Services (formerly Phoenix International). Prior to joining Phoenix, he was President and CEO of Drug Royalty Corporation Inc and of Monsanto Canada Inc. Mr Lennox holds a Master's Degree in Business Administration from the University of Western Ontario, and attended Columbia Business School's Advanced Management Programme. He is a board member of several publicly-traded companies and has represented industry in government-community associations.*

After graduating from Oxford, ***Dr Nigel Brown*** *spent two years with the Massachusetts Institute of Technology's Division of Toxicology where he carried out analyses of food-borne mutagenic compounds. He then went on to develop bioanalytical methods for the analysis of samples from clinical and preclinical pharmacokinetic and metabolism studies at Upjohn Laboratories before joining SmithKline Beecham as Senior Investigator. There he was responsible for scientific direction and management within the department of drug metabolism and pharmacokinetics. Dr Brown is currently General Manager and Senior Vice-President, Preclinical Drug Development Services, MDS Pharma Services.*

References

1 Sansom, C. Translating a ten-fold increase in drug targets into good leads. Scrip Magazine. July/August 2000:6-7.
2 Engel, S. Pipeline 2000. R&D Directions. January 2000:36-42.
3 Hall, JM, Reynders L. The future role of CROs. DDW. Summer 2000:13-22.
4 Schneider, J. The next wave of molecular medicine. R&D Directions. March 2000:65-70.