NRDOs: theory meets practice

The rise of 'no research, development only' firms has been accompanied by accusations that they are new in name only. But the NRDO that stays faithful to the business model offers a vision of a more efficient clinical development future, believes Dr Michael Bowden

NRDOs are an attractive alternative to investment in small biotechs

Of the many hundreds of biotechnology companies out there, it is estimated that less than 20 have a stand-alone future. Discovery-based small biotechs have, with few exceptions, become synonymous with the consumption of cash rather than the generation of profits. These companies face the full risks inherent in bringing new pharmaceutical products to the market. And, stung by the downside of the genomics-driven bubble leading up to the end of the last millennium, investors have become much more savvy with their investments and more demanding, wanting more profits, and sooner.

As a result, 'no research, development only' (NRDO) companies have become increasingly attractive to investors. These firms offer to de-risk investment by participating in the latter parts of the value chain. NRDOs can bypass the risk and cost of discovering molecules, instead licensing-in later stage compounds, mainly those already in clinical development. They can then concentrate on developing these assets through to the next stages or even to market.

Interest in NRDOs, as an alternative to small biotechs, has led to a boom in the number of this type of company. There were over 30 at the last count, mainly based in the US. In 2002, almost a third of US-based venture capital went into this sector and last year Jazz Pharmaceuticals raised a staggering US$250 million despite having no discernible product assets.

NRDOs are accused of merely putting a new face on the more traditional, speciality pharma model - buying products already approved in other countries or developing older molecules into new indications – or even the large pharma model of licensing-in molecules to bolster product pipelines. So what is new about NRDOs?

If all that happens is that the management of NRDOs aspire to become vertically integrated pharma companies then the answer is at best "probably not a lot". Already some are beginning to look suspiciously like development-based biotechs as they chase products at ever earlier stages. Some see the integration of their in-licensing and development activities as an essential component of a sustainable business. Commentators seem to suggest that NRDOs will evolve into mini-pharma companies doing the same things as ever before. However, the fundamental NRDO business model is very attractive if companies can resist the temptation to vertically integrate and remain tight and efficient value creators at the early clinical development stages.

Offering a sustainable model

The current mantra says there is enormous competition for in-licensed products. This is true when seeking products to license-in at Phase II or Phase III, by which stage the product should have achieved proof-of-concept, have a satisfactory background package of non-clinical studies and a GMP supply of product. All this equals hefty licensing fees, milestone payments and royalties to reward the innovation and investment to date.

But one NRDO model currently being discussed is based on leveraging both a portfolio and capital effect, ie, having sufficient critical mass of products in the company at any one time to give a high probability of at least one being successful (NRDOs are unlikely to buck the statistic that four in five products entering man fail in clinical development), and having sufficient capital to develop those products without constantly looking over the shoulder for the next bit of development cash. This latter point

is key to success. We have seen promising products fail because poor development decisions have been made through lack of money. Cheap development is a worthy aim, but when lack of funding means it becomes company dogma then failure is the most likely outcome.

With sufficient products and money, this type of NRDO will be free to construct the best possible, lean, development strategy and implement it in the most effective way. No longer will a product persist because the company has 'bet the farm' on it – instead an ingrained philosophy centred around, "we only progress those products we fail to kill" will ensure that at every stage of development, rigorous hurdles are set which the product must clear in order to progress. To date there have been very few companies that can remain this dispassionate about their products and can remain sufficiently well funded to concentrate purely on highly-efficient development processes. To be brutally frank, despite the advent of biotechs and virtual development companies, as well as the massive efforts made by medium to large pharma with their internal organisations, there has – with a few notable exceptions – been little discernible benefit to development efficiency.[1] NRDOs can do better, not by producing some magic solution but by doing the basics well in the highly-focussed early development environment.

The NRDO operating structure

Traditionally, there have been two choices – build internally, or outsource to contract research organisations (CROs). It is unlikely that many NRDOs will want to incur the large overhead of a development structure that is globally capable (nowadays, a pre-requisite for accelerated development). Instead, they will remain relatively small and dependent on outsourcing. For example, AlgoRx conducted half a dozen clinical trials in 2004 despite only having 14 people in the company.[2]

But the people employed by a successful NRDO will be unusual. They will combine a great deal of experience, not just in their respective disciplines but in the wider context of drug development. Put simply, they will have a clear understanding, if not at the detailed level of a specialist, of where all the bits of the development jigsaw fit together. The history of pharma companies has been to avoid these 'generalists' – putting promising staff through accelerated management career paths creates an entirely different animal – but they do exist, often in smaller organisations to which they tend to gravitate. Empowerment and accountability will be the company's philosophy; enjoying new challenges and maximally exerting their professionalism to lead success will be the philosophy of the people. A common pitfall to be avoided is the occurrence of the 'silo mentality' that creates internal barriers to change and quick decision-making. In part it is the very existence of this mentality in other pharma business models that will provide the NRDO with its advantage.

Many start-up companies begin as great ideas centred on a small group of founders. Recently-established NRDOs are founded by exceptionally skilled financiers, lawyers and senior management executives. Add to this the individual with a sound senior scientific track record and one cannot but bet on success. But the reality of drug development is different. Failure rates in these companies can be high, as there are insufficient people working at the 'coal face' and grinding out the successes. At the outset a clear operational plan must be designed and implemented, because in a capital shortage the tide goes out for everyone – even the good science suffers – and the whole point of NRDOs is not to waste capital on poorly-performing operations. NRDOs must only invest capital in functions in which they have capability from day one, and not fall into the trap of attempting to develop skills in the hope they will pay off at some point in the future. This means not indulging in speculative activities outside the only key area of focus for an NRDO – finding and developing molecules which are winners.

Scaleability will be achieved by assigning the product to a dedicated product development team (PDT) under the direction of a product leader. As each product's development strategy demands, the PDT will draw on team members from the NRDO's internal experts (eg, project management, statistics, regulatory) and external providers (see Figure 1).

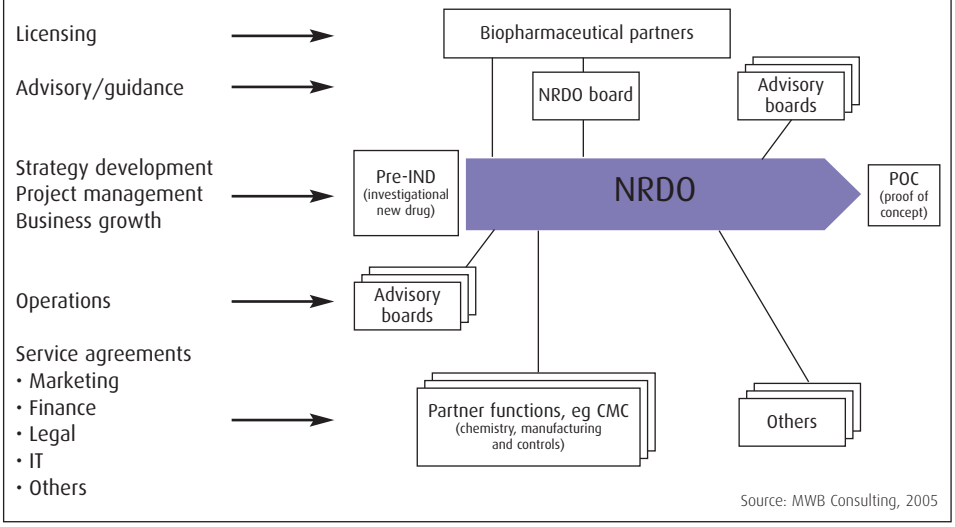
PDTs will be tasked with producing lean development strategies, efficiently executed in the shortest time possible. This level of development efficiency will be critical to the NRDO's commercial success, as shown by the analysis conducted by the Tufts Center for the Study of Drug Development in their 2002 IMPACT report (see box).

However, no matter what internal skills it has the NRDO will be highly dependent on outsourcing. This presents an opportunity to the new generation of CROs.

Dependent on 'thinking' CROs

Assuming the NRDO sets an internal rate of return (IRR) of 25% per annum and a ten-year investment horizon, then it must produce

Figure 1 – NRDO development model



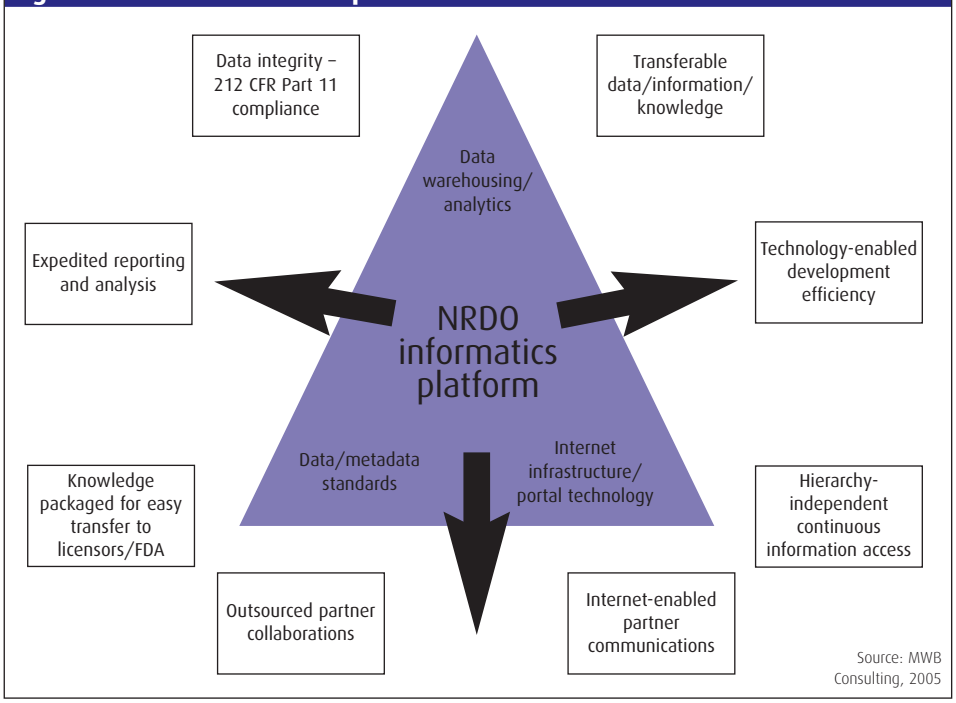
Source: MWB Consulting, 2005

The financial impact of improving R&D efficiency

- Boosting clinical success rates from 1:5 to 1:3 reduces capitalised total cost per approved drug by US$250 million.
- Shifting 5% of clinical failures from Phase III to Phase I reduces out-of-pocket expenses by up to US$20 million.
- A reduction in 'time per clinical phase' of 41% gives a US$200 million reduction in total development costs.

Source: Tufts Center for the Study of Drug Development

Figure 2 – NRDO informatics platform



at least an 8-fold increase in value over that period. Any corporate activity that does not yield a 25% IRR will be highlighted for outsourcing. This means a dependence on strategic outsourcing. NRDOs will require a range of services from the CRO industry including Phase I capabilities, central laboratories, product manufacturing, labelling and distribution, quality assurance, data management, statistics and medical writing, and drug safety management.

However, they will want to buy the best-in-breed in the market. It is probably fair to say that no clear winner has yet emerged as best-in-breed within the CRO market – it is not just about size or number of worldwide staff, but about consistent adherence to timelines and deliverables. Thus, what will change is the relationship between the NRDO and the CRO. The NRDO will require timely execution of high quality clinical trials. CROs will need to participate in a much more sophisticated tendering process to win work.[3] Detailed patient recruitment strategies will be the norm and enrolment delays will not be tolerated without good reason.

The CRO project team will be invited to form an integral part of the NRDO's PDT, fostering product ownership and shared objectives – perhaps even with CRO participation in the upside of the value created by the NRDO. The NRDO will require rapid data turnaround from clinical trials to inform go/no-go decisions; this being incorporated into an informatics platform (see Figure 2). Unlike many biotechs aiming to license-out at proof-of-concept at minimal cost, the NRDO will see the product data package as an important part of its intellectual property asset and will avoid the need for the licensee to repeat earlier studies. The informatics platform will also serve to enhance communications and act as a knowledge base.

CROs in turn will need to provide stable staffing structures and project managers capable of adapting to the inclusive relationship. They should be clear about how to add value in terms of drug development experience, project management skills and, above all, an ability to predict and overcome the inevitable issues that will arise during development programme execution. This latter skill is certainly present in CROs but is relatively under-developed, largely because CROs have been seen as primarily involved in execution of development strategy rather than designing that strategy. The word 'partnership' is often used in this industry, but NRDOs and CROs will be reliant on mutual win-win in their relationships in order for NRDOs to meet their development objectives and for CROs to win the business. The good news is that CROs have been moving in this direction for some time.[4]

Above all, CROs will need to communicate better with the NRDO, not just through project meetings or update reports but with day-to-day communications driven by data. The industry now has electronic systems that can deliver data from a site to the CRO or company the same day as it is collected. This represents a significant opportunity to highlight issues as they occur and to propose resolutions, to track the performance of the product (especially in open-label studies), and to quickly and seamlessly complete one study and move onto the next. Needless to say, experienced people are needed to review and analyse the data received and turn them into information on which decisions can be made, otherwise the technology remains just another expense.

As usual we are talking about the quality, innovation and experience of people that will make the difference – those within the NRDO and those within the CRO. It is quite possible to see the NRDO-CRO relationship driving not just enhanced training but an environment where international drug development experts can be created to the benefit of all – something which is often lacking at present in departmental cubicles, where breadth of experience is easily overlooked.

Done correctly, NRDOs with sufficient products and money, working with 'thinking' CROs, could finally offer something new and exciting in the pharmaceutical world – a means by which promising drug candidates can be quickly cycled through early clinical development and where products doomed to fail can be quickly identified and discarded, allowing new promising products to enter the pipeline.

References

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