editorial

Steven Hutchins

Theodore Torphy

Christophe Muller

Open partnering of integrated drug discovery: continuing evolution of the pharmaceutical model

Discovering and developing new drugs is a high risk, high cost and, only occasionally, high reward enterprise. Industry data suggest that for every 10,000 new molecular entities prepared, only one will make it to market and the process from concept to market often takes in excess of ten years. Moreover, very few marketed drugs ever recoup the significant R&D investment required to bring them to patients, which today by conservative estimates can exceed $800 million [1].

These issues, coupled to a general decline in R&D productivity (as measured by the number of NDAs granted per year versus industry expenditures) [2] and the loss of exclusivity on high revenue marketed products explain the distress currently felt within the pharmaceutical industry. The consequences are all too apparent – mega-mergers, consolidation and significant reductions in R&D headcount.

Despite this, global R&D budgets remain largely unaffected and the proportion of global R&D expenditure dedicated to outsourcing has continued to increase over the past few years, particularly in the exploratory phase of drug discovery, which however remains relatively low when compared to pre-clinical and clinical outsourcing. This latter point highlights a growing trend of pharmaceutical and biotech organisations to use external research solutions earlier in the drug discovery process. The relationship between the sponsor and the external provider is also evolving as the focus moves from functional to integrated collaborations. To understand these trends further, drug discovery outsourcing will now be discussed in further details.

Evolution of discovery outsourcing

The pharmaceutical industry began to embrace outsourcing in the early to mid 1990s, initially outsourcing straightforward synthetic chemistry to CROs in the US and Western Europe, to support internal medicinal and combinatorial chemistry efforts. As success was shown, the industry began to implement external teams of full time equivalents (FTEs) and the term medicinal chemistry support was invented. These were teams of external chemists assigned to an internal medicinal chemistry team to augment their internal resource. These external chemists were used for various activities including scale-up, hit explosion libraries or were working on back-up series of compounds. The key here is that all of the compound designs were coming from the client. Initially, all of this chemistry work was placed with CROs in the United States and Europe, as this was where the client base was comfortable and where the CROs had facilities. As clients were able to show success with functional synthetic chemistry outsourcing, they began to

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expand sourced activities to include functions like ADME profiling, counterscreening, PK profiling and some aspects of biology, including protein production and purification to name just a few. These US and European based CROs developed a breadth of services that covered the drug discovery process although at this time, there was no real appetite from the market for an 'integrated' drug discovery solution.

Around 2000, as we saw the peak of functional synthetic chemistry outsourcing in the West, CROs began setting up shop in India and China with a focus on synthetic chemistry services as this was their strength; they provided the lowest barrier of entry for a CRO and there was a large talent pool of trained synthetic organic chemists in these regions. The synthetic chemistry CRO base in the United States and Europe quickly eroded as costs in the East were much more competitive and in synthetic chemistry, differentiation based on expertise and track record of success cannot be easily monetised. As this began to happen, many Western CROs transitioned their business model from a pure services base to a blended model taking on their own innovative research.

The solution to the innovation gap?

There are several options that the pharmaceutical industry has adopted to help address the innovation gap. They include:

1. Breaking up their internal R&D groups into smaller units to help reproduce the biotech entrepreneurial atmosphere [3].
2. Mergers and acquisitions between themselves and with smaller companies.
3. In-licensing of clinical stage compounds.
4. Strategic alliances including R&D and marketing alliances between themselves and with smaller biotech partners.

The licensing of late stage clinical candidates quickly dried up as every company was looking to bring in late stage compounds to augment their own pipelines and to have near term impact on their financials. The dearth of late stage assets has led to them becoming highly sought-after candidates and the deal terms have risen dramatically. As a result of this there was the move towards more strategic alliances initially with biotech companies that allowed the biotech and pharmaceutical partner to work closely to advance early stage assets. This allowed the pharmaceutical company to help shape the outcome of the asset. These strategic alliances have now shifted to include CROs that have the capability to deliver pre-clinical candidate compounds into the pharmaceutical company's development pipeline.

The formation of strategic alliances within the drug discovery process is heralded as one way to address the aforementioned productivity and innovation challenges faced by the pharmaceutical industry today. The benefits of strategic alliances within the drug discovery process are many-fold. First, there is the obvious benefit of providing a more flexible business model by eliminating fixed costs and accessing expertise and different approaches to a scientific problem that might not otherwise be available internally. In addition, there is the opportunity to outsource complete programmes thus balancing the risk associated with the sponsor's pipeline.

In pursuing such alliances many external partners are using the term 'integrated drug discovery' to describe the research solutions they provide. What does this mean or rather, what *should* this mean?

At the very least all of the *crucial* disciplines and technologies required to advance a drug discovery programme need to reside with the partner and be freely available. This involves the successful integration of disciplines such as high throughput screening, medicinal chemistry, *in vitro* and *in vivo* pharmacology, structural biology, and ADMET/PK. driven by the experience, proven track record and disease area expertise of industry-seasoned drug hunters. It is crucial that the partner has experience of all phases of the discovery and early development process as this provides the insight needed to place each piece of the puzzle into context. In addition to this technical expertise the partner's scientists must have a thorough awareness of the importance of intellectual property in their work. This includes the ability to establish and evolve patent strategy as well as a sound knowledge of the level of information required to patent a novel compound or methodology.

It is not necessary that *everything* is available at the partner. Indeed, a more pragmatic and more cost-effective approach is to seek one-off, specialist services and technologies through extended networks. The ideal partner will bring a host of existing, tried-and-tested academic and commercial relationships and will manage these as part of the alliance. In addition, a partner should bring a different approach and perspective as well as access to enabling technologies.

However, *truly* integrated drug discovery is much more than the coming together of technical experts and the use of a partner's external capacities. For an alliance to succeed and prosper the partners need to work together to leverage respective strengths – providing opportunities for gains in productivity, efficiency and speed above and beyond traditional outsourcing. This fundamentally requires the fostering of an environment which places a high value on close and open communication and project teams which are aligned around the same strategic goal – to bring innovative, efficacious and cost-effective treatments to patients.

Because of this close relationship, the longer term associated with an alliance and the opportunity to typically work on multiple targets, integrated drug discovery alliances have been structured in many different ways. In the next section, a look at the current trend in deal structure will be discussed

Integrated deal structures

The outsourcing of functional or single discipline services like synthetic organic chemistry or ADME profiling lends itself to a traditional fee for service business model with a narrow vendor base to allow for the most competitive pricing structure. As the industry shifts from functional outsourcing to innovative and integrated drug discovery projects [4], we believe that the traditional business model needs to be re-evaluated. The same CRO base is involved in both functional and integrated projects; however, different business models are required. Indeed, the reason integrated projects are being partnered is to gain access to different points of view on how to tackle these programmes and the client is looking for companies who can bring innovation to the collaboration and not just capacity as is the case with functional outsourcing. This will mean additional collaborations for the client to manage, but as the CRO moves further down the innovative path, this will also mean that they will require less oversight as they become more independent.

In general, as work has shifted from the West to the East, the CRO base has not been as mature and clients have invested a lot of time and effort in training the CROs on how to perform the projects their way. This type of functional work is prescriptive and amenable to this *modus operandi* as the training is relatively straightforward. As the complexity of the work increases within the functional areas and the projects move further down the innovative and integrated path, this model begins to break down as the timelines required to train increase and nothing replaces a decade's worth of experience. Now that we are moving towards more innovation required to successfully execute on complex integrated drug discovery projects we are beginning to see a shift from East to West. This is mainly driven by the fact that pharmaceutical scientific knowledge is being redistributed as pharmaceutical companies are downsizing and a highly experienced talent pool is becoming employed by CROs. Most of these scientists are joining CROs in the West as they are located close to where the pharmaceutical companies are. That being said, there are a few cases where this talent is 'returning' to the East.

Increasingly, deals are structured to mirror this approach where research funding is provided to meet the running costs of the alliance partner (CRO) and success is rewarded in the form of milestones. While the fully funded FTE model is still being utilised, this new model provides additional incentive to the alliance partner to drive the project to a successful end point, which is typically a pre-clinical candidate.

The pharmaceutical industry will continue to evolve its business model and the CRO industry will match this direction. The business models are beginning to evolve from the traditional functional based sourcing to the more risk-sharing model. The pools of CROs that are utilised for functional versus integrated sourcing will more and more diverge with a larger pool of partners being called upon for the innovative, integrated drug discovery projects.

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Steven Hutchins*
Evotec, 114 Milton Park, Abingdon, Oxfordshire OX14 4SA, United Kingdom

Theodore Torphy
Johnson & Johnson Pharmaceutical R&D, Welsh and McKean Roads, Spring House, PA 19477, United States

Christophe Muller
Evotec, 114 Milton Park, Abingdon, Oxfordshire OX14 4SA, United Kingdom

**Corresponding author:*
e-mail: Steven.hutchins@evotec.com