Value to the Fore

Flexible CRO Solutions Aim to Improve Pipeline Success

WHITE PAPER

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Trends indicate a return to value, as Contract Research Organizations (CROs) continue to grow their skill sets and ally with the global R&D industry to tap flexible solutions aimed at improving pipeline success. **Bruce Molino**, Ph.D., Senior Director of Medicinal Chemistry, and **Christopher Conway**, Senior Director of Business Development, AMRI, analyze the increasing demand for R&D outsourcing and examine how CROs are evolving to better meet industry needs.

R&D outsourcing is widely used by pharmaceutical, biotechnology, agricultural and related industries to augment research and development and achieve objectives in a more cost effective manner. The pharmaceutical industry spends far more money on R&D outsourcing than other industries, and as a result pharmaceutical R&D budgets are an important barometer for R&D outsourcing for the broader industry looking forward. The forecast for pharmaceutical R&D spending through 2016 is estimated at about 2.5% increase per annum with a total spend in 2011 estimated around $133 billion.[4] Prior to 2008, pharmaceutical R&D budgets increased slightly more than 10% per annum. A key reason for the slower growth forecast in R&D spending is attributed to the loss of revenue from blockbuster drugs that are losing patent protection.

R&D outsourcing is rapidly growing as pharmaceutical companies look to the expertise of CROs to improve productivity, increase speed and flexibility, minimize risks, and to gain access to technology and facilities. Global drug discovery outsourcing experienced a compound annual growth rate (CAGR) of 15% per annum from 2005 through 2010 with a total market size of $7.2 billion dollars in 2010. The global drug discovery outsourcing market, which includes total revenue for four service areas – chemistry, biology, high throughput screening (HTS), and lead optimization, is anticipated to continue to grow at compound annual growth rate of 15% per annum through 2015 to reach a market size exceeding $16 billion dollars by 2015.[1]

This paper analyzes some of the reasons for the increasing demand for R&D outsourcing and examines trends in the type of work being outsourced and how CROs are changing to better meet the industry needs. Moving forward, it will be imperative for CROs to make higher value contributions in collaborative drug discovery programs with Pharma.

The crux of the matter

Fiscal, regulatory, and productivity challenges are among the key issues being faced by the pharmaceutical industry. An ongoing patent cliff is anticipated to erode $78 billion in worldwide sales from branded drugs that are facing patent expirations through 2014. About half of this erosion was expected to occur as a result of losses of patents in 2011 for major blockbuster drugs. Pfizer Inc.'s Lipitor, the most prominent drug to lose U.S. patent protection in 2011, was responsible for $11 billion in revenues in 2009. Many pharmaceutical companies will struggle to replace such revenue with new products.[5]

To deal with revenue shortfalls, pharmaceutical companies continue to look for ways to reduce operational costs, which has resulted in facility closures and staff reductions, and consequently, a decrease in Pharma's internal R&D capacity. More and more of the R&D functions – once performed exclusively within Pharma laboratories – are now being outsourced. Many pharmaceutical companies are using R&D outsourcing to create variable capacity and to improve efficiencies in R&D cycle times, by reducing the time from drug target validation to pre-clinical drug candidates (PDCs), and ultimately clinical proof of concept (POC).

Regulatory challenges are well-documented. Attrition rates for clinical development candidates in late stages of human clinical trials remain unsustainably high despite an industry-wide effort to reduce attrition. Phase II success rates for new development projects have fallen from 28% (2006-2007) to 18% (2008-2009) and the current likelihood of a drug successfully progressing through Phase III to launch is 50%.[3] In another recent report on pharmaceutical industry R&D productivity, success rates for Phase I, II, III clinical trials and submission to launch were reported to be 54%, 34%, 70% and 91% respectively.[6] Based on these success rates, it was estimated that more than eight clinical candidates must enter Phase I to ultimately launch one NME. Applying success rates for earlier stages of drug discovery, i.e. target-to-hit (80%), hit-to-lead (75%), lead optimization (85%) and preclinical development (69%) means that more than 24 screening programs must be run to yield the eight clinical candidates that lead to one launched drug.[6] These statistics point to an urgent need for improving efficiencies in pharmaceutical R&D in order to replace the lost revenue for the blockbusters coming off patent.

Formative face-lift

The challenges faced by the pharmaceutical industry translate into opportunities for R&D outsourcing companies. Some of these opportunities include formation of partnerships and alliances, as well as the implementation of new business models. These collaborations and flexible platforms share one common goal, developing the next generation of new drugs.

Some pharmaceutical companies are increasingly turning to academic laboratories to tap into early drug target research and innovation. The academic environment provides a fertile environment for exploration of high risk, novel drug targets, which are often the outcome of basic R&D initiatives. Pharmaceutical companies desperately crave new approaches and targets but such basic research is outside of a typical large pharma's R&D mission. In addition to academic research initiatives, non-profit organizations that have typically funded academic research have adopted a more venture-based approach as they are now funding drug discovery and full development in some cases. The Cystic Fibrosis Foundation, which has already helped achieve landmark success, and the CHDI Foundation are two prominent examples of an approach being pursued by many others.

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In addition to all of these changes, the National Institutes of Health (NIH) has also begun to carve out a portion of funding to support translational efforts in a move to spur more applied benefits from the basic research it has traditionally funded. Most academic and other groups involved in basic research lack adequate resources and expertise to progress discoveries to proof of concept stage, which is typically where a program becomes attractive to a pharmaceutical licensing team. Contracting with various CROs by the NIH has created a network of highly skilled and experienced drug discovery and development professionals, available to provide the resources and know-how necessary to take promising early stage results to a stage where Pharma may be willing to license and develop.

Elemental expertise

The outsourcing marketplace, cognizant of the changing landscape within the pharmaceutical industry, has expanded the range of discovery and development services that are offered. Select CROs have built strong capabilities in *in vitro* biology, ADME, pharmacology, and drug safety to complement more traditional discovery and development chemistry offerings. A few, select CROs now provide integrated drug discovery capabilities as well and these can span the range of simply providing support in the multiple areas to encompassing decision making and providing strategic contributions to a program's progress. At the high end, these CROs possess the know-how, project management and decision making skills to collaborate effectively to progress programs to rightful decision points, which could mean success or failure of an approach. The opportunity to partner virtually all elements of R&D through a coordinated and global network has the potential to improve R&D productivity and efficiency, and the accountability required of an outsourcing partner is motivation to put forth best efforts to deliver.[6]

Outsourcing of lead optimization has experienced rapid market growth. An average annual growth of 19% has occurred from 2005 through 2011 and the forecast suggests this trend will continue to increase at this rate over the next five years.[2] As previously described, this outsourced work could encompass simply following direction, with decisions being made by the Sponsor, to a more collaborative arrangement in which testing results are generated or shared with the outsourcing provider, and decisions made on merit regardless of who has the idea. While pharmaceutical companies traditionally preferred to keep lead optimization as an internal core competency, budget constraints and layoffs have trimmed the internal bandwidth to keep this entirely in house. Since this function is critical in regards to intellectual property (IP) positioning, companies rightfully remain cautious with whom and where they will outsource this stage of discovery.

Effective communication and coordination within the lead optimization team is critical for assigning resources, meeting tight timelines, and addressing rapidly changing priorities. Pharmaceutical R&D organizations have long realized the value of internally involving knowledgeable process R&D chemists early in the drug discovery process. These organizations often begin to work and plan with the medicinal chemists to prepare for the scale up of non-GMP test compounds and intermediates in the lead optimization stage. Often adjustments to a synthetic route can pay dividends much later in a program. Quality CROs with strong chemical development and scale-up capabilities can offer this same practice. Integrating discovery, development, and scale up with a quality CRO has the potential to offer more efficient chemistry that could save time and money in the short term, while substantially increasing the overall long-term value of the project.

Planning and open communication is necessary to stay on top of the critical development path, which will vary for each candidate compound. Early involvement of the chemical development team allows time to identify possible bottlenecks and to implement substantive improvements in the synthetic route that otherwise could keep compound scale-up and supply on the critical development path and a rate limiting step for program advancement.

Making the global grade

During the past decade, the drug industry has experienced a steady decline in innovative small molecule NMEs reaching the marketplace. A number of factors are likely at cause. However, during this same period, pharmaceutical R&D outsourcing strategies were employed by many companies whereby globalization was used to drive down labor costs – as measured on an FTE basis. This led to outsourcing a vast amount of R&D in low cost environments like China and India where projects were often awarded to the lowest bid. While it would be an oversimplification to attribute a cause and effect relationship between a decrease in number of NMEs with low cost outsourcing, it certainly is not a ringing endorsement for investing exclusively in the "cheapest FTE model". In addition, many companies now understand that the true cost associated with the "lowest cost FTE" model is far greater because of the indirect costs of managing the work as well as a number of risks. Perceived cost savings are quickly offset by cost of managing the relationship with dedicated project management teams and the inability of low cost outsourcing companies to achieve performance levels required to deliver high value results. At the end of the day "lowest cost FTEs" gain the industry nothing if they have not filled the R&D pipeline with drug candidate compounds.

In recognition that R&D has not been delivering new drugs at an appropriate pace, various companies are exploring new strategies to conduct research. In many cases, new business models are being considered. For others, more emphasis is being placed on achieving value defined by the number of pre-clinical candidates resulting from such investments rather than decisions being made based solely on a "low cost FTE model." Achieving this successfully, however, requires matching the appropriate skill sets to the difficulty and level of expertise required for a particular program or target. As a result, many companies are therefore beginning to, or considering to, return to the West for truly collaborative outsourcing.

A better return on investment should result as companies restore the balance between value and cost. The most important factors that should drive decision-making in CRO selection are performance (results), trust, communication and cost. Past performance is usually a good indicator of future results. CROs who have demonstrated experience in discovering and developing drugs are best positioned to repeat this success for their customers. Experienced project managers, familiar with discovery and development processes and pitfalls to avoid, possess the decision making and communication skills required to interface between organizations and help maximize the chances for success. The customer must also have trust that the CRO they have selected has high ethical standards and takes appropriate steps to protect the intellectual property that may be developed. All of this must be delivered at a price that is competitive and provides the CRO the wherewithal to continue to invest in its business.

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These are difficult and uncertain times for anyone touched by the pharmaceutical industry. Many in the industry are placing more emphasis on selling their products in emerging markets, at the same time cutting back operations substantially in the mature markets of North America and Western Europe as a recognition of tighter margins to be made in these new markets. Although many believe that the era of the blockbuster drug is coming to a conclusion, new medicines that meet substantial and unmet need will still command good margins. Innovative drug discovery is key to maintaining growth. Established markets possess some of the most innovative minds in the world and the pace of discovery of new targets and an improved understanding of disease biology continues to be led in the West. The impetus of drug discovery conducted in academia and other novel business models may be precisely the infusion of innovation that the industry needs. Unique partnerships and business models have the potential to help reconnect academia, private research institutions, and pharmaceutical companies with the investment community. CROs are uniquely positioned to play an important role in translating this innovation into the novel drugs that the industry desperately needs.

Moving forward, it will be imperative for CROs to make higher value contributions in collaborative drug discovery programs. The climate is changing and the pharmaceutical and outsourcing industries will continue to evolve from past lessons learned. Successful CROs will continue to embrace the changing industry dynamics and position themselves to meet the challenges and adapt to new opportunities to achieve sustained growth, domestically and internationally. As the face of R&D outsourcing continues to change, the outsourcing companies that can deliver value will prosper.

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