Pharmaceutical industry R&D partnering strategies

With a sustained rate of more than 250 R&D partnering deals each year many valuable lessons are being learned. Although there is no exact 'formula for success' there are many 'success factors' that can be utilised to reduce the risk of failure.

By Riccardo Pigliucci

Research & Development is the engine that drives growth in many industries, but none more so than the pharmaceutical industry. This is an industry characterised by enormous R&D expenses, long and high-risk product development time-lines, high margins on successful products, and product lifecycles highly defined by patent expirations. It is estimated that research-based pharmaceutical companies spent more than $26 billion on R&D in the year 2000[1]. This industry is now spending in the order of 20% of revenues on R&D whereas the average R&D-to-sales ratio for US industries is less than 4%[2]. According to PhRMA in its Annual Survey, 2000: "Based on corporate tax data compiled by Standard & Poor's Compustat, pharmaceutical manufacturers invest a higher percentage of sales in R&D than virtually any other industry, including high-tech industries such as electronics, aerospace, computers and automobiles."[3]

Simply stated, R&D partnering strategies have become more important to the pharmaceutical industry than other industries because R&D is more important to them. Consider a successful new pharmaceutical product with a market potential of $1 billion per year; every day lost in the R&D pipeline represents $4 million in lost revenue and as much as $1 million in lost profit. Even at their current levels, R&D expenditures pale in comparison to the lost opportunity costs of delaying a new product for even a brief period.

It is difficult to know exactly how much is actually spent in this industry for total R&D and even more difficult to know exactly how those expenses are allocated. By some estimates, two-thirds of R&D spending goes to pharmaceutical development and the remaining third to discovery research which includes activities such as target identification and validation, synthesis and purification of experimental compounds, development of assays to test these compounds against targets, and the actual testing (screening) of the compounds[4]. With $8-10 billion in annual expenses/revenues at stake, the pharmaceutical industry and potential research collaborators have been prolific and creative in their partnering activity.

In this report, we will attempt to examine the following areas with regards to R&D partnering in the pharmaceutical industry:

The discovery 'relationships' landscape
Trends in R&D partnering
Key partnering success factors

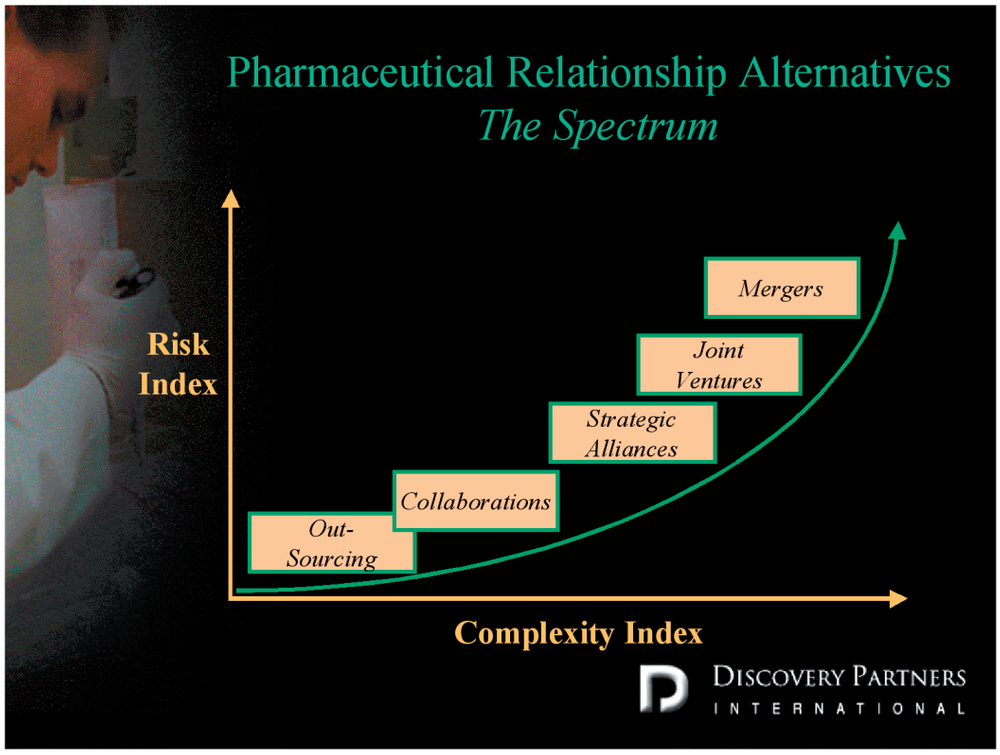
The discovery 'relationships' landscape

The spectrum of R&D partnering alternatives is very broad ranging from the simplest outsourcing contract to collaborations to strategic alliances to joint ventures to outright mergers and acquisitions (**Figure 1**).

Each of these relationships has associated with it its own elements of risk, potential reward and complexity. Let's examine some of the drivers and dynamics of each of these partnering alternatives.

Out-sourcing. This is by far the simplest of the relationship alternatives. The risk is generally limited to the scope of a specific contract. Timeframes and deliverables are typically specified up-front or if they are not, the scope of the project will often be defined by the number and duration of full time equivalents (FTEs) assigned to the project. These outsourced services are generally on a fee-for-service basis with no 'reach through' provisions to

Figure 1



intellectual property (IP) that results from the outsourced project. The business driver for outsourcing is usually cost control or the desire to shift fixed expenses to variable expenses by avoiding the development or expansion of a specific type of internal R&D infrastructure.

Collaborations. This term is widely used to describe external R&D relationships and therefore is the most difficult to characterise. The term as used here describes an R&D relationship in which the provider has a higher degree of proprietary content in their offering than a typical outsourcing provider. Collaborations are higher on the complexity scale because they often contain IP sharing or reach through provisions and the specific deliverables may or may not be well defined. However, they tend to be low on the risk scale since they generally have pre-defined costs and timeframes. The business driver for collaborations is usually either cost reduction or minimal risk access to some innovation.

Strategic alliances. There is certainly a very grey and fuzzy line between what most people refer to as collaborations and strategic alliances. Unlike outsourcing or collaborations, however, strategic alliances are rarely, if ever, driven by cost reduction; they are virtually always driven by the desire to access innovation. They are more complex since they are often non-exclusive or exclusive with field of use restrictions, and multiple parties may be accessing highly related IP. Strategic alliances are also higher on the risk scale since significant upfront commitments of capital and/or equity are usually required. The perceived value of the IP is what provides the support for the increased complexity and risk.

Joint ventures. Joint ventures are a seldom-used form of R&D relationship. Depending on their nature and structure they can be high on the risk and complexity scales both on initiation and on termination. Most joint ventures are driven by a desire for market expansion where one partner possesses technical or scientific expertise and the other partner possesses the market expertise and/or the required capital. Although there are exceptions, joint ventures are inherently unstable relationships that typically end in divorce or acquisition of the joint venture by one of the partners.

Mergers. Traditional big pharma mergers have provided mass, market share and new product pipeline to the merging entities. R&D strength, pipeline aside, is rarely the motivation for this type of merger activity. Merger activity between big pharma organisations and start-up companies with

emerging discovery technology has become quite common. Big pharma has repeatedly demonstrated its willingness to pay a premium for early, proprietary access to new discovery technologies. We have shown this type of relationship as the highest on both the risk and complexity indices. They are high risk in that virtually all of the costs are upfront and significant human capital is usually involved. Because of their magnitude, these deals are usually complex to construct and then involve the complex merging of a typically small entrepreneurial group into a large corporate environment (**Figure 2**).

With a sustained rate of more than 250 R&D partnering deals announced each year, we are sure to continue to see new examples of each of these types of relationships. The specific areas of R&D partnering, however, will continue to evolve as they have over the past few years as new discovery technologies evolve.

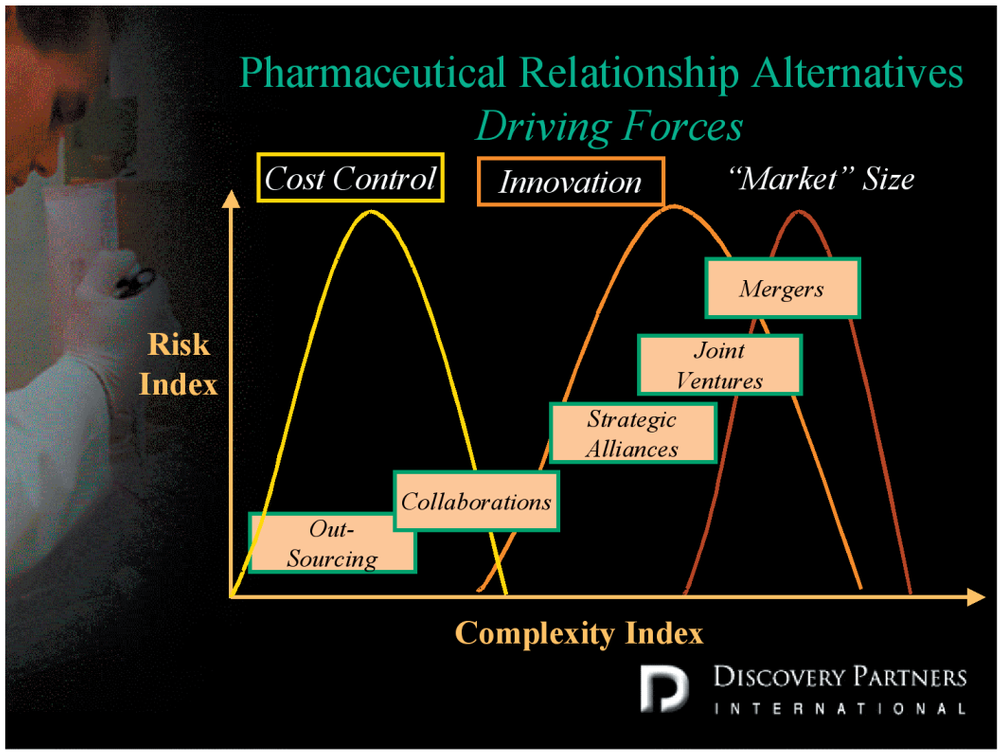
Trends in R&D partnering

As expected R&D partnering trends follow the trends in discovery technology innovation and development. The roll-out of technology advancements relevant to the modern drug discovery process has included the following:

High Throughput Screening (HTS). High throughput screening was among the first and most fundamental elements of the modern drug discovery process and dramatic advancements in HTS technology preceded most other modern drug discovery technology advancements. By the early 1990s highly automated robotic systems were the norm in many HTS laboratories. Later in the decade, second and third-generation HTS automation systems were being introduced. Systems such as the AURORA Ultra High Throughput Screening Platform were adopted by Merck, Bristol-Myers Squibb, Pfizer and Eli Lilly. Other systems, such as the Zymark Alegro System, were adopted by J&J, Boehringer Ingelheim and Rhone-Poulenc Rorer (now Aventis). Many other customised and internally developed HTS systems are also now being utilised in many HTS laboratories around the world.

Combinatorial chemistry. The dramatically increased HTS capacity within the pharmaceutical industry fuelled a demand for more compounds to screen. Virtually every pharmaceutical organisation developed a combinatorial chemistry strategy and infrastructure to meet this increased demand for compounds. Some organisations sought solutions

Figure 2



to their combinatorial chemistry needs via the mergers and acquisitions route. For example, Glaxo and Lilly acquired Affymax and Sphinx, respectively. Other companies made major technology acquisitions such as Boehringer-Ingelheim's acquisition of the Ontogen combinatorial chemistry platform. Other organisations such as Bristol-Myers Squibb, Aventis, Bayer, SmithKline, Roche, Schering-Plough and others acquired the IRORI 'directed sorting' platform. Regardless of the internal infrastructure for combinatorial chemistry, most pharmaceutical companies also developed relationships with chemistry providers to gain access to additional compounds. These relationships include major strategic alliances such as the Pfizer deal with Arqule that included both compound supply and technology transfer, major compound supply and lead optimisation collaborations such as that between Pharmacopeia and Schering-Plough, and consortium models such as those from Axys Advanced Technologies and SIDDCO (both now Discovery Partners International) and many pharmaceutical industry partners. It is inevitable that as the pharmaceutical industry acquires large numbers of new targets from their genomics collaborations and develops high throughput screening assays for these targets, the demand for additional novel new chemical entities will continue to increase.

Genomics. HTS is a drug discovery engine fuelled by targets and compounds. Combinatorial chemistry and other high output medicinal chemistry methodologies have rapidly increased the number of compounds available for screening, but more, new, meaningful targets have been slower to emerge. Genomics is rapidly addressing this limitation of targets and is expected to yield on the order of 5,000-10,000 new targets. In the last three years, no drug discovery area has been more prolific than genomics in terms of deal making. Virtually every pharmaceutical organisation has developed in-house proprietary genomics programmes and then augmented these programmes with an extensive network of collaborations and licences. These relationships range from the gene database subscriptions provided by Incyte and Celera to the strategic alliances between the likes of Bayer and Aventis with Millennium. In the latter cases, Millennium virtually becomes a factory producing validated targets for its partners – a factory that would have cost far more and taken far longer to develop in-house.

Proteomics. Proteomics, the study of the proteome or proteins expressed from the genome, has become the evolutionary extension of genomics. Since proteins direct virtually all biological

functions and proteins are the expression products of the genes, understanding the connection between the genome and the proteome and the functions of those proteins is critical to understanding the role of these proteins in disease pathways and their potential values as drug targets. The comprehensive study of proteins has many facets including protein isolation, purification, analysis, crystallisation and structure determination and expression profiling. Each of these areas brings with it significant technological challenges that are still being addressed today. As a result, the partnering activities in the proteomics field are highly varied and still rapidly emerging. Delivering on the genomics promise of finding and validating new drug targets will require immense proteomics efforts to establish the linkages between gene sequence, protein structure and protein function. Look for genomics collaborations and alliances to evolve into proteomics-based partnerships.

SNPs. The study of Single Nucleotide Polymorphisms (SNPs), also a consequence of genome mapping, will allow pharmaceutical discovery organisations to more effectively interpret and potentially design clinical trials. Eventually new therapeutics that result from or are associated with particular SNPs will be developed. In the early stages, consortium-partnering models have been implemented for the distribution of SNP information and new SNP measuring technologies are being rapidly developed.

ADME/Tox. It has long been recognised that most drug candidates that fail in the clinic fail for ADME (absorption, distribution, metabolism and excretion) and toxicology reasons rather than for lack of efficacy. Developing better *in silico* predictive toxicology models and better *in vitro* toxicology screens is a top priority for most discovery organisations. Similarly, there is a need for more effective and higher throughput methods for the early assessment of ADME properties. This area is predicted to be fertile ground for future partnering activity.

The pace of outsourcing and partnering in pharmaceutical discovery organisations has grown significantly during the past decade with an estimated 20% of R&D budgets dedicated to external alliances in 2000 compared to less than 4% as recently as 1994. Given the increasing requirements for more productivity from pharmaceutical R&D assets and the expanding number and complexity of specialised technologies involved in the process, this trend is likely to continue.

References

1 Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey, 2000, page 113.
2 Ibid, page 20.
3 Ibid.
4 Ibid, page 26.

Key partnering success factors

With hundreds of discovery partnerships of all forms being entered into each year, many valuable lessons are being learned. Although there is no exact 'formula for success', there are many 'success factors' that can be utilised to reduce the risks of failure. Outlined below are success factors for consideration when entering into discovery partnerships:

Establish expectations. As discussed earlier, discovery partnerships span the range from relatively low risk outsourcing contracts to high risk strategic alliances that often include fundamentally new scientific exploration or the development of new discovery technology. It is critically important for both partners to be fully aware of and agree upon the potential risks associated with their discovery partnership. Is a specific work product expected or does the application of FTEs to the project constitute fulfilment of obligation? Do both partners recognise the partnership as developmental in nature or does one of the partners believe the core technology has already been developed and their partnership only involves the application of that technology to a specific discovery programme? Establishing mutually acceptable expectations is the most fundamental success criteria and much of this expectation setting should be resolved long before definitive agreements are drafted by legal staff.

Define the work product. Defining the work product, project scope and acceptance and remuneration criteria are specific expectations too important not to be specifically addressed. Defining the scope of the partnership upfront allows scope changes, if required, to be more easily identified and agreed to. If the partnership has milestones and milestone payments associated with it, the acceptance criteria that trigger the milestones should be clearly specified. Clear definition of the work product and scope greatly eases the burden of partnership governance and administration.

Control and management of the alliance. The governance of a discovery partnership can range from trivial to extremely burdensome depending largely on how well the expectations have been set and the actual performance of the partners. A well designed partnership diligently executed often requires no governance beyond the direct interaction of the scientific staff. However, even the most diligently crafted and executed partnership may require management intervention for conflict resolution or it may simply fail to deliver the expected results. In these cases, it must be clear how the partnership is to be controlled and managed. Specifying how control will be exercised is often a primary role of the definitive agreement.

Ownership of and rights to the intellectual property. Another important role of the definitive agreement is the specification of ownership and rights to intellectual property. Although this may be a difficult negotiation, it is so fundamental to any discovery partnership that it is usually highly specified from the very beginning.

Expansion of scope and extension. Another success-related issue concerns the expansion or extension of the partnership. Though these issues can be negotiated during or at the end of the partnership, a better means to deal with these issues is to address them to the extent possible in the original partnership agreement.

Termination with and without cause. Most partnerships are exactly that – partnerships, not marriages. They are expected to have an initiation, a duration and a termination. The expectations concerning how and under what conditions and terms the partnership can be terminated are actually very important to its success. Termination provisions should take into account how the partnership will terminate in certain foreseeable (with cause) circumstances as well as how the partnership will terminate in certain unforeseeable (possibly with or without cause) circumstances. An important element of the termination provisions is a clear definition of post termination conditions.

None of these factors will ensure success. Success requires excellent execution on a fundamentally good idea with a healthy dose of luck. After all, these are discovery research programmes and small failures and setbacks are a normal course of events on the road to success. Addressing these factors upfront in the design of a partnering relationship will ensure that both party's expectations are understood regardless of the specific outcome of the partnered programme and to help ensure that everyone involved will live to partner again. DDW

Prior to joining Discovery Partners as Chairman, President and CEO, ***Riccardo Pigliucci*** *has served as Chief Executive Officer for Life Sciences International PLC. Before that he held numerous management positions during his career at Perkin-Elmer Corporation, including President and Chief Operating Officer. Mr Pigliucci is also a director of Epoch Biosciences Inc, Biosphere Medical and Dionex Corporation and a trustee of The Worcester Foundation for Biomedical Research.*