The extended pharmaceutical enterprise

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The availability of widespread contractual services led to the birth of the virtual company in the 1990s. As the concept has matured, and the biotechnology sector diversified, interchange of intellectual property in the form of collaborative and license arrangements opens up still further the opportunities for outsourced forms of pharmaceutical R&D.

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▼ The idea of the virtual company was born in the last decade of the last century, when communication technology and management theory compounded to focus business strategy on core competence and outsourcing of non-core activities. Virtual companies have existed in a range of business sectors, including clothing manufacture (e.g. Nike and Benetton) and computer hardware manufacture (e.g. Dell). Ten years on, as it applies in the pharmaceutical sector, it is time for a performance check, and to ask what (if anything) of the original premise has changed?

The virtual company

The virtual pharmaceutical company is one that concentrates on project management of the disciplines responsible for whatever section of R&D it chooses to operate within, and outsources the activities necessary to achieve the project advancement it seeks. The management and direction of the project(s) are retained in-house, and the operations are conducted externally by a network of suppliers, with whom the virtual company has strong contractual relationships.

As mentioned previously, the concept is not unique to pharmaceuticals. Nike, for instance, legally does only marketing and R&D. It manages its suppliers as part of a corporation, putting its own personnel in production sites, visiting plants regularly, running co-development teams and sharing information extensively. Its strength relies substantially on the tight relationships it has with its suppliers.

However, there are two problems with this concept. First, the word 'virtual' is difficult insofar as it combines a place in business strategy theory with concepts associated with virtual reality and computer technology and, in respect of pharmaceutical discovery, with *in silico* techniques of compound database mining for hit molecules. Second, and more profound, dividing the pharmaceutical world into 'real' and 'virtual' over-simplifies the actuality. Outsourcing in pharmaceutical R&D involves more than just contractual relationships in a supply chain. In particular, it involves the trading of intellectual property, and this can be done through collaborations and licensing. Almost all companies are involved in external relationships of one or more of these kinds, and it is instructive to look at the patterns of interaction between companies in the large pharmaceutical, biotechnology and service sectors, interactions that signify the conception of the Extended Enterprise (EE).

In the recent PanEuropean Mediscience Review, Deloitte&Touche (http://www.deloitte.co.uk) forecast a greater role for the EE in the biotechnology sector [1,2]. The accepted definition of an EE is a 'dynamic, networked organization'. The phrase has both a broader meaning and applies to a wider range of businesses than 'virtual'. Companies with their own internal focus might couple that with external elements to accomplish certain goals. The methods used to establish and manage these relationships are the same, regardless of size and strategy.

Whereas virtual pharmaceutical companies typically work with contractual relationships to providers of specific technology or services, the scope of relationships that are possible in pharmaceutical EEs encompasses three forms: contracts, collaborations and licenses. As will

1359-6446/03/$ – see front matter PII: S1359-6446(03)02634-5

Table 1. Advantages and disadvantages of external contracts and collaborations

Advantages	Disadvantages
Reduction in fixed costs (traded against increased variable costs)	Loss of control, difficulties of management
Better allocation of resources in a project with variable demand	Greater difficulty of co-ordination and management of external collaborations/contracts [18]
Access to specific technology, expertise or skills either: not present internally or cheaper than internal alternative or quicker than internal alternative	Increase in variable costs, traded against reduced fixed costs
Flexibility in disengagement from unsuccessful research; greater objectivity in making that decision	Differing cultures of contract research organizations and academic partners (or other external party)
Better management of risk	Time taken to agree contracts Difficulties in agreeing ownership/split of intellectual property rights Instability in case external party becomes financially insolvent, merges or is acquired

become clear, all three forms are used by both large pharmaceutical companies and biotechnology companies in their operations and, increasingly, the service provider sector involves licenses to technology in addition to contractual relationships. A good example of this is in controlled release formulation technology.

Advantages and disadvantages of outsourcing

Much has already been written on this subject, and it is not the intention here to repeat the detailed points (see Ref. [3] for details). The main advantages and disadvantages are shown in Table 1.

Relative to other business sectors, pharma has some features that particularly suit it to an outsourced approach. One is the multiplicity of scientific disciplines and skills necessary to advance a project through R&D; not all are likely to be present inside one organization. Another is the fact that specialized providers exist in offering expertise in all required skills for project advancement to be accomplished. Third, the product from a pharmaceutical development is essentially knowledge, either in terms of intellectual property in the narrow sense of a patent, or in the broader sense of an information package for regulatory submission. In an era of electronic communication, the mobility of such packages across international boundaries makes pharmaceutical outsourcing a global enterprise.

There are other features of the industry that mitigate against outsourcing, notably the complexity of the development process, which makes project management a difficult task in the absence of adequate competence in a wide range of disciplines (nevertheless, other complicated projects, such as large-scale building projects, are conducted through a framework of outsourcing). Second, for historical reasons, the pharmaceutical industry has been late in adopting EE forms of operation. It is a relatively new industry, heavily regulated and most ethical pharmaceuticals are protected from free market competition by patent coverage. As long as large companies intended to keep corporate secrecy at or near their top priority, the incentive to outsource has until recently not been strong enough.

Trends

The three modes of link employed in pharmaceutical EEs, namely collaboration, contracts and licensing, are typically found at different stages of discovery, development and marketing, and between different players in the overall process. Figure 1 represents some of the forms of interaction between the main components of the pharmaceutical R&D supply chain. For simplicity, the role of large pharma has been represented in development and marketing, whereas in reality, such companies also have large investments in pharmaceutical discovery, and indeed the primary purpose of collaborations with platform biotechnology companies are to support these efforts.

Discovery: a collaborative approach to increased efficiency

During the early 1990s, the first generation of new technology in genomics, combinatorial chemistry and HTS broached a step change in the way in which pharmaceutical discovery was conducted. Unlike the past, where individual compounds were crafted by the chemist and carefully

tested by the pharmacologist, drug discovery would become a mass-production industry and thus lose its cottage industry past. Right or wrong – and this is not the topic for debate here – the development of this new technology outside the main companies provoked a rush to collaborate with new, small, high-tech start-up companies, and changed the attitudes towards outsourcing of pharmaceutical discovery.

An analysis of pharmaceutical collaborations and alliances (which involve one of the top 20 pharmaceutical companies), and categorization by phase of alliance, has been published for the period 1988–1998, (see Table 2; [4]). These data, which concerned both therapeutic products and technology, are soon to be updated for the later period to 2002 at the Recombinant Capital website (http://www.recap.com). The phase of alliance relates to the stage of development of the technology or compound at the point of entering into the alliance. As a function of new alliances, therapeutics-oriented deals grew from 56% of 1988–1990 alliances to 74% of 1997–1998 alliances. This analysis demonstrates that in the period 1997–1998, 72% of alliances related to projects in discovery or lead stages, 17% in preclinical development, Phase I or Phase II, and 9% in Phase III, NDA filing or approved.

These figures do not differentiate between collaborations and licenses but it can be assumed, given the preponderance of early stage alliances, that a significant proportion are collaborations. The drop-off in deals from discovery into development does not indicate attrition: as shown previously, the phase is referenced to the beginning of the alliance.

Today, despite having neared an innovative plateau with regard to the original technologies, companies from both the multinational and biotechnology sectors are open to collaborating with specialists to provide specific technology for their product development.

Large company collaborations in this area are well known. An example of a small biotechnology company involved with a formulation specialist is provided by Ionix Pharmaceuticals (http://www.ionixpharma.com), a specialist pain-therapeutics company. The company has extensive

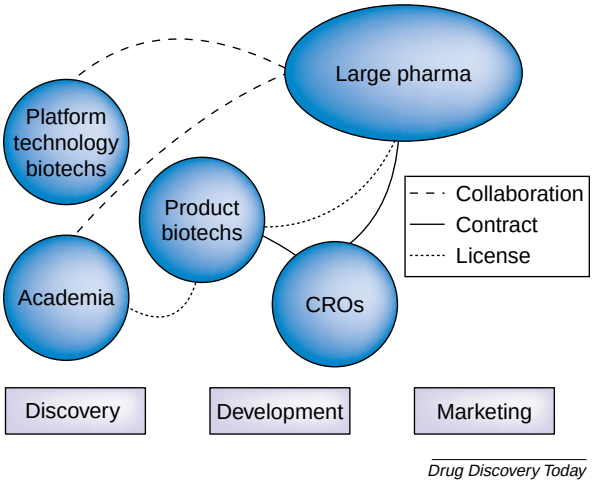

Figure 1. Examples of contractual, collaborative and licensing arrangements between different components of the pharmaceutical R&D supply chain. Abbreviation: CRO, contract research organizations.

discovery relationships with a variety of chemical and formulation companies, including EvotecOAI AG (http://www.evotecoai.com) and Tripos (http://www.tripos.com) for medicinal chemistry, West Pharmaceuticals Services (http://www.westpharma.com) for intranasal formulation, and Xenome (http://www.xenome.com) for peptide chemistry. Ionix is developing the compound IP01 as a novel combination of unspecified familiar analgesics, for the potential treatment of acute and chronic pain, using intranasal formulation technology provided by West Pharmaceutical Services; this is Ionix' most advanced project, currently in Phase I trials.

Collaborative relationships of this kind are appropriate for the discovery phase because management of external discovery is more difficult than development. Sufficient expertise and project direction needs to be left with the external collaborator to enable them to deal with problems and failures, to see their way around problems and apply their particular expertise in the most appropriate way. As they are earlier in the R&D process, collaborations are

Table 2. Number of alliances by stage involving a top 20 pharmaceutical company over the period 1988–1998

Period	Discovery, Lead	Preclinical, Phase I, Phase II	Phase III, NDA filed, approved
1988–1990	62	18	5
1991–1993	100	35	18
1994–1996	151	55	30
1997–1998	162	38	26

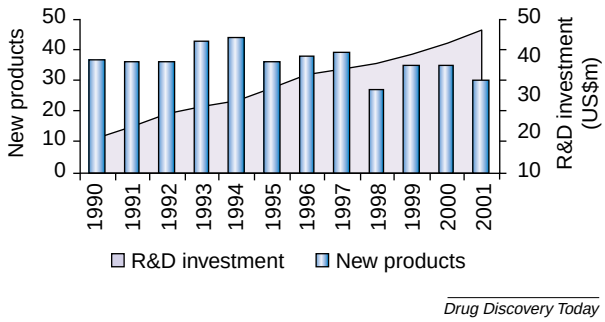

Figure 2. New product introductions have not matched R&D spending increases over the past decade.

inherently more risky than later stage development projects, and a component of the monetary exchange is often success-related. This might take the form of milestones and low rates of sales-based royalties as the project develops.

In some recent cases, drug discovery collaborations do not involve milestone or royalty components. For instance, in December 2001, Pfizer (http://www.pfizer.com) signed a collaborative deal with Arqule (http://www.arqule.com) involving contractual payments of US$117.5 million over 4–5 years and additionally an equity purchase arrangement. ArQule would provide expanded lead generation capabilities using its automated solution phase chemistry and would transfer, on a non-exclusive basis, its proprietary library design and informatics platform. ArQule and Pfizer would work together to improve this platform to enhance the process of lead generation for early drug discovery. ArQule might also collaborate with Pfizer on lead optimization during the alliance.

The trend towards discovery collaborations becoming more contractual in nature indicates increased competition among discovery technology providers and their offerings being considered increasingly generic in quality. This trend was foreseen as early as 1997, but has only recently become a major impediment to the growth of platform technology companies in the biotechnology sector [5].

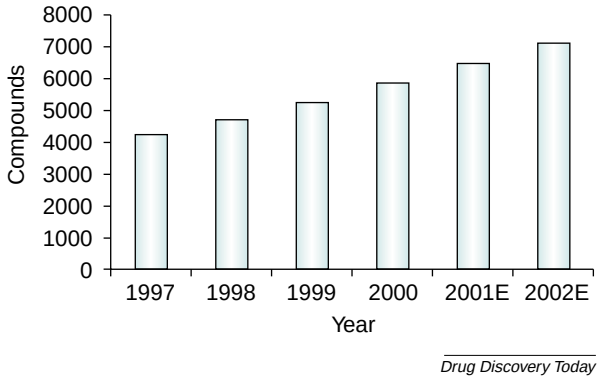

Figure 3. Estimated products in the drug development pipeline worldwide (see Ref. [19]). E = estimate.

Product development: a contractual outsourcing approach to reduced development times and lower infrastructure investment

Among the set of problems facing the industry today, the most prominent is the failure to create sufficient new and improved products. Over the past few years, large companies have been able to deliver 10% year-on-year increases in sales, and 15% per annum growth in earnings. Currently, the largest companies – such as Pfizer-Pharmacia – have annual sales of US$50 billion; this means that in the next year the increase in sales required to fit this historic performance will be roughly the equivalent of that of Amgen (http://www.amgen.com); the year after, the equivalent of Schering Plough (http://www.schering-plough.com). In ten years time, a continuation of the trend will results in a company with annual sales of US$125 billion.

In reality, the gathering storm is signified by the dearth of new drug approvals. The corollary of sales growth is R&D productivity, and a company the size of Pfizer is looking for the equivalent of 6–10 NCEs per year with peak sales of US$1 billion per compound. Despite growth in R&D spending of around 15% year-on-year for the past decade, there has been a flat – or slightly declining – trend in new drugs over the same period (Fig. 2).

Since 1998, industry pundits have called for paradigm shifts in R&D practice to address this product gap [6]. New technology, such as the advent of genomics, combinatorial chemistry and HTS, was seen as one way of tackling the problem. In the event, the hoped-for improvements in outcomes have not been achieved despite the heavy investments. It is true that the number of active compounds in clinical development worldwide has increased from 1455 to over 2042 in the period 1995–2001, but these increases have yet to filter through into NDAs (Fig. 3) [7].

Taken holistically, the outsourced approach does offer improved efficiency across the industry, as well as substantial improvements in time to achieve certain goals. Protodigm, as a subsidiary of Roche (http://www.roche.com) and through comparisons with its parent, was the first to document a 38% advantage in the time taken to advance a cancer project through Phase I/II trials, relative to the internal alternative. In 2000, the company separated from its parent and changed its name; FulcrumPharma (http://www.fulcrumpharma.com) now

operates as a contractual resource to provide customized development programmes that lead to early proof-of-concept studies for client pharmaceutical companies. It does so using a bespoke network of contract research organizations assembled on a project-by-project basis. Similar comparisons conducted by Barnett International Benchmarking Group and reported on the internet [8] have established reductions on 31–41% during Phase II and Phase III trials and an overall time saving of at least two years on conventional drug development times, using the outsourced alternative (Fig. 4) (see also Box 1).

In the biotechnology sector, the R&D gap offers the 'carrot' of an enhanced appetite among major companies for licensing products at or after proof-of-concept human studies, and has driven a strategic change in direction towards product focussing, achieved by the heavy use of outsourced development capabilities. For technology platform companies, the carrot has been accompanied by a stick.

In the past 12 months, a radical change in the environment for funding has occurred in the biotechnology sector, with technology platform companies finding themselves much less attractive as investment targets. Opportunities for collaboration with large companies have also declined because much of the first generation new technology has already been integrated into large companies, and second generation technology needs to be impressive and unique compared with other offerings.

Many biotechnology platform companies are changing their business model to incorporate a product pipeline, despite being established with a technology focus, rather than with a multidisciplinary project development capability. To become credible in their product development activities, without incurring substantial fixed investment costs, this strategic change requires a substantially outsourced approach. The pressure is particularly acute in Germany [9], but in other countries too, companies are aggressively in-licensing early stage products to bolster their product pipelines, and shifting resource away from internal research to EE development.

For Exelixis (http://www.exelixis.com), the strategic decision three years ago to shift from a genomics platform to a product company was validated by the recent 'landmark' deal with GlaxoSmithKline (GSK; http://www.gsk.com) involving payments of up to US$570 million for future provision of several small molecule Phase II compounds in the fields of vascular biology, inflammatory disease and oncology [10].

Other examples of companies employing a hybrid approach, namely pursuing both technology platforms and products, include Cambridge Antibody Technology

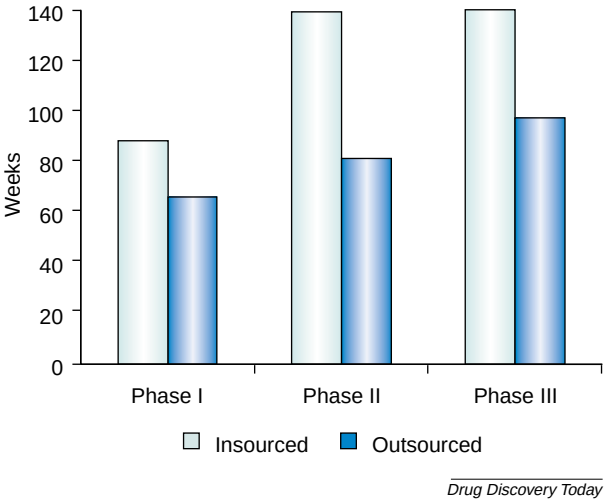

Figure 4. Reductions in pharmaceutical development cycle times using internal and outsourced resources (see Ref. [8]).

(http://www.cambridgeantibody.com), Oxford Glycosciences (http://www.ogs.com) and, more recently, Genset (http://www.genset.fr). MorphoSys (http://www.morphosys.de) recently announced a redundancy programme to reduce its burn rate and shift resources to its product development programme [11]. In October 2002, Ribotargets (http://www.ribotargets.com) looked outside its internal R&D and licensed a neurosteroid (alphadolone) for the treatment of pain, with particular emphasis on the treatment of pain in cancer patients, as the company's most advanced compound, in preclinical development [12].

These changes are not always successful: Lion Biosciences (http://www.lionbioscience.com), one of the star performers form the German sector, has recently had to curtail its brief foray into product development. In an effort to reduce annual costs of Eur20 million, it has focussed on its core bioinformatics and software business, at the same time conceding that revenues will fall by ~25% for 2002. Although Lion is not likely to become profitable until 2004 at the earliest, the company represents one of several technology platform companies who are looking to a future of pure contract service provision in an increasingly price-sensitive market, rather than the value-added collaborative model upon which they were founded [9].

Product pipelines: licensing approach to increased market commercialization

Large pharmaceutical companies spend about twice as much on marketing as on R&D. The reason for this is the increased competition for market share, with similar products

Box 1. Contract research organization sector: new models of working

Most of the increases in outsourcing in pharmaceutical development employ the services of contract research organizations (CROs). For instance, the 60–70% increase in active development compounds referred to previously has been resourced mostly through the use of CROs. Outsourcing today, industry wide, is estimated at 30–35% and growing. In some disciplines, such as toxicology, it has been estimated as 50% and this could represent a broad average across all areas with time. The market for outsourced pharmaceutical development by CROs in 2001 has been estimated at US$6.4 billion, growing at 15% per annum.

Alongside these increases, some quite interesting and profound strategic changes are occurring in the way large pharmaceutical companies and CROs interact. These are best appreciated by selected case histories, as follows:

Aventis–Quintiles

In January 1999, Hoechst Marion Roussel, now Aventis Pharmaceuticals' (http://www.aventis.com) Kansas City drug development facility, was operating below capacity: there were not enough projects assigned to the facility to keep it functioning at efficient levels. The company sought a solution that would increase efficiency, continue ongoing projects and keep the services of the site's experienced development employees.

The solution was a new kind of business model for working relationships between CROs and their customers. Quintiles (http://www.quintiles.com) bought Aventis' Kansas City centre for US$93 million, and ~500 if its development personnel became Quintiles employees. Quintiles became a strategic partner for Aventis' drug development and signed a 5-year US$436 million revenue contract, with potential as a preferred provider for additional contracts. It is the largest outsourcing agreement ever signed in the pharmaceutical industry.

Aventis still has access to capability and expertise at the Kansas City site, but at significantly reduced infrastructure costs; development projects continued without interruption. Quintiles gained significant capacity and an experienced workforce. By December 1999, Quintiles was conducting development projects for over 40 different customers covering a range of services from preclinical research through regulatory approval. Quintiles plans to build more alliances based on this business model.

Quintiles is also one of the few CROs to offer product development and/or commercialization services to customers, as well as the funding of such services, in return for royalties or commissions based on the sales of the customer's product. Quintiles is also developing a portfolio of proprietary products to market through its contract marketing arm, Innovex.

PPD Genupro

PPD GenuPro (http://www.ppdvirtual.com) was founded in 1998 out of collaboration between the CRO Pharmaceutical Product Development (PPD; http://www.ppdi.com) and Eli Lilly & Company (http://www.lilly.com) to develop genitourinary compounds. PPD GenuPro funds and manages development of the Lilly compounds through Phase II proof-of-concept clinical trials, after which Lilly retained first option to license the compounds. If declined, PPD GenuPro retained the rights to develop and relicense the compounds to other pharmaceutical companies.

Dapoxetine, one of the genitourinary compounds in development, completed Phase II proof-of-concept trials in less than a year. Dapoxetine is a selective serotonin reuptake inhibitor thought to have promise as a possible treatment for premature ejaculation. The compound demonstrated clinically and statistically significant prolongation of ejaculatory latency compared to placebo in a double-blind, placebo-controlled trial. The results provide proof-of-concept clinical data for a condition affecting up to 30% of men and for which there is no approved medical therapy. Lilly declined to take up the license, but the offer was taken up by Alza, who committed to manufacturing, clinical, regulatory, sales and marketing costs, and returned to PPD Genupro an upfront payment, milestones and royalties on sales.

This case history serves as an example of a CRO committing risk finance to a stage in pharmaceutical development; successfully advancing the compound as intended; and then successfully licensing the product on to another company.

PPD–Apothogen

In October 2001, PPD entered into an agreement with various venture capitalists to set up a technology aggregator company called Apothogen (http://www.apothogen.com). In return for investment, PPD became a preferred provider to Apothogen, the purpose of which was to acquire, develop and commercialize pharmaceutical products.

In the wake of the Enron accounting scandal, in which more than US$1 billion in debt was hidden behind complicated partnerships, the cross-pollination between Apothogen and PPD has raised red flags among analysts. In April 2002, Apothogen was acquired by IntraBiotics, a biopharmaceutical company engaged in the development of novel antibiotics and became a subsidiary of that organization.

Although the Apothogen case was not tested to fruition, the strategy after its acquisition remains to develop compounds using a virtual form of operation.

eroding market exclusivity and making price a major factor in product choice. Such companies are seeing their strengths in later stages of product development and in global marketing, with increasing proportions of products deriving from external collaborations and in-licensing. Jurgen Drews, commenting in 2002 about the past 15 years of the pharmaceutical industry, pointed out that: 'Virtually all the new discoveries and inventions, which are about to reshape drug discovery, came from the outside, from academia and from science-driven small companies.' [13]

To redress the product deficit, particularly as it grows more acute, large companies are focussing on later stage products with substantial sales potential. In October 2001,

Novartis (http://www.novartis.com) set up a 10-strong team of in-licensing scouts to identify early-stage opportunities from biotech companies [14]. In April 2002, GSK was reported to be in a spate of alliances, with an in-licence to a Phase III μ-opioid antagonist for post-operative ileus and opioid-induced constipation from Adolor, in return for an up-front payment of US$50 million, milestones of US$220 million, and a co-promotion deal. In addition, the company was reported to have completed an in-licence to a discovery-stage oral parathyroid hormone analogue for osteoporosis from Unigene, for up-front and milestone payments of up to US$150 million and undisclosed royalties [15].

One measure of the increased competition among the major companies for attractive in-licensing opportunities (in addition to the huge licensing payments exemplified previously) is the way in which they are promoting themselves to smaller companies. For companies not in the largest tier, this is likely to include factors other than marketing capability. Roche, for instance, is emphasizing its ability to do deals more quickly than other companies – 4.5 months as opposed to the industry average of 9–10 months. Such factors can have a substantial impact on development time, period of marketing exclusivity and extent of competition when the product is introduced.

In their use of licensing as a tool to compensate for internal R&D failures, large companies are seeking to build value through applying their marketing muscle in collaboration with others' discoveries. Again, in sum, this is a positive outcome for the global industry. Through the use of licensing, good products are maximally commercialized and not left insufficiently promoted by a small or medium-sized company; again, this is an EE form of operation.

Total outsourcing

To some, the breadth of the possibilities for outsourced pharmaceutical R&D presents in itself a problem. Theoretically, the whole process, from target identification through to new molecule optimization and then development can be conducted by contractual or collaborative relationships. One could argue that this has been done when a late stage compound is licensed from an inventor to a marketing partner. Two recent examples of that are Elan's take-up of frovatriptan from Vernalis (then Vanguard Medica) and Purdue Pharma's license to levobupivacaine from Chiroscience (later Celltech).

In the case of frovatriptan, the compound originated from SmithKline Beecham (SKB) through an arrangement in which Vanguard as the licensee was paid for achievement of various clinical milestones and the licensor retained an option to license back at Phase II. In fact, SKB did not exercise that option and Vanguard needed to invest further before a successful alternative partner was found in Elan. The commercial risks of licenses are a subject outside the remit of this paper, and despite the problems that this history identifies for the small company, there are opposite risks for the large company seeking a significant addition to its portfolio of marketed products.

To my knowledge, fully outsourced R&D based on a contractual rather than license arrangement has not (yet) successfully resulted in a marketed compound. However, a successful case of totally outsourced discovery from the identification of a lead molecule and continuation successfully through to Phase II trials has been reported from Napp Pharmaceuticals (http://www.napp.co.uk) [16]. This is not a widely replicated model and the difficulties should not be underestimated. As indicated previously, one of the main problems in conducting such an effort with multiple partners is the management of diverse contracts in different scientific disciplines in a research setting. In research, changes in direction and iterative methods of working are essential, and this is difficult to manage via contractual relationships.

Conclusion

A summary of the place of contracts, collaborations and licensing in the pharmaceutical value chain is outlined in Table 3. Although contracts do not involve transfers of intellectual property, collaborations and licenses allow more efficient opportunities for trading in intellectual property in a global marketplace. These modes of interaction permit association of the companies and institutions that are most capable of inventing new products and technology with those that are most capable of commercializing and mass marketing. Complementarily, contractual relationships enable better risk management, as well as more efficient resource allocation.

There is an important trend towards increased availability of contractual providers of drug discovery services and technology, in addition to those historically available for development. These providers come from a background of collaborative forms of operation, and need to adapt to a more price-sensitive commoditized marketplace. As a result, it is theoretically possible to use contractual arrangements for the complete process, from target identification to compound discovery and development; in practice the management of diverse discipline in research is a significant operational challenge, whose difficulties should not be underestimated.

In 1999, an architectural analogy for modern pharmaceutical R&D was drawn in which the advent of construction techniques like the box-girder framework was seen as

Table 3. Summary differentiating characteristics of contracts, collaboration and licensing

	Contracts	Collaborations	Licenses
Requirement	Access to resources not available or not sufficient internally	Access to technology for improved research productivity	Access to products (or occasionally technology) for enhancing development pipeline
Payments	Based on work done	Based on time allocated plus related milestones and low royalties	Based on value of product development, plus success related milestones and royalties
Optimum stage of establishment	Development, and to a lesser but increasing extent, discovery	Discovery	Development
Reliance on external technology	Low	Medium	High
Aim	Completion of defined piece of (developmental) work	Integration of external technology into intramural discovery	Commercialisation of external technology/product

the basis for lightweight and more efficient high rise buildings [17]. Under the analogy, the vertical components of different technologies were linked by horizontal cross beams of communication, co-ordination and project management.

Today, there are more options than merely steel for the modern skyscraper. In pharmaceuticals, there are more options than merely contractual relationships between different components of the R&D supply chain.

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