



Outsourcing lead optimization: constant change is here to stay

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Since last reviewed in 2004, the market for outsourcing lead optimization has continued to grow and to change. Here, I review some of the key events that have taken place in this time, particularly merger and acquisition activity, and also seek to delineate some of the emerging trends. Of special note are the rise of low-cost companies providing contract services in Eastern Europe and Asia, and the varying responses to this trend by established companies in Western Europe and the USA. Overall, the marketplace remains highly competitive and dynamic and, as such, is a challenging and exciting place in which to conduct business.

Introduction

In mid-2004, together with Chris Newton [1], I published an article describing the 'quiet revolution' that was taking place in the market for outsourcing lead optimization. Since then, the landscape has changed substantially: key events have taken place and new trends have begun to emerge. The market remains strong, however, as indicated by the continued outsourcing activity of pharmaceutical and large biotechnology companies in the past two years (Table 1). Kalorama Information (<http://www.kaloramainformation.com/>) estimates that the contract drug discovery market will continue to grow from US\$4.7 billion in 2006 to US\$7.165 billion in 2009 (Figure 1) and an increasing share will be taken by lead-optimization services [2].

Although the market might be strong, it is anything but static: several companies offering lead-optimization services have been repositioning themselves within the market in response to new challenges and opportunities. Thus, it seems timely to produce an updated survey of the arena for outsourced lead optimization. In this review, I examine some of the events that have influenced the market and some of the trends that have become evident since the last overview.

Definitions

The two terms 'outsourcing' and 'offshoring' have entered common parlance in recent years and so, at the start of this review, it is useful to distinguish between them [3]:

- in outsourcing, a company uses another firm as a contractor;
- in offshoring, a company runs its own facility abroad.

Thus, outsourcing does not necessarily refer to work done in another country, but offshoring does.

Key events

Since the last review, some market-shaping events have taken place. In particular, there has been significant merger and acquisition activity and the termination of a key contract with a major pharmaceutical company.

Mergers, spin-offs and acquisitions

Much merger and acquisition activity has taken place since mid-2004 (Table 2). In May 2004, Pharmacoepia completed the spin-out of its drug discovery services business (which has retained the Pharmacoepia name) and renamed the software solutions part of the company as Accelrys. Another spin-off took place later the same year in the UK in which KuDOS Pharmaceuticals announced that it would spin-out ChemOvation, which it had previously acquired in 2001. More recently, SCYNEXIS sold its European subsidiary to its management, leading to the creation of Selcia, which specializes in custom radiolabelling and analytical technologies.

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TABLE 1

Examples of outsourcing deals involving pharmaceutical and large biotechnology companies

Company	Outsourcing partner	Date of deal announcement	Nature of deal	Refs
Alcon	AMRI	7 Jan 2005	Use of AMRI's natural product collections, high-throughput screening and custom chemical synthesis services	[47]
Genentech	Argenta Discovery	15 Dec 2005	Computer-aided drug design, medicinal chemistry, biology and absorption, distribution, metabolism, excretion–pharmacokinetics (ADME–PK) to discover new chemical entities	[48]
Ono Pharmaceutical	Array Biopharma	3 Nov 2005	Creation of small-molecule drug candidates against a series of kinases	[49]
Biovitrum	Asinex	22 Nov 2004	Finding and optimizing leads suitable for advancing into preclinical development for multiple targets proposed in the field of metabolic diseases	[18]
Novo Nordisk	Aurigene	10 Feb 2006	Optimization of lead series and discovery of novel leads	[16]
Amgen	Biofocus (Galapagos)	7 Dec 2005	Biology, computational and/or medicinal chemistry services and supply of biologically directed library compounds for ion channel lead-discovery programs	[50]
Schering	ChemDiv	1 Sep 2005	Services for chemistry development, synthesis of hit and lead series and scale up production of advanced intermediates	[51]
Merck	ChemBridge Corporation	7 Dec 2004	Support of multiple research intensive discovery chemistry projects	[52]
Mitsubishi	DPI	25 Oct 2005	Access to comprehensive drug-like compound collection and expertise in assay development, high-throughput screening and computational chemistry	[53]
Boehringer Ingelheim	Evotec	17 Jan 2006	Joint identification and development of preclinical development candidates suitable for future selection as drug candidates for clinical testing	[54]
Wyeth	GVK Biosciences	13 Jan 2006	Establishment of a dedicated discovery chemistry research site to engage 150 synthetic chemists working exclusively for Wyeth	[14]
Eli Lilly	Jubilant Organosys	14 Jan 2006	Five-year agreement to provide a range of collaborative drug discovery services	[15]
Organon	Pharmacopeia	30 Aug 2005	Extension of collaboration to produce advanced preclinical lead compounds meeting stringent criteria for potency, physicochemical properties, <i>in vivo</i> pharmacokinetics and efficacy in relevant animal models	[55]
Teijin	SCYNEXIS	13 Oct 2005	Provision of comprehensive medicinal and analytical chemistry services	[56]
Servier	Tripos	30 Aug 2005	Application of proprietary technologies and chemistry to identify additional novel chemistries against a specified target	[57]

Two significant mergers have taken place. First, Argenta Discovery and Etiologics merged in October 2004, bringing together the drug discovery services of the former and the expertise in respiratory disease of the latter. The result of the merger is a company with expanded service capabilities and an internal therapeutics focus on chronic obstructive pulmonary disease (COPD),

severe asthma and cystic fibrosis. Second, a different kind of merger (a so-called 'reverse merger' [4]) took place in April 2006 when Discovery Partners International (DPI) announced that it was merging with Infinity Pharmaceuticals to create an oncology-focused drug discovery company. As a result of this merger, DPI sought to transfer ownership of its drug discovery services units in

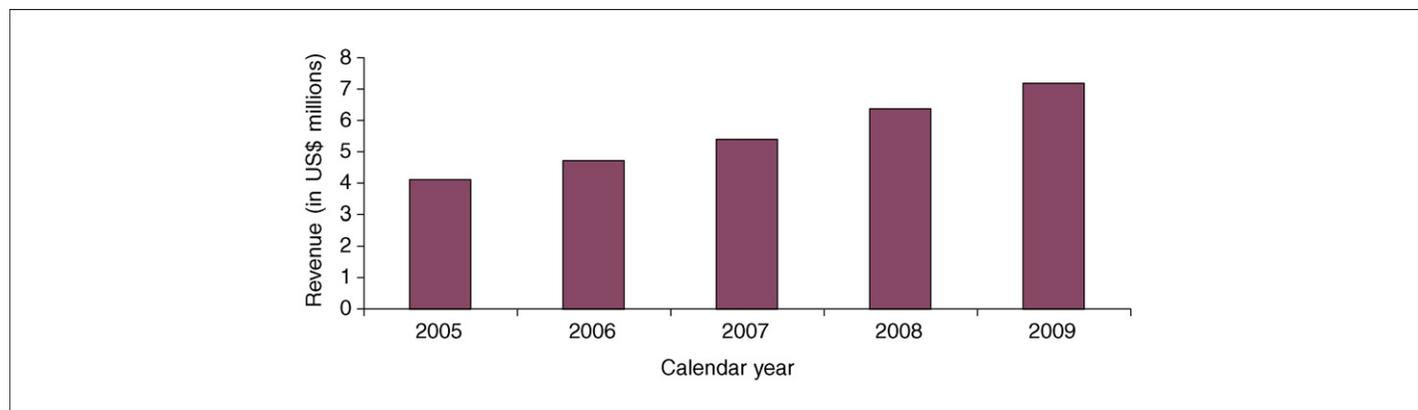


FIGURE 1

Projected growth of the drug discovery outsourcing market. Data are from Ref. [2].

TABLE 2

Merger, spin-off and acquisition activity among providers of lead-optimization services

Companies involved	Nature of event	Date	Refs
Pharmacopeia	Spin-off of drug discovery services business (Pharmacopeia), software solutions business renamed as Accelrys	3 May 2004	[58]
Argenta Discovery and Etiologics	Merger to create expanded Argenta Discovery	4 Oct 2004	[59]
KuDOS	Spin-off of chemistry services business (ChemOvation) acquired in 2001	23 Nov 2004	[60]
DPI and Biofrontera Discovery	Acquisition of Biofrontera Discovery by DPI	1 Mar 2005	[61]
Biofocus and Galapagos	Acquisition of Biofocus by Galapagos	17 Oct 2005	[62]
SCYNEXIS	Spin-off of SCYNEXIS Europe to form Selcia	5 Jan 2006	[63]
AMRI and Comgenex	Acquisition of Comgenex by AMRI	1 Mar 2006	[35]
DPI and Infinity Pharmaceuticals	Merger to create a new public entity focused on cancer drug discovery and development	12 Apr 2006	[9]
Galapagos and DPI	Acquisition by Galapagos of DPI's drug discovery services business	13 Jun 2006	[25]

San Diego, USA, Basel, Switzerland and Heidelberg, Germany, to an organization or organizations that would assume DPI's existing fee-for-service commitments. In June 2006, it was announced that Galapagos was acquiring this part of DPI's business. Thus, DPI has effectively exited the outsourcing marketplace.

In addition to spin-offs and mergers, four acquisitions have occurred. In early 2005, DPI took over Biofrontera Discovery, based in Heidelberg. At least part of the rationale for this acquisition was to increase the medicinal chemistry capability of DPI in Europe. Later on that year, the Netherlands-based company Galapagos acquired UK-based Biofocus, which continues to offer contract drug discovery services including target identification capabilities gained as a result of the combination of the two companies. In early 2006, Albany Molecular Research Inc. (AMRI) acquired the Hungarian chemical synthesis company Comgenex (now called AMRI Hungary), giving AMRI a strategic presence in Europe in addition to its facilities in the USA and Asia. Lastly, as mentioned, Galapagos has recently acquired the drug discovery services business of DPI for US\$5.4 million. This acquisition has given Galapagos a presence in the USA, which it did not previously have. The merged discovery services division of Galapagos is now known as Biofocus DPI.

Termination of Pfizer file enrichment programme

In the late 1990s, Pfizer embarked on a major project with an estimated total investment of US\$1 billion to expand its corporate compound collection, making it more diverse and druglike. The four companies with which Pfizer collaborated for this purpose were ArQule, ChemRx (a subsidiary of DPI), ChemBridge and Tripos [5]. The end of this project has had a considerable impact on most of the service companies involved.

For example, ArQule has committed to exit the chemical services market altogether [6] and to focus entirely on its oncology project portfolio. It seems unlikely that this decision was based solely on termination of the Pfizer project, but it might have been a contributory factor. The effect on Tripos and DPI has been more clear-cut. Tripos made 76 employees redundant at its Bude site in the UK [7], whereas DPI announced the consolidation of its chemistry facilities to its San Diego site and the cessation of all operations at its south San Francisco facility, except for compound management [8]. As mentioned above, DPI has merged with

Infinity Pharmaceuticals and sold its discovery services business to Galapagos [9].

Such events underline the potential for vulnerability in the outsourcing sector, particularly when large deals come to a close and cannot be replaced quickly. For its part, ChemBridge announced an amended agreement with Pfizer in early 2004 that seems to have moved the focus of their collaboration from file enrichment to more downstream discovery chemistry support [10].

Significant trends

The impact on the marketplace of the events described earlier in this review is overlaid on some underlying emerging trends.

Companies emerging from Asia and the former Soviet Union

One of the key drivers for change in the market has been the burgeoning of service companies in the Asian subcontinent and the former Soviet Union (Table 3).

Perhaps foremost among the emerging companies is WuXi PharmaTech, which is based in Shanghai, China. Established in early 2001, WuXi is headed by Ge Li, formerly one of the founding chemists of Pharmacopeia [11]. The company has expanded rapidly: it now has >700 employees and claims that its current customers include 18 of the top 20 pharmaceutical companies and eight of the top ten biopharmaceutical companies in the world (<http://www.pharmatechs.com/about.asp>). The move of executives from West to East might be another emerging trend. In this regard, it is notable that another Asian outsourcing company based in South Korea, Chemizon, has recently been established by Anthony Piscopio, who was a co-founder of Array BioPharma [12]. Another significant development in China is the collaboration of Eli Lilly with Shanghai ChemExplorer, which was initiated in 2003. Under this agreement, >230 scientists are currently working for Eli Lilly on an exclusive basis [13]. Another company offering chemistry services in China is PepTech. This company is headquartered in Burlington, USA, but the chemistry is carried out in Shanghai (<http://www.peptechcorp.com/pages/aboutus.asp>).

Three Indian outsourcing companies have recently announced deals with major pharmaceutical companies. The largest of these deals (thought to be worth around US\$40 million over five years [13,14]), between GVK Biosciences and Wyeth, has attracted a lot

TABLE 3

Examples of outsourcing companies emerging from the Asian subcontinent and former Soviet Union

Company name	Location	Number of employees	Services offered	Significant deals	Refs
WuXi PharmaTech	Shanghai, China	>700	Lead discovery, optimization, bioanalytical services, development to commercial manufacturing	Website includes testimonials from Merck, Pharmacoepia and AstraZeneca	http://www.pharmatechs.com/about_customertestimonials.asp
Shanghai ChemExplorer	Shanghai, China	~230	Purification, synthesis and analysis of compounds	Collaboration with Eli Lilly	[64,65]
GVK Biosciences	Hyderabad, India	Unknown	Medicinal chemistry, informatics, biology, process R&D, clinical R&D, bioavailability and/or bioequivalence studies	Wyeth	[13,14,17]
Jubilant Organosys	Delhi, India	Unknown	Drug discovery services, custom research and manufacturing services, advanced intermediates and fine chemicals, active pharmaceutical ingredients, dosage forms and regulatory affairs services	Eli Lilly	[15,17]
Aurigene Discovery Technologies	Bangalore, India	Unknown	Molecular biology and protein sciences, structural biology including X-ray crystallography, high-field NMR and computational chemistry, assay biology including high-throughput screening, medicinal chemistry, preclinical biology	Novo Nordisk	[16]
ASINEX	Moscow, Russia	~200	Computational chemistry, medicinal chemistry, biochemical screening	Biovitrum	[18]
ChemBridge Corp. and ChemBridge Research Laboratories	San Diego, USA; Moscow, Russia	~350	Computational chemistry, discovery chemistry services	Merck	[52]
ChemDiv	San Diego, USA; Moscow, Russia, Europe	~500	Synthetic chemistry, medicinal chemistry, preclinical development	Schering	[51]

of attention. The deal calls for GVK Biosciences to recruit 150 chemists who will work solely for Wyeth in a dedicated research centre. Another five-year deal has been signed by Jubilant Organosys and Eli Lilly [15]. Under the terms of this agreement, Jubilant Organosys, together with its subsidiaries, Jubilant Biosys and Jubilant Chemsys, will provide a range of collaborative drug discovery services to Lilly. Lastly, Aurigene and Novo Nordisk have initiated a two-year collaboration in which Aurigene will work on the optimization of a lead series of Novo Nordisk. In addition, Aurigene will use its structure-based drug design capabilities to identify novel leads [16]. These three agreements represent landmark deals for the Indian lead-optimization outsourcing market [17] and are likely to be harbingers of similar collaborations.

In terms of the former Soviet Union, and Russia in particular, three companies comprise the vanguard: ASINEX, ChemDiv and ChemBridge. ASINEX began operations in 1994, synthesizing and selling screening compounds and reagents for use in drug discovery. Since 1998, discovery services have become an increasingly important part of the company's business (<http://www.asinex.com/about/index.html>). Notable among its deals of recent years is a three-year collaboration with Biovitrum of Sweden [18] that draws on the capabilities of ASINEX in computational and medicinal chemistry, and also biochemical screening. A first milestone payment has been made to ASINEX by Biovitrum for achieving screening results that met predefined criteria for an undisclosed G-protein-coupled receptor target [19]. Similar to ASINEX, ChemDiv

is well known for its provision of screening compounds, but it has also been rapidly expanding its discovery services over the past three years, enjoying a 35–40% growth in annual revenue during the same period [20].

Historically, the main incentive for outsourcing to companies such as these was their lower costs as compared with their North American or European counterparts. Typically, a chemist in a pharmaceutical company in the USA might cost around US\$237,000 per annum; for a chemist in India, by contrast, the cost is more likely to be in the range of US\$55,000 to US\$85,000 [13]. In terms of cost alone, companies in the USA and Europe clearly cannot compete and the 'low end' of the market has been largely lost to them.

Until recently, Western contract research organizations held the upper hand in terms of essential issues such as security of intellectual property and quality of infrastructure [13]. Although these issues might not be fully resolved [21], the up-and-coming companies and their countries' governments have been addressing them, giving greater confidence to pharmaceutical companies seeking a lower-cost outsourcing partner for more demanding projects that generate intellectual property. As a result, there is now increasing financial pressure within the more expensive lead-optimization market, which has traditionally been the preserve of outsourcing companies in the USA and Europe.

The existing Western outsourcing companies have been responding to the afore-mentioned events and trends in several different ways, as described in the next sections.

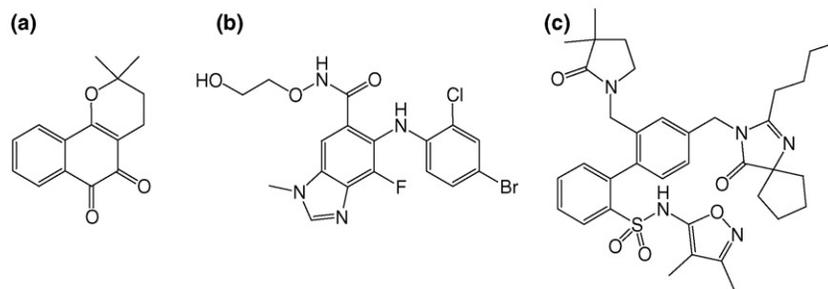


FIGURE 2

Chemical structures of lead compounds in preclinical development or clinical trials. (a) ARQ501 (Investigational Drugs Database, <http://www.iddb3.com>). **(b)** ARRY-142886. **(c)** PS433540 (Investigational Drugs Database).

Companies exiting the outsourcing arena

At least two companies, ArQule and DPI, have formally exited the outsourcing arena. From the timing, it seems that the termination of the Pfizer file-enrichment project might have been a contributory factor in the decision in both cases. For several years, ArQule has been making the transition towards becoming an oncology-focused drug discovery company, and finally it announced its decision to cease providing chemistry services in September 2005 [6]. At the time of writing, ArQule has two compounds in the clinic. The most advanced, ARQ501 (Figure 2a), is an activator of the E2F1 pathway that is being developed in partnership with Roche. ARQ501 has completed Phase I trials of the drug as a monotherapy and in combination with existing therapeutics, and Phase II studies in combination with gemcitabine are underway [22,23]. The second clinical compound, ARQ197, is a c-Met receptor tyrosine kinase inhibitor and this drug entered Phase I trials early in 2006 [24]. Another activator of the E2F1 pathway, ARQ171, is in preclinical development.

As mentioned, in April 2006 Infinity Pharmaceuticals and DPI announced a merger, through which a publicly held, oncology-focused drug discovery company would be created [9]. As a result, DPI has divested itself of its drug discovery services capabilities (acquired by Galapagos in June 2006 [25]) and thereby exited the marketplace.

Companies focusing on internal drug discovery programmes

In recent years, several of the more well-established outsourcing companies have noticeably increased their commitment to proprietary drug discovery programmes while still providing contract services (Table 4). In the following text, I provide details of the more advanced programmes.

AMRI's most advanced programme is its biogenic amine uptake inhibitor project, which is currently at the preclinical development stage. Compounds with various combinations of amine-transporter inhibition profiles, including selective, dual and triple inhibitors, have been developed. The most advanced compounds are 'triple inhibitors', which show the greatest inhibition at serotonin and noradrenaline transporters, but have moderate inhibition at dopamine transporters – a profile that is thought to be highly appropriate for the treatment of major depressive disorders (<http://www.albmolecular.com/rnd/biogenic.html>). AMRI's strategy is to pursue discovery programmes to an appropriate phase

before out-licensing or partnering. The choice of timing and type of partner will vary with the programme: some will be partnered at the lead-optimization stage, whereas others will be progressed through Phase I clinical trials first.

Amphora Discovery has recently announced that it is forming two separate business units and moving into the discovery services arena, including hit to lead optimization [26]. The contract research arm will retain the 'Amphora Discovery' name, and 'Amphora Pharmaceuticals' will focus on exploiting the company's drug candidates and on creating partnerships with pharmaceutical and biotechnology companies. Thus, Amphora can be considered to have adopted the twin-track business model, but from the opposite direction to that of the other companies mentioned in this section. The leading programmes of Amphora Pharmaceuticals are at the lead-to-candidate stage and are targeted at kinases, specifically, AKT1, FLT3/KIT/PDGFR and P38 α (<http://www.amphoracorp.com>).

Before its merger with Etiologics in October 2004, Argenta Discovery had pursued proprietary drug discovery programmes in various therapeutic areas, including oncology and metabolic disease. The incorporation of Etiologics' expertise in respiratory diseases, particularly COPD and asthma, has led to a focus in this therapeutic area. Argenta Discovery's strategy is directed towards the development of therapies that will deliver improved bronchodilator symptomatic relief in combination with treatment of the underlying inflammatory disease process. In February 2006, Argenta Discovery announced a research collaboration with Dr Reddy's in the field of COPD [27]. Under the terms of this agreement, Dr Reddy's and Argenta Discovery are seeking to identify clinical candidates from a specific class of compounds of Dr Reddy's for use as potential treatments for COPD. Both of the parties will jointly develop the selected candidates from the preclinical stage up to Phase IIa (proof of concept).

Array Biopharma's leading project, which has been partnered with AstraZeneca since 2003, is in the field of MAPK kinase (MEK) inhibition for oncology. It has been recently announced that the lead compound, AZD6244 (ARRY-142886; Figure 2b), has entered a Phase II clinical trial [28]. The trial announced is a randomized study that will compare AZD6244 to temozolomide in the treatment of stage III–IV melanoma. AstraZeneca expects to enrol up to 180 participants at about 40 centres worldwide. A milestone payment of US\$3 million was made to Array on dosing

TABLE 4

Examples of drug discovery programmes being pursued by outsourcing companies

Company	Example programmes with indications/therapeutic areas	Refs
AMRI	Biogenic amine uptake inhibitors (CNS/neurology, urology) Vinca alkaloids (oncology) Cyclosporins (psoriasis, tissue rejection, immune disorders) 5-HT ₃ antagonists (irritable bowel disease, emesis) Non-steroidal glucocorticoid modulators (anti-inflammatory, asthma)	http://www.albmolecular.com/rnd/
Amphora Discovery	AKT1 inhibitors (solid tumours) FLT3/KIT/PDGF inhibitors (leukaemia and solid tumours) P38- α inhibitors (inflammation, chronic and acute pain, autoimmune disease)	http://www.amphoracorp.com
Argenta Discovery	COPD, severe asthma, cystic fibrosis	http://www.argentadiscovery.com/r_and_d/respiratory_disease.html
Array BioPharma	MEK inhibitors (oncology, inflammation) ErB2/EGFR inhibitors (oncology) P38 α inhibitors (inflammation) KSP inhibitors (oncology) ErB2 inhibitors (oncology)	http://www.arraybiopharma.com/ProductPipeline/Default.asp
Cerep	No details available	http://www.cerep.fr/cerep/users/pages/collaborations/drugdiscovery.asp
Evotec	GABA _A modulator (insomnia) NMDA NR2B antagonists (Alzheimer's disease, Parkinson's disease, neuropathic pain)	http://www.evotec.com/opencms/export/evotec/en/pharma_rd/index.html
NiKem Research	ORL-1 antagonists (multiple CNS indications) V-ATPase inhibitors (oncology) Pyrrolidone nootropic analogues (neuropathic pain) Combined NK-1/NK-2 antagonists (multiple indications)	http://www.nikemresearch.com/pipeline.htm
Pharmacopeia	Dual-acting receptor antagonist (cardiovascular) JAK3 inhibitor (transplantation) CCR1 antagonist (arthritis/MS) A2A antagonist (Parkinson's disease) $\alpha_v\beta_3/\alpha_v\beta_5$ integrin inhibitors (anti-angiogenesis)	http://www.pharmacopeia.com/wt/page/product_portfolio

Abbreviations: 5-HT₃, serotonin-gated ion channel; CNS, central nervous system; MS, multiple sclerosis.

of the first participant [29]. Additional Phase II studies for a range of other tumours are planned. On its own, Array is pursuing a different MEK inhibitor, ARRY-438162, for treating inflammatory disease, and a Phase I trial of this compound is currently underway [30].

Since 2001, Cerep has been undertaking self-funded drug discovery programmes in addition to its service business, although few details are available. In addition, Cerep has collaborative research agreements with several companies including BMS, with whom it is developing an LFA-1 antagonist that has completed Phase I trials [31].

In March 2005, Evotec announced its acquisition of the outstanding 78% of Evotec Neurosciences that it did not own already, and also raised €47 million to develop its central nervous system drug pipeline [32]. This move has enabled Evotec to expand its proprietary programmes significantly and to create its own proprietary drug discovery and development company specializing in diseases of the central nervous system. To boost its pipeline, Evotec has licensed-in two monoamine oxidase B inhibitors from Roche, although one of these, EVT 301, has recently failed in a Phase I trial [33]. The most advanced compound in the Evotec pipeline is EVT 201, a modulator of the GABA_A receptor for treating insomnia, which has recently entered a Phase II clinical trial [34].

NiKem Research has developed a portfolio of four preclinical projects: two derive from the company's previous existence as part of SmithKline Beecham; the other two are the result of independent internal research programmes.

Pharmacopeia is currently pursuing five internal drug discovery programmes, the most advanced of which is a first-in-class, dual acting receptor antagonist (DARA) active at the endothelin A and angiotensin 1 receptors. The DARA compound, PS433540 (Figure 2c), is in preclinical development and so far studies have demonstrated that the compound is both highly efficacious in many disease models, and safe and well tolerated in animal safety studies, with a pharmacokinetic profile consistent with once-daily oral administration (<http://www.pharmacopeia.com/wt/page/PS433540>). Four other programmes against a diverse set of targets are currently in lead optimization. In addition to these internal programmes, Pharmacopeia also has a sizeable pipeline of projects partnered with other companies, the most advanced of which are in Phase I clinical trials.

From the above it is clear that the 'hybrid' business model combining outsourcing and internal research has become increasingly popular. It will be interesting to see in the future whether sustaining such a hybrid model is a viable long-term business objective in its own right or is simply a step on the road to becoming a pure drug discovery company in the same manner as ArQule.

Companies adopting a hybrid onshore–offshore model

Realizing the irresistible attraction to potential customers of low full-time equivalent rates, some Western outsourcing companies have adopted the ‘if you can’t beat them, join them’ philosophy and developed a hybrid onshore–offshore business model. Some have accomplished this hybrid model by building their own offshore facilities, whereas others have gained access to the capacity offered by companies in Asia and Eastern Europe by collaboration and/or acquisition.

AMRI has taken both approaches to gain offshore capacity. As mentioned, it has acquired a presence in Eastern Europe through its acquisition of Comgenex [35]. Before this, the company opened facilities in India and Singapore [36], and has recently announced the construction of an expanded research centre in Hyderabad, India [37], which, when fully operational in 2007, will house ~140 staff.

For lead-discovery and -optimization services, SAFC Pharma possesses two centres, one in Manchester, UK, and the other in Bangalore, India. SAFC Pharma’s customers have the option of working either directly with the chemists in India or via highly experienced medicinal chemistry teams in Manchester. The latter arrangement gives the customer access to the reduced costs of India but also to a facility designed to Western standards, and removes the need to manage the additional logistics of time zones, relationships and intellectual property systems required by working directly with a provider in India (http://www.sigmaaldrich.com/SAFC/Pharma_Small_Molecule/bServices_Overviewb/Lead_Discovery__Optimization.html).

To gain access to offshore capacity, Pharmacoepia established a strategic alliance with WuXi PharmaTech in 2003, which enables Pharmacoepia to offer USA-based scientific project management at the highly competitive pricing that offshore sourcing provides [38]. The alliance is perhaps not surprising given the provenance

of WuXi’s Chief Executive Officer (ex-Pharmacoepia!). In 2002, Ricerca initiated a three-year collaboration with GVK Biosciences for a similar purpose [39], although it is not known whether the collaboration has been extended beyond 2005. More recently, Galapagos has taken a collaborative route to gain access to facilities in India: its services division, BioFocus DPI, has signed agreements with Indus Biosciences, a subsidiary of CiVentiChem LLC in Hyderabad, and with ProCitius, a division of Sanmar Speciality Chemicals Limited in Chennai, India [40]. Both companies will carry out chemistry services for the BioFocus DPI Discovery Products division and might also provide support for client projects conducted by the BioFocus DPI Medicinal Chemistry division.

Companies with lead optimization alongside synthesis services

In the last review of the market, it was noted that companies such as ASINEX, ChemDiv and ChemBridge had added medicinal chemistry and/or lead-optimization offerings to their traditional compound and/or reagent synthesis businesses [1]. The following examples are indicative of a continuing trend in this direction.

In the UK, Peakdale Molecular has moved to strengthen its medicinal chemistry services over the past year with the appointment of a medicinal chemistry services director and the addition of computer-aided drug design capabilities [41,42]. Enamine in Kiev, Ukraine, is now also advertising lead-discovery and -optimization services (http://www.enamine.net/index.php?option=com_content&task=view&id=21&Itemid=58) and has recently signed a collaboration with Carna Biosciences for the discovery and development of compounds against a kinase target [43]. In the USA, Nanosyn has begun to offer medicinal chemistry services alongside its compound collection (<http://www.nanosyn.com/medicinal.php>) and has entered a multi-year research collaboration with Amphora Discovery, again focusing on kinases [44].

TABLE 5

Examples of outsourcing companies remaining focused on lead-optimization services

Company name	Location	Drug discovery services offered
Kalexsyn	Kalamazoo, Michigan, USA	SAR development, lead optimization, ADMET problem solving through structural modification, synthetic organic chemistry, asymmetric synthetic techniques, heterocyclic chemistry, stable label synthesis and parallel synthesis techniques
Scottish Biomedical	Glasgow, UK	Ethical tissue acquisition, molecular biology, protein technology, primary and secondary assay development, high-throughput and high-content screening, medicinal chemistry, pharmacology
SCYNEXIS	Research Triangle Park, North Carolina, USA	Medicinal chemistry, custom synthesis, high-throughput purification and analysis, ADMET and bioanalytical services
ChemOvation	Horsham, UK	Organic chemistry and synthesis, computational chemistry and design, medicinal chemistry, analysis and purification, screening
Charnwood Molecular	Loughborough, UK	Medicinal chemistry, computer-aided molecular design, outsourced research, outsourced synthesis, solid-phase organic chemistry
NCE Discovery	Cambridge, UK	Lead development, lead optimization, hit to lead, consultancy, molecular modelling
deCODE Chemistry	Woodridge, Illinois, USA	Medicinal chemistry, computational chemistry, focused libraries
Ricerca	Concord, Ohio, USA	Medicinal chemistry, lead optimization, analytical chemistry, <i>in vitro</i> and ADMET screening
Tripes	Bude, Cornwall, UK	Hit-finding, hit-to-lead, lead optimization, screening libraries
Idealp-Pharma	Villeurbanne, France	Contract synthesis research, cheminformatics, medicinal chemistry
Creagen Biosciences	Woburn, Massachusetts, USA	Synthetic, natural product, medicinal and combinatorial chemistry
iNovacia	Stockholm, Sweden	Assay development and screening, medicinal chemistry, compound analysis and purification

Abbreviations: SAR, structure–activity relationship; ADMET, absorption distribution metabolism excretion and toxicology.

TABLE 6
Outsourcing companies and website addresses

Outsourcing company	Website address
AMRI	http://www.albmolecular.com
Amphora Discovery	http://www.amphoracorp.com
Argenta Discovery	http://www.argentadiscovery.com
Array Biopharma	http://www.arraybiopharma.com
ArQule	http://www.arqule.com
ASINEX	http://www.asinex.com
Aurigene	http://www.aurigene.com
Biofocus DPI	http://www.biofocus.com
Cerep	http://www.cerep.fr
Charnwood Molecular	http://www.charnwood-molecular.com
Chembridge Research Laboratories	http://www.chembridgeresearch.com
Chemdiv	http://www.chemdiv.com
Chemizon	http://www.chemizon.com
ChemOvation	http://www.chemovation.com
Creagen Biosciences	http://www.creagenbio.com
deCODE Chemistry	http://www.decodechemistry.com
DPI	http://www.discoverypartners.com
Enamine	http://www.enamine.net
Evotec	http://www.evotec.com
GVK Biosciences	http://www.gvkbio.com
Idealp-Pharma	http://www.idealp-pharma.com
iNovacia	http://www.inovacia.se
Jubilant Organosys	http://www.jubl.net
Kalexsyn	http://www.kalexsyn.com
Nanosyn	http://www.nanosyn.com
NCE Discovery	http://www.ncediscovery.com
NiKem Research	http://www.nikemresearch.com
Peakdale Molecular	http://www.peakdale.co.uk
Peptech	http://www.peptechcorp.com
Pharmacopeia	http://www.pharmacopeia.com
Ricerca	http://www.ricerca.com
SAFC Pharma	http://www.sigmaaldrich.com/SAFC/Pharma.html
Scottish Biomedical	http://www.scottish-biomedical.com
SCYNEXIS	http://www.scynexis.com
Tripos	http://www.tripos.com
WuXi PharmaTech	http://www.pharmatechs.com

Companies remaining focused on lead-optimization services

There remain companies that seem to be continuing to focus on providing lead-optimization services and that are not obviously undertaking proprietary research or developing offshore capabilities. Details of some such companies are summarized in Table 5. In addition, all outsourcing companies mentioned in this review, together with their website addresses, are listed in Table 6.

Conclusions

Characteristically, the pharmaceutical industry has been slow to embrace outsourcing, but the momentum in this direction is now growing as the benefits are appreciated. Indeed, some in the industry consider outsourcing as no longer optional, but mandatory [45]. Fundamentally, outsourcing makes economic sense, providing access to technology or capacity without the need for costly investment in equipment or personnel [46]. Outsourcing also offers great flexibility, facilitating management of the inevitable peaks and troughs in the demand for resources. A less tangible, but no less valuable, benefit to be gained is the access to different perspectives and experience that can be of great help when tackling a difficult problem [45].

The ever-present economic pressures on drug discovery are currently driving the use of low-cost suppliers, particularly those in China and India [13]. Despite this apparent headlong rush to the East, the market for outsourcing to Western providers still seems to be fairly robust. The inevitable conclusion is that more outsourcing is happening: companies are perhaps adopting a 'horses for courses' approach – that is, selecting different companies for distinct types of outsourcing task and/or seeking to spread the risk by not concentrating all outsourcing with one vendor.

In summary, the state of the outsourcing market is well summarized by the titles of two short articles published recently: 'Contract drug discovery industry is changing as fast as it's growing' [2] and 'Chemistry outsourcing going global' [13]. As noted by Heffner [2], the market for outsourced drug discovery services is characterized by growth and change. The pace of change is almost bewildering, forcing much rewriting during the course of preparing this overview, which will probably be out of date as soon as it is published! What is certain is that constant change is here to stay and that the outsourcing marketplace will continue to be a very dynamic, stimulating and challenging environment in which to conduct business.

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