Outsourcing lead optimization: the eye of the storm

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This article is the third in a series examining the evolution of the market for outsourced lead optimization services and covers developments from late 2006 to the present. Following an analysis of the significant events that have impacted the marketplace in recent years, a brief survey of the growing number of companies offering lead optimization services is presented. Subsequently, three notable trends that can be perceived in this highly dynamic field are discussed: the continuing rise of outsourcing companies in Asia and Eastern Europe, the increase in deals with not-for-profit organizations and, finally, the emergence of a variety of business models under which outsourced work is conducted.

It is clear, even to a casual observer, that pharmaceutical R&D is experiencing a period of unprecedented turbulence. Faced with a 'perfect storm' of increasing R&D costs, static R&D productivity levels and looming patent cliffs [1,2], the industry is being forced to adopt radical survival strategies. Thus, in 2009 there was a new wave of consolidation in the industry [3,4] with a trio of mega-mergers (Fig. 1) and a soaring number of redundancies [5], a trend that has continued unabated into 2010 [6]. Fundamental questions are now being asked about the viability of the current pharma R&D model [3,4,7]. Among the anticipated trends is the likelihood that the traditional dependence on in-house small-molecule-based products will shift to an increasing reliance on biologicals [8] and externally derived drug candidates [9].

The move towards 'externalized' drug discovery is also reflected in the increasing use of outsourcing in the preclinical stages of research, including the lead optimization phase. It is during lead optimization that much of the proprietary knowledge and intellectual property underpinning pharmaceutical R&D is generated and, until relatively recently, this phase of drug discovery has been largely the preserve of internal efforts. The development of outsourced lead optimization services over the past decade has been charted by the author of this paper in two previous reviews from 2004 and 2007 [10,11], and also by others [12]. In this article, the significant events in the marketplace over the past three years are highlighted and emerging trends are presented to give an updated picture of a thriving and highly dynamic business arena.

For the purposes of this article, 'lead optimization' is defined as chemistry and allied disciplines applied to a project after the hit (lead) identification stage until preclinical candidate selection. Thus, herein, 'lead optimization' includes the period that is often now termed the 'hit-to-lead' phase of a project as well as the subsequent, more traditional optimization work.

Significant market-shaping events

The principal events affecting the marketplace for lead optimization services over the past three years or so fall into two categories: changes to existing companies through, for example, merger and acquisition (M&A) activity; and changes caused by companies entering and exiting the field.

Changes to existing companies

Table 1 summarizes, in chronological order, the key events that have changed the landscape of the marketplace in the period of time since the previous review from this series was published [11]. In general, the trend has been towards agglomeration. As an example of this, Beijing-based BioDuro was bought by PPD (http://www.ppdi.com) for approximately US$77M in November 2009 [13]. As well as adding drug discovery service capabilities to PPD, the deal gives the US firm a strong foothold in China, which is expected to become the second-largest global biopharmaceutical market, after the USA [14]. More recently, in April 2010 the North

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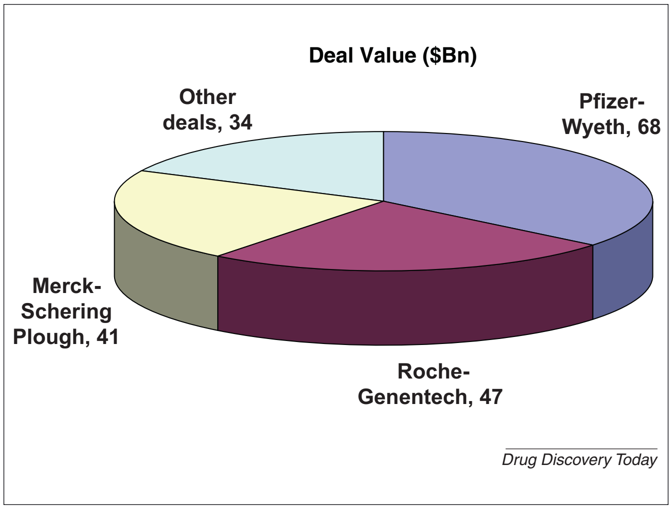

FIGURE 1

Pharma M&A deals in 2009 showing the dominance of the three mega-mergers.

American company Charles River (http://www.criver.com) made moves to purchase WuXi Apptec in a US$1.6B transaction [15] but the acquisition was subsequently cancelled after opposition from several of Charles River's shareholders.

In Europe, Belgium-based Galapagos (http://www.glpg.com) has made several acquisitions following on from its 2005 purchase of BioFocus, culminating in its procurement of Argenta Discovery's service operations in February 2010 for €16.5 million [16]. The combination of BioFocus and Argenta (with a total of 390 employees) gives Galapagos a significant position in the drug discovery services market. Evotec has also seen considerable changes in recent years by acquiring various companies (Neuro3d, RSIPL, Renovis, Summit's zebrafish screening capability and Develogen) and divesting itself of its chemical development business (to Aptuit) and closing down the former Renovis site in the USA.

Elsewhere, Pharmacopeia was acquired by Ligand (http://www.ligand.com) in December 2008 in a deal worth up to US$70 M and was thus effectively removed from the drug discovery services arena. In March 2010, Ricerca Biosciences significantly expanded its operations by the acquisition of MDS Pharma Services gaining additional facilities in three countries and a further 600 employees [17].

Companies exiting the field

In addition to Pharmacopeia, mentioned above, several other companies have left the lead optimization outsourcing marketplace. Table 2 lists companies that have exited the field since the

TABLE 1

Events affecting lead optimization outsourcing companies.

Companies involved	Nature of event	Date	Refs
Galapagos, Inpharmatica	Acquisition of Inpharmatica by Galapagos	6 December 2006	[49]
Commonwealth Biotechnologies, Tripos Discovery Research	Acquisition of TDR by Commonwealth Biotechnologies	14 March 2007	[50]
Evotec, Neuro3d	Acquisition of Neuro3d by Evotec	29 March 2007	[51]
NiKem Research, Brane Discovery	Spinout of Brane Discovery by NiKem Research	23 April 2007	[52]
Albany Molecular Research	Rebranding as 'AMRI'	1 May 2007	[53]
Domainex, NCE Discovery	Domainex merges with NCE Discovery	May 2007	[54]
WuXi Pharmatech	Initial Public Offering	14 August 2007	[55]
Evotec, Aptuit	Sale of chemical development business by Evotec to Aptuit	11 September 2007	[56]
Evotec, Renovis	Acquisition of Renovis by Evotec	19 September 2007	[57]
Tripos Discovery Research	Renamed 'Exelgen'	29 November 2007	[58]
WuXi PharmaTech, Apptec Laboratory Services	Acquisition of Apptec by WuXi	31 January 2008	[59]
Galapagos, Sareum	Acquisition of Sareum's structure-based drug discovery assets	26 August 2008	[60]
Ligand Pharmaceuticals, Pharmacopeia	Acquisition of Pharmacopeia by Ligand	23 December 2008	[61]
Evotec	Restructuring, wind-up of US operations	5 May 2009	[62]
Evotec, Summit Corporation	Acquisition of Summit's zebrafish screening operations by Evotec	7 May 2009	[63]
Evotec, Research Support International Private Limited	Acquisition of controlling majority stake in RSIPL by Evotec	31 August 2009	[64]
PPD, BioDuro	Acquisition of BioDuro by PPD	30 November 2009	[13]
Galapagos, Argenta Discovery	Acquisition of Argenta's drug discovery services operations by Galapagos	02 February 2010	[16]
AMRI, Excelsyn	Acquisition of Excelsyn by AMRI	18 February 2010	[65]
Ricerca Biosciences, MDS Pharma Services	Acquisition of the discovery and preclinical business of MDS Pharma Services by Ricerca	08 March 2010	[17]
Evotec, Develogen	Acquisition of Develogen by Evotec	14 July 2010	[66]

TABLE 2

Companies previously active in lead optimization outsourcing that have now exited the field.

Company	**Notes**
Amphora Discovery	Amphora's assets were acquired by Nanosyn in November 2008 [67]
Array Biopharma	In recent years, Array has become focused on its collaborations and in-house programmes and no longer provides outsourced medicinal chemistry services
Cerep	In December 2006 Cerep announced that it was ceasing to provide chemistry services, blaming exchange rate fluctuations and growing competition from Asia [68]
DeCode Chemistry	Presumed to have ceased operations following closure of Woodbridge facility by parent company Decode Genetics [69]
Pharmacopeia	Following its acquisition by Ligand Pharmaceuticals in 2008, it is presumed that Pharmacopeia no longer offers outsourcing services
Tripos Discovery Research	Exelgen (formerly Tripos Discovery Research) went into administration on 23 September 2008 [70]. A new company, Exelgen Discovery, was started in January 2009 by former employees of Exelgen

last review (*cf*. Table 6 in Ref. [11]) and gives the reason in each case for each company's departure.

A snapshot of the marketplace

A revised and expanded list of companies active in lead optimization outsourcing is given in Table 3. This includes several companies entering the field in the past five years particularly, although not exclusively, from India and China. Outsourcing companies are now distributed throughout Europe, the USA and Asia. Typically, however, in terms of FTE (full-time employee) numbers, the Asian companies significantly outnumber their counterparts elsewhere and, thus, the balance of employees lies in the East. Companies founded since 2000, or thereabouts, tend to have been formed specifically to provide lead optimization services. Those that can trace their history back further usually began life with a slightly different aim, perhaps as a screening compound vendor, combinatorial chemistry specialist or fine chemical provider.

It is instructive to plot the number of outsourcing companies founded against the year of formation, as in Fig. 2. This illustration shows a significant peak in the 2000–2009 decade as companies were formed to take advantage of the growing market for outsourcing [10]. The small number formed in the past five years perhaps indicates that the marketplace is now well provided for and that any additional demand for services is being met primarily by the organic growth of existing companies.

Notable trends

As well as the changes in the outsourcing marketplace in terms of individual companies, there are also some more general trends that can be perceived from the events of the past few years.

The continuing rise of outsourcing to Asia and Eastern Europe

The growth of outsourcing companies in Asia, particularly India and China, over the past five years or so has been phenomenal and has gone hand-in-hand with the restructuring of R&D that has taken place in Big Pharma [18–20]. What is notable is not merely the number of companies that has emerged but also their scale in terms of the breadth of their service offerings, and the number of FTEs they have at their disposal. Some exemplary figures are given in Table 4. By contrast, the largest of the non-Asian companies is AMRI (Albany Molecular Research, Inc) with some 1300 employees (of whom a good number are employed in AMRI's Asian facilities [21]).

The growth has been fuelled in part by several large deals with Western pharmaceutical companies. For instance, in 2009 Syngene opened a 400-scientist R&D centre in Bangalore which it operates on behalf of Bristol-Myers Squibb (http://www.bms.com) [18,22]. This follows a similar collaboration announced by GVK BIO and Wyeth (http://www.wyeth.com) in 2007 [23]. Eli Lilly (http://www.lilly.com) has extensive deals with companies in both China and India. Lilly was one of the first pharmaceutical companies to outsource R&D to China on a significant scale, establishing ChemExplorer in 2002 to serve its needs exclusively [24]. More recently, the Indian company Jubilant Organosys announced a five-year extension to an R&D collaboration with Lilly that began in 2005 [18,25]. Elsewhere, AstraZeneca (http://www.astrazeneca.com) and Roche (http://www.roche.com) both signed deals with BioDuro in 2009 for drug discovery services [26,27].

Although outsourcing drug discovery projects, rather than more-straightforward custom synthesis tasks, to Asia still presents challenges, it is clear that it is now an integral part of R&D strategy for many pharmaceutical companies. It is, however, worth noting that, whereas India and China have many similarities as outsourcing locations, there are significant differences between both destinations that must be understood and considered before making a commitment to either. For instance, India is reckoned to have stronger capabilities in small-molecule R&D and China is believed to be superior in biologicals. In terms of culture, Indian companies tend to have a business operation style and philosophy that is more in common with Western firms than that seen in China. This could explain why several large Western companies have set up joint ventures with Indian companies but have preferred to invest heavily in large, wholly owned facilities in China [28].

Asia is not the only lower-cost destination for outsourced research. As noted by a recent market research report [29], the collapse of the former Soviet Union led to many experienced chemists losing their jobs as funding became scarce. The more entrepreneurial of these scientists formed companies offering services to European and US pharma and biotech companies, often beginning with the supply of screening compounds. Nowadays, companies such as Asinex, ChemDiv and ChemBridge are established names in the broader drug discovery service outsourcing market; the Hungarian company Comgenex was purchased by AMRI in 2006.

Of course, the burgeoning of Asian and Eastern European outsourcing facilities has had a knock-on effect on the Western providers that have been forced to differentiate their offerings from those

TABLE 3

Companies currently active in the lead optimization outsourcing arena.

Company name	Website address	Location(s)	Year founded	Notes
Advinus	http://www.advinus.com	India	2005	Owned by TATA Enterprises. The name is derived from 'Advantage India US'
AMRI	http://www.amriglobal.com	USA, Hungary, Singapore, Asia	1991	European operation was formerly known as Comgenex
Aptuit	http://www.aptuit.com	Italy	2004	Gained medicinal chemistry and allied capabilities by acquiring the Medicines Research Centre, Verona, Italy (formerly a GSK R&D site) in July 2010
Argenta	http://www.argentadiscovery.com	UK	2000	Acquired by Galapagos NV in 2010
Asclepia	http://www.asclepia.com	Belgium	2009	Also offers targeted libraries
Asinex	http://www.asinex.com	Russia	1994	Initially a compound vendor but has gradually increased its medicinal chemistry expertise
Asischem	http://www.asischem.com	USA, Russia	2005	Small medicinal chemistry team backed up by synthetic chemistry in St. Petersburg
Aurigene	http://www.aurigene.com	India	2002	Independent subsidiary of Dr Reddy's Laboratories
Axxam	http://www.axxam.com	Italy	2001	Has its roots in Bayer Healthcare R&D
BioDuro	http://www.bioduro.com	China	2005	Now owned by PPD
BioFocus	http://www.biofocus.com	UK, USA, Switzerland	1997	Acquired by Galapagos NV in 2005
Cayman Chemical	http://www.caymanchem.com	USA	1980	Medicinal chemistry services group established ca. 2007
Charnwood Molecular	http://www.charnwood-molecular.com	UK	1998	Founded by two academics from Loughborough University
Chembiotek	http://www.chembiotek.com	India	2001	Part of TCG Lifesciences
ChemBridge	http://www.chembridge.com	USA, Russia	1993	Discovery chemistry services based in Moscow
ChemDiv	us.chemdiv.com	USA, Russia	1990	Also offers preclinical and clinical development services
Chemizon	http://www.chemizon.com	Korea, China	2005	Owned by Optomagic Corp. Founded by former Array Biopharma chemistry VP
ChemOvation	http://www.chemovation.com	UK	1999	Formed with backing from the Novartis Venture Fund
ChemPartner	http://www.chempartner.cn	China	2003	A wholly owned subsidiary of ShangPharma, which also owns ChemExplorer (provider of services exclusively for Eli Lilly)
CreaGen Biosciences	http://www.creagenbio.com	USA, India	2003	Founded by a former ArQule scientist
Dalton Pharma Services	http://www.dalton.com	Canada	1986	Also offers process and GMP facilities
Domainex	http://www.domainex.co.uk	UK	2002	Merged with NCE Discovery in 2007
Elexopharm	http://www.elexopharm.de	Germany	2005	Spin-off from the Department of Pharmaceutical and Medicinal Chemistry of Saarland University
Ennova Medchem	http://www.ennovamedchemgroup.com	USA, China	2002	Provides pharmaceutical intermediates and specialty chemicals in addition to medicinal chemistry services
Epichem	http://www.epichem.com.au	Australia	2003	Has labs in Perth and Melbourne

TABLE 3 (*Continued*)

Company name	Website address	Location(s)	Year founded	Notes
Evotec	http://www.evotec.com	UK, Germany	1993	Evotec Biosystems merged with Oxford Asymmetry International in 2000 to form the basis of the present-day company
Exelgen Discovery	http://www.exelgendiscovery.com	UK	2009	Founded by former employees of Exelgen (formerly Tripos Discovery Research)
GVK BIO	http://www.gvkbio.com	India	2001	Part of larger, more diverse GVK group
Idealp Pharma	http://www.idealp-pharma.com	France	2000	Self-funded company based in Lyon
iNovacia	http://www.inovacia.se	Sweden	2006	Partly owned by Biovitrum (10%) and Asinex (20%)
iThemba Pharmaceuticals	http://www.ithembapharma.com	South Africa	2001	As well as providing discovery services, iThemba seeks to discover drugs to treat infectious diseases prevalent in sub-Saharan Africa
Jubilant Organosys	http://www.jubl.com	India	2004	Entered medicinal chemistry arena through formation of Jubilant Chemsys
Kalexsyn	http://www.kalexsyn.com	USA	2003	Formed after the closure of Discovery Research operations at Pharmacia in Kalamazoo. Name is derived from 'Kalamazoo Experts in Synthesis'
Medicilon	http://www.mediciloninc.com	China, USA	2004	Headquartered in Shanghai with additional lab space in Chicago
Nanosyn	http://www.nanosyn.com	USA	1998	Started out as a combichem company, now focused on discovery services
Nikem Research	http://www.nikemresearch.com	Italy	2001	Founded by staff formerly employed by SmithKline Beecham Discovery in Milan
O2h	http://www.o2h.com	UK, India	2005	Co-located in Cambridge, UK and Ahmedabad, India
Pacific World Discovery	http://www.pacificworlddiscovery.com	USA	2007	Founded by former Pfizer and AMRI scientists [71]
Peakdale Molecular	http://www.peakdale.co.uk	UK	1992	Began as a fine chemicals business, now offers broader drug discovery services
Peptech	http://www.peptechcorp.com	China, USA	1995	HQ in USA, R&D in Shanghai
Pharmaron	http://www.pharmaron.com	China, USA	2003	Primarily located in Beijing with compound logistics and business development in the USA
Polyphor	http://www.polyphor.com	Switzerland	1996	Services are provided by Polyphor's Small Molecules Business Unit
Prestwick Chemical	http://www.prestwickchemical.com	France, USA	1999	Founded by Prof. C. G. Wermuth
Provid Pharmaceuticals	http://www.providpharma.com	USA	2001	Provid also has internal programmes in autoimmune disease and oncology
ProXyChem	http://www.proxychem.com	USA	2005	Has strategic alliance with Creagen Biosciences for chemistry
Pyxis Discovery	http://www.pyxis-discovery.com	The Netherlands	2003	Primarily focused on lead discovery. Has collaboration with iThemba for lead optimization
Ricerca Biosciences	http://www.ricerca.com	USA	1986	In 2007–2008, Ricerca completed a US$75M financial restructuring in which three private equity firms retained ownership
Scottish Biomedical	http://www.scottish-biomedical.com	UK	1994	Private, self-funded company located in Glasgow, Scotland.

TABLE 3 (*Continued*)

Company name	Website address	Location(s)	Year founded	Notes
SCYNEXIS	http://www.scynexis.com	USA	2000	Privately held spin-off created by a team of researchers from Aventis CropScience in Research Triangle Park, NC
Selcia	http://www.selcia.com	UK	2001	Formerly SCYNEXIS Europe. Radiolabelling expertise
Selvita	http://www.selvita.com	Poland	2007	Also has proprietary drug discovery programmes that originate from research at Polish universities
Sundia	http://www.sundia.com	China	2004	Founded by a group of veterans from the US biopharmaceutical industry
Sygnature Chemical Services	http://www.sygnaturechem.com	UK	2004	Chemistry specialists. Alliance with Cyprotex for ADME services
Syngene	http://www.syngeneintl.com	India	1994	India's first contract research services company
SYN|thesis med chem	http://www.synmedchem.com	China, Australia, USA, UK	2007	New company co-founded by founder of Cytopia
Wuxi Apptec	http://www.wuxiapptec.com	USA, China	2000	Subject of an attempted acquisition by Charles River in 2010 [15]

of their cheaper rivals. In many cases, this has involved emphasizing the often significant drug discovery experience and knowhow of their scientists (many of whom have Big Pharma backgrounds); others have sought to diversify their product offerings to offer niche technologies or services not yet available from Eastern providers.

Alliances between service providers

Another trend that has become apparent in the past few years is the forging of alliances between service providers with the aim of expanding their offerings to potential clients. Alliances provide a straightforward means of accessing complementary technologies or skills without the expense of investing in new facilities or personnel. A selection of agreements of this type has been compiled in Table 5.

Deals with not-for-profit and/or academic organizations

Whereas commercially oriented companies continue to furnish the bulk of the revenues from contract research providers, deals with not-for-profit organizations have become more common (Table 6) and of increasing size. For instance, BioFocus is eligible to receive US$41M during the five-year collaboration recently signed with the CHDI Foundation (http://www.highqfoundation.org) [30] and the total value of the deal between AMRI and the Cystic Fibrosis Foundation could reach US$23.7M [31].

As well as developing their own drug discovery capabilities [32], academic groups have also begun to draw upon the drug discovery services provided by outsourcing companies. In the UK, the Wellcome Trust's Seeding Drug Discovery Initiative (SDDI) has provided funding for academic groups seeking to

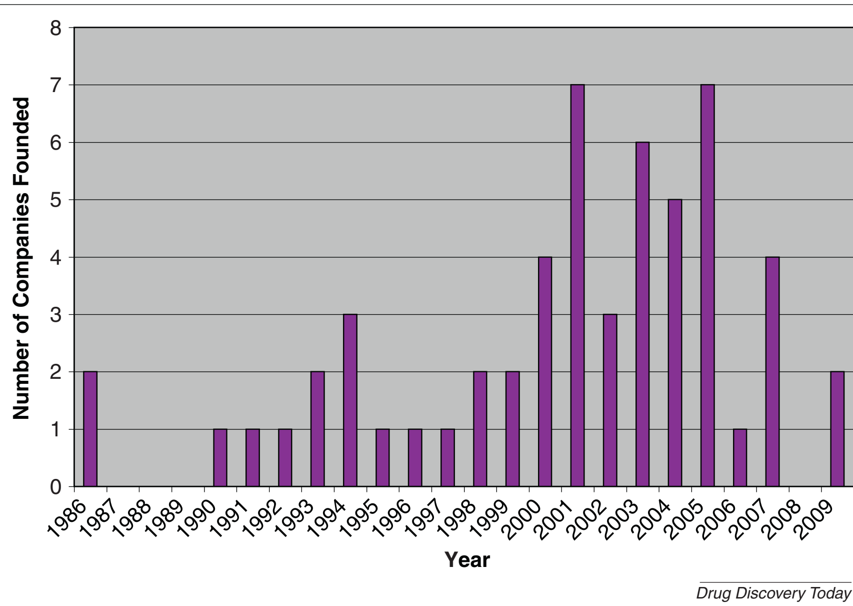

FIGURE 2

Graph showing the number of outsourcing companies formed in each year from 1986 to 2009.

TABLE 4

Number of FTEs employed by selected Asian outsourcing companies.

Company	Number of employees
WuXi Apptec	>4000
ChemPartner	~2000
GVK BIO	>1400

develop new therapeutics in conjunction with service providers [33]. The SDDI was launched in 2005 and funding has recently been extended for a further five years [34]. In the past few years, at least five academic–CRO deals funded by the SDDI have been publicized: two each with Domainex [35,36] and BioFocus [37,38], and one with Sygnature Chemical Services [39]. In the USA, two academic institutions have struck wide-ranging deals with the Indian CRO (contract research organization) Jubilant Organosys to expedite the commercialization of academic discoveries [40,41].

A variety of business models

Given the diversity of companies now involved in the lead optimization outsourcing market (Table 3), it is not surprising that various business models are being pursued by these companies. Differences can be found not only in the internal business models of the service providers but also in the types of deals made with companies seeking services.

Internal business models

Broadly speaking, the service providers can be split into two groups: those following a 'services only' model and those with a 'services plus therapeutics' model. The former is self-explanatory; in the latter case, a company uses the revenues generated by its service business to offset the cost of funding one or more internal drug discovery programmes.

Some examples of companies pursuing a 'services only' model include Sygnature Chemical Services and Peakdale Molecular in the UK, Ricerca Biosciences and Kalexsyn in the USA, and most of the providers from India and China. Some companies with a 'services plus therapeutics' model are listed in Table 7 together

TABLE 5

Examples of alliances between service providers.

Companies involved		Purpose of alliance	Date of announcement	Refs
iNovacia	Provid	Combination of complementary early-stage drug discovery service offerings	17 January 2008	[72]
Chemizon	Crown Bioscience	Combination of chemistry from Chemizon and biology and pharmacology from Crown Bioscience	31 March 2008	[73]
Provid	Acesys	Provid gains access to lower cost chemistry services in China via Acesys	03 September 2008	[74]
BioFocus	ZoBio	BioFocus gains access to ZoBio's NMR-based fragment discovery capability	13 November 2008	[75]
Argenta	PRECOS	Provision of integrated oncology drug discovery services	18 February 2009	[76]
Dalton Pharma Service	ProCitius Research	Allows Dalton to offer low-cost chemistry services in India to clients	11 May 2009	[77]
Argenta	Porsolt & Partners	Provision of integrated pain/CNS drug discovery services	14 May 2009	[78]
BioFocus	OncoDesign	Provision of integrated oncology drug discovery services	27 July 2009	[79]
BioFocus	DiscoveRx	Allows BioFocus to perform screening using DiscoveRx assays and associated cell lines	08 October 2009	[80]
Evotec	DiscoveRx	Allows Evotec to perform screening using DiscoveRx assays and associated cell lines	20 October 2009	[81]
Pyxis Discovery	iThemba Pharmaceuticals	Couples Pyxis' computational chemistry and lead discovery expertise with iThemba's service division to provide medicinal and synthetic chemistry services	09 November 2009	[82]
Prestwick Chemical	Caliper Life Sciences	Combines Caliper's *in vitro* and *in vivo* research capabilities and Prestwick's expertise in medicinal chemistry	19 November 2009	[83]
Sygnature	Cyprotex	Enables a fully integrated discovery chemistry/DMPK service	09 December 2009	[84]
Jubilant Biosys	DiscoveRx	Allows Jubilant to perform screening using DiscoveRx assays and associated cell lines	18 January 2010	[85]
WuXi Apptec	Qiagen	Provision of an integrated single solution for molecular biomarker development, validation and personalized healthcare targets	18 January 2010	[86]
Domainex	Pharmidex	Combination of Domainex's hit-finding and medicinal chemistry capabilities with Pharmidex's *in vitro* and *in vivo* DMPK capabilities	28 January 2010	[87]
Epichem	Industrial Research Ltd	Enables Epichem to offer cGMP manufacture for clinical trials plus expertise in carbohydrate chemistry	23 March 2010	[88]

TABLE 6

Deals between service providers and not-for-profit or academic organizations.

Not-for-profit or academic organization	Service provider	Nature of deal	Date	Refs
CHDI Foundation	AMRI	Five year extension and expansion of collaboration initiated in April 2009 focused on the discovery of new therapeutic agents for the treatment of Huntington's disease	20 April 2010	[89]
CHDI Foundation	BioFocus	Five-year collaboration focused on discovering novel drugs for Huntington's disease. Extends collaboration initiated in August 2005	29 April 2010	[30]
CHDI Foundation	Evotec	Three year extension of collaboration initiated in 2006	14 January 2010	[90]
Medicines for Malaria Venture	Advinus	Optimization of active compounds against key target enzymes that are essential for the survival of the malaria parasite	26 August 2008	[91]
Medicines for Malaria Venture	BioFocus	Identification of new natural products and small molecules that demonstrate anti-malarial activity	16 April 2009	[92]
Medicines for Malaria Venture	SCYNEXIS	Provides MMV with access to SCYNEXIS' proprietary HEOS® drug discovery software platform for use in MMV's research projects	13 May 2009	[93]
Institute for One World Health	BioFocus	High-throughput, cell-based functional screening to identify potential new drugs for the treatment of diarrheal diseases	11 September 2008	[94]
Drugs for Neglected Diseases Initiative	Advinus	Discovery and development of therapies for visceral leishmaniasis	11 October 2007	[95]
TB Alliance	BioFocus	Three-year compound management deal	08 January 2010	[96]
Cystic Fibrosis Foundation	AMRI	Four-year research collaboration aimed at identifying novel treatments that address the core defect in cystic fibrosis	04 October 2007	[31]
Cystic Fibrosis Foundation	BioFocus	Screening of natural products in cell-based assays to identify CFTR modulators	29 November 2007	[97]
The Leukemia & Lymphoma Society	Provid Pharmaceuticals	LLS contracted Provid to supply medicinal chemistry services in support of an LLS-funded grant at the University of Virginia	10 June 2008	[98]
University of Bristol	BioFocus	Wellcome Trust SDDI-funded project to optimize small-molecule inhibitors of protein kinase B activation for the treatment of cancer	15 February 2007	[37]
University of Bristol	BioFocus	Wellcome Trust SDDI-funded project aimed at developing treatments for diabetic neuropathic pain.	16 July 2010	[38]
St George's Hospital Medicinal School (University of London) and The University of Manchester	Domainex	Wellcome Trust SDDI-funded research collaboration seeking improved treatments for asthma	25 June 2009	[35]
Institute of Cancer Research	Domainex	Wellcome Trust SDDI-funded research collaboration seeking improved treatments for breast cancer	07 April 2010	[36]
University of Leicester	Sygnature Chemical Services	Wellcome Trust SDDI-funded research programme aiming to identify new treatments for the serious neurological handicaps associated with invasive pneumococcal diseases	20 May 2010	[39]
Duke University	Jubilant Organosys	Multi-faceted 5 year partnership to expedite translation of discoveries by Duke scientists into clinical therapies	10 November 2009	[40]
University of Alabama at Birmingham and Southern Research Institute	Jubilant Organosys	Exploitation of collective innovation and enabling technologies in the areas of oncology, metabolic disease and infectious diseases	23 November 2009	[41]

with a selection of their therapeutic interests. In almost all cases, these companies will be seeking to partner their programmes with a larger pharmaceutical company before expensive late-stage clinical trials – often much earlier.

External business models

Traditionally, most service providers have operated on a fee-for-service basis (which can be FTE- or task-based) with all intellectual property generated during a collaboration residing with the client

TABLE 7

Information from company websites June 2010 (projects partnered with third parties not included).

Service provider	**Internal drug discovery programmes**
Advinus	Metabolic diseases, inflammatory diseases, neglected diseases
Axxam	BKR1 antagonist (pain), TRPM8 blocker (pain), CB2 agonist (pain), $Na_v1.7$ blocker (pain), $K_v1.3$ blocker (autoimmune disease), I_{CRAC} blocker(autoimmune disease), P2X7 blocker (pain/autoimmune disease), GPR120 agonist (metabolic disease)
AMRI	Tubulin inhibitors (cancer), MCH-1 antagonists (obesity), 5-HT_6 modulators (obesity, cognition), 5-HT3 partial agonists (irritable bowel syndrome), GlyT1 inhibitors (schizophrenia)
Evotec	$P2X_7$ antagonists (inflammatory disease), histamine H3 antagonists (cognition, narcolepsy), bradykinin B1 antagonists (pain, inflammation), $P2X_3$ and $P2X_{2/3}$ antagonists (pain, urological disease)
Galapagos (parent of BioFocus & Argenta)	Nanocort (acute multiple sclerosis and rheumatoid arthritis flares), GLPG0187 (cancer metastasis), GLPG0259 (rheumatoid arthritis), selective androgen receptor modulator (cachexia, Duchenne muscular dystrophy), GPR3 (Alzheimer's disease), disease-modifying therapeutics for cystic fibrosis
Scottish Biomedical	PDE11 inhibitors (schizophrenia), EPAC activators (Alzheimer's disease), PDE4 inhibitors (inflammation), dual PDE3/4 inhibitors (asthma), tyrosine kinase inhibitor (cancer), 11β-HSD1 inhibitors, PTP-1B inhibitors
SCYNEXIS	Cyclophilin inhibitors (hepatitis C, infectious/inflammatory diseases)

company. Such agreements minimize the risk for the service providers, but they also exclude them from sharing in the benefits if compounds that are discovered during the project progress to later stages of drug discovery or to the market. More recently, 'risk-sharing' has become an alternative mode of structuring outsourcing deals. In this type of agreement the service providers agree to share some of the risk involved in the project and typically charge a reduced price for their services in return for a share of the later stage, success-based rewards [42]. An example of such a shared risk–reward arrangement is the collaboration between AstraZeneca and Jubilant, announced in May 2009 [43]. Under the terms of this agreement Jubilant aims to deliver a steady stream of discovery programs to AstraZeneca. Jubilant will be eligible to receive research funding spanning an initial five-year period. In addition, AstraZeneca will also pay Jubilant success-based development milestones, as well as royalties based on successful global commercialization of any of the compounds. For its part, AstraZeneca will own the compounds developed under the collaboration with worldwide development and commercialization rights.

An innovative model for collaboration was announced by Peakdale Molecular and Pfizer (http://www.pfier.com) early in 2010 [44]. Under the terms of this agreement Peakdale is building a team of 50 chemists on-site at Pfizer's UK research centre in Sandwich, Kent. This facility will provide not only on-site chemistry resources for Pfizer but also a resource for other developing companies in the vicinity.

Concluding remarks

At the present time, the service sector is flourishing because it is taking increasing proportions of R&D out of Big Pharma and biotech, even though the overall amount of R&D is probably dwindling, at least within pharma. The sentiment for outsourcing has grown as a means to improve R&D productivity, even while doubts grow about the value of R&D as a whole (particularly small molecule as opposed to biological R&D). The greater provision of the lead optimization phase by outsourced companies is an important trend, because it represents the heart of the value creation process in pharmaceutical R&D. Its move implies not only a greater confidence on the part of the clients in the quality of the services provided but also a greater confidence in the business relationships, because trust and confidentiality are of the utmost importance.

Overall, the market for outsourced drug discovery services appears to be robust with an optimistic outlook, even in the face of the current economic troubles [45]. Although Big Pharma has been cutting back on R&D [46] and laying off thousands of employees [5], for at least some of the workforce a refuge has been found in the CRO industry [47,48]. Thus, in recent times, outsourcing companies have very much been the relatively tranquil 'eye' at the centre of the current storm within the pharmaceutical industry. A storm is perpetually on the move, however, and those wishing to shelter at its centre must follow its progress and react to its vicissitudes. For the same reasons, the providers of drug discovery services cannot afford to become complacent or static, but must be ready to adapt to take advantage of an ever-changing market.

Conflict of interest statement

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