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Outsourcing chemical synthesis in the drug discovery process

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The positive effects of outsourcing chemical synthesis are enhanced if the provider offers, as the strategic partner, unique expertise and complements the existing internal competencies of pharmaceutical companies. The emerging cooperation model of leased competence offers additional access to high-level specialist knowledge: external service providers are temporarily integrated into internal R&D teams and can support R&D projects flexibly and quickly. Practice examples show that this cooperation model supports the efficient realization of milestones and, in the long-term, helps to build up a high internal competence level, especially in small pharmaceutical companies.

Introduction

In the pharmaceutical industry, innovation is recognized as the cornerstone for competitive advantage and is fostered by strong investments in biological and chemical expertise [1]. Cockburn *et al.* [2] have shown that drug discovery productivity is dependent on the internal organization of R&D. For these reasons, pharmaceutical companies are being forced to reassess their R&D operations – including outsourcing activities [3,4]. Outsourcing, traditionally thought of as a short-term strategy to reduce costs or to provide additional capacity, is now being considered as the best way to increase performance in pharmaceutical R&D by levering core competencies [5].

Because outsourcing R&D also bears potential risks as a result of project complexity and loss of flexibility, the potential value of R&D outsourcing arises as a key question for R&D managers – especially because outsourcing does not automatically improve competitiveness. A good example that demonstrates the increasing outsourcing activities is chemical synthesis, which includes all activities for the synthesis of chemical compounds within the drug discovery and development process. Whereas chemical synthesis in drug discovery primarily refers to the large-scale synthesis of lead compounds including lead optimization [6], in drug development the topic focusses on the synthesis of an optimized chemical compound for preclinical (e.g. pharmacology and toxicology) and clinical trials.

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This article will discuss how chemical synthesis is offered by specialized service providers within the drug discovery process of pharmaceutical companies (the term pharmaceutical industry mentioned in the paper also includes the biotechnology industry). After a short evaluation of the outsourcing market within pharmaceutical R&D, the discussion will focus on the behaviour of pharmaceutical companies as customers (e.g. requirements of pharmaceutical companies depending on their size) as well as service providers as vendors (e.g. service offerings and established and/or emerging cooperation models). The intention of this article is not to describe the service companies in the chemical synthesis area but instead to demonstrate the trends and mechanisms of the outsourcing decisions.

The empirical background is mainly based on interviews with managers and experts of 19 pharmaceutical companies and 12 pharmaceutical service providers between 2007 and 2008 (Fig. 1). The interviews were conducted in different rounds where each interviewee was questioned in sessions of approximately 60 min and an interview guideline with a reference set of questions was developed to secure the comparability of the answers and to leave enough room for spontaneous answers, which gave a semi-structured nature to the interviews. Additionally, in 2008, the outsourcing behaviour of the interviewed companies and 61 additional pharmaceutical and biotechnology companies was analysed through desk research using different public sources (e.g. business databases) and company disclosures (e.g. websites

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Interviews: pharma companies

- Aeterna Zentaris
- Bayer Schering
- Bionorica
- Böhringer Ingelheim
- Eisai
- GlaxoSmithKline
- Lichtwer Pharma
- Meda
- Merck Serono
- Merz
- Novartis
- Nycomed
- Orion Pharma
- Pfizer
- Roche
- Sanofi-Aventis
- Speedel
- Stada
- Wyeth

Interviews: service providers

- Accovion
- Avecia
- Clariant
- Dottikon Exclusive Synthesis
- DSM
- Dynamit Nobel/ Novasep Synthesis
- Eurofins Medigenomix
- Evonik Degussa
- Focus Clinical Drug Development
- Genedata
- Lonza
- Solvias

Additional analysis: pharma/biotech companies

- 4SC
- Actelion
- Addex Pharmaceuticals
- Alsachim
- Amgen
- Antisense Pharma
- Apogenix
- Apogepha Arzneimittel
- Astex Therapeutics
- AstraZeneca
- Basilea Pharmaceutica
- Berlin Chemie
- Biofrontera Pharmaceuticals
- BioGenerix
- Biovertis
- Bristol Myers Squibb
- Celgene
- Cellzome
- ChemBridge
- Coley Pharmaceuticals
- Decode
- Develogen
- Dolorgiet
- Engelhard Arzneimittel
- ESBA Tech
- Evotec
- GlaxoSmithKline
- Grunenthal
- Heidelberg Pharma
- Idenix
- Janssen Cilag
- Jerini
- Johnson & Johnson
- Lilly Pharma
- Lipideon Biotechnology
- Medice
- Medigene
- Micromet
- Midas Pharma
- Mologen
- Morphochem
- Morphosys
- MSD Sharp & Dohme
- Neurotune
- Noxxon
- Oncalis
- OSI Prosidion
- Ratiopharm
- Respiratorius
- Sandoz
- Santhera Pharmaceuticals
- Sirtris Pharmaceuticals
- Solvay Pharmaceuticals
- Spirig Pharma
- Stada Arzneimittel
- Syncom
- Takeda Pharma
- Tocris Bioscience
- U3 Pharma
- Ugent
- Wilex

Drug Discovery Today

FIGURE 1

List of companies interviewed and analysed between 2007 and 2008 for this article.

and press releases). Furthermore, telephone calls with individuals responsible for chemical synthesis clarified open questions, which could not be answered using other sources. The complete research methodology including the evaluation of the market data as well as the discussion of service offerings and cooperation models has already been published elsewhere [7].

The outsourcing market for chemical synthesis

Outsourcing activities are well established along the whole pharmaceutical R&D value chain. In total, all external service providers in pharmaceutical R&D had a turnover of around US$ 30 billion in 2008 and a market growth between 2.5% and 10% in the period from 2008 to 2010, depending on the specific area (Fig. 2), compared with an average growth of around 6% in pharmaceutical R&D [8]. The worldwide market volume of chemical synthesis services was US$ 2 billion in 2008 and shows a growth rate of 10% per year – making this service one of the fastest growing outsourcing segments in the area of pharmaceutical R&D. Chemical synthesis includes activities in the discovery phase (discovery chemistry to synthesize and optimize lead compounds) and development phase (development chemistry to provide chemical substances for the clinical trials) but no production activities and process development (i.e. the development of a technical synthesis route, which is shown separately). Pharmacology and toxicology, for example, also showed a market volume of US$ 2 billion but a growth rate of only 2.5%. Here, pharmacology means safety pharmacology that is performed during preclinical development and not activities during lead optimization.

The drive towards outsourcing has led to the emergence of numerous service providers focussed on chemical synthesis, also partly covering process development and small-scale production. One major trend is that service providers from Asia (especially China and India) are showing stronger growth and gaining global importance owing to a flourishing pharmaceutical industry and cost advantages compared with competitors in Europe and North America [9,10]. Also, Asian providers are increasingly acquiring service providers in Europe and North America (e.g. the acquisi-

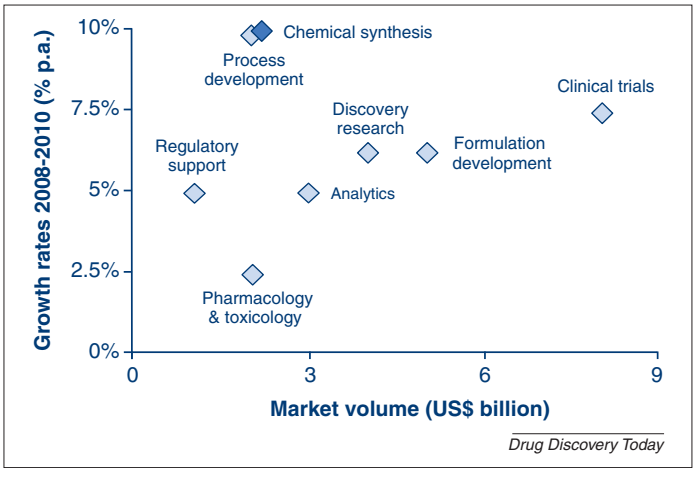

FIGURE 2

Market volume of external services in pharmaceutical R&D during 2008 and growth rates 2008–2010.

tion of Carbogen Amcis and SynProTec by Dishman Pharmaceutical & Chemicals) to get a foothold in these markets.

Requirements of pharmaceutical companies

When analysing requirements, the size of the pharmaceutical companies is an important factor. Most large and mid-size pharmaceutical companies have their own in-house capacities for chemical synthesis. These companies outsource services not only to reduce costs (e.g. reducing fixed costs or reducing people on the payroll) nor only to acquire additional capacity but also, in some cases, to obtain additional, external synthesis know-how (e.g. special catalytic expertise) not available in-house or otherwise too expensive, should it need to be built up internally [11]. Therefore, their major interests and requirements in cooperating with service providers include the following aspects.

- Clear competence profile of the service provider focussed on specific areas with leading edge know-how and equipment while adhering to the highest possible technical standards for discovery chemistry.
- Highly standardized cooperation model covered by general agreements with precise definition of the ownership of intellectual property.
- Familiarity with the specific requirements of large and mid-size pharmaceutical companies.

Small companies (e.g. start-ups) have very different needs and, in contrast to large and mid-size companies, often depend on external services [12]. They see outsourcing as an effective method to capture capacity and expertise without investing much money in resources in-house. In particular, many start-ups lack experience and expertise around chemical synthesis, which consequently forces them to rely on external service providers. In doing this, they have the following requirements.

- Lean and flexible capacities on the side of the providers, easily adaptable to smaller demands.
- Full service range and know-how around chemical synthesis with capabilities for the support of project management.
- Flexible and transparent cost structures, similar or equivalent to their own in-house structures to avoid additional administrative resource burdens.
- Familiarity with the specific requirements of small pharmaceutical companies.

Service offerings of chemical synthesis service providers

One major question for service providers as well as pharmaceutical companies is: how should the optimal service offering look? Taking a closer look at the market, there are three typical service-offering models for chemical synthesis services within the drug discovery process from target identification and validation through to hit identification, lead identification and lead optimization, as well as preclinical development as the first step of the development phase (Fig. 3). The analysis of the interactions between service provider and pharmaceutical company shows the advantages and disadvantages of the different service offerings. Pharmaceutical companies have to choose between these alternatives depending on their specific situation and use a systematic evaluation of these options based on company-specific criteria.

Service offering 1: late-stage drug discovery capabilities

The pharmaceutical company outsources synthetic chemistry work within the later drug discovery and preclinical development process for which in-house resources are not available, or if it is less expensive to do so. Interface is the chemical structure written on paper that is given to the synthesis service provider who synthesizes chemical substances for further lead optimization activities within the pharmaceutical company or in larger quantities for preclinical testing. Laboratory scale route finding is included but not process development for technical scale production processes.

The synthesis service provider requires almost no medicinal chemistry expertise and can concentrate on supporting the pharmaceutical company with inexpensive and reliable capacity. It requires only a simple interface to the customer and provides a high degree of flexibility. It is the approach taken should the pharmaceutical company have sufficient in-house resources for the early drug discovery process and would like to add flexible and inexpensive external synthesis capacity for later stages. For example, large pharmaceutical companies, such as Novartis or Roche,

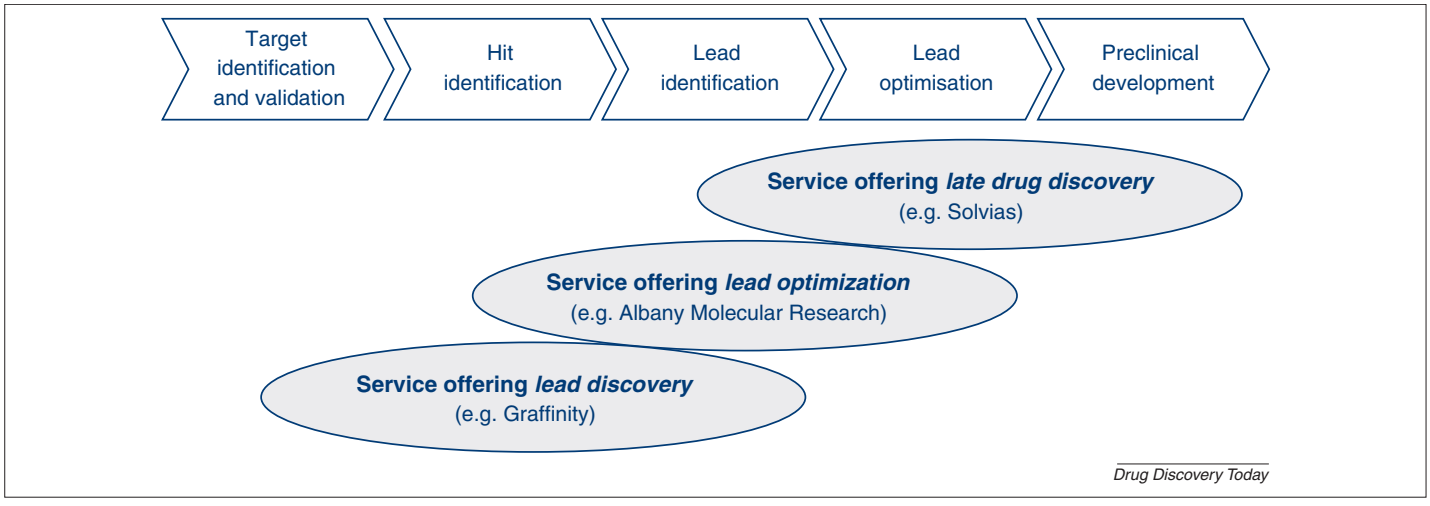

FIGURE 3

Options for service offerings in the field of chemical synthesis.

have a preference for this service offering because it combines high efficiency and flexible capacities.

Service offering 2: lead optimization

The service provider synthesizes compounds for screening libraries or covers parts of the lead optimization process. This requires an intensive information exchange between pharmaceutical company and chemical synthesis provider, for example for validating results along the lead optimization process. The synthesis service provider needs medicinal chemistry expertise, and works at a higher cost level. Involving the service provider in the screening process broadens the interfaces and the need for information exchange between pharmaceutical company and service provider, which increases complexity. This is particularly true regarding the contractual agreements between the two companies, which are more complex because of the intellectual property issues and possible payment of royalties. With this option small and mid-size pharmaceutical companies in particular, such as Lundbeck, can speed up the whole drug discovery process, because additional external know-how is made available.

Service offering 3: lead discovery

In this example, the pharmaceutical company outsources early stages of the drug discovery process, for example hit-to-lead identification. The service provider has research teams covering biological, medicinal and chemical expertise and independently creates hits and leads that are transferred to the pharmaceutical companies for further development. As with the lead optimization service offering, this service requires an intensive information exchange between pharmaceutical company and service provider (e.g. for linking hit identification to validated targets of the pharmaceutical company).

This approach can be recommended should in-house resources not be available or if the company is experiencing time and capacity constraints; and it is especially appealing for small biotech companies without, or with very limited, expertise and resources in chemistry. This offering needs deep trust at all levels between companies concerned because crucial information about targets and lead compounds is shared outside the company before patent applications have been filed.

Established cooperation models

Normally, employees at pharmaceutical companies think intensively about the optimal supplier structure and suitable cooperation models if they do decide to outsource services. In the area of chemical synthesis three typical cooperation models between pharmaceutical companies and service providers have been established.

- *Price competition*: a long list of service providers is systematically put into competition to secure the lowest purchasing prices. This model serves to achieve the demand for the most cost-efficient fulfillment, for example the purchase of standardized synthesis services for routine tasks (e.g. first quantities for toxicology studies). It can be applied successfully only if the outcome can be easily measured.
- *Project selection*: the selection of service providers is based on a project-by-project basis from a core list of pre-selected service providers. The service providers are engaged according to the fit of their core competence to the specific project requirements (e.g. the choice of the best-fitting synthesis provider based on special synthesis knowledge).
- *Strategic partnership*: a handful of preferred service providers are given the preferential right of first refusal. A framework contract covers all the relevant aspects such as compensation, quality control, intellectual property and project management (e.g. contracts with service providers to deliver new hits or leads).

Analysing the relevance of these cooperation models for different outsourcing areas shows that the most frequently used cooperation

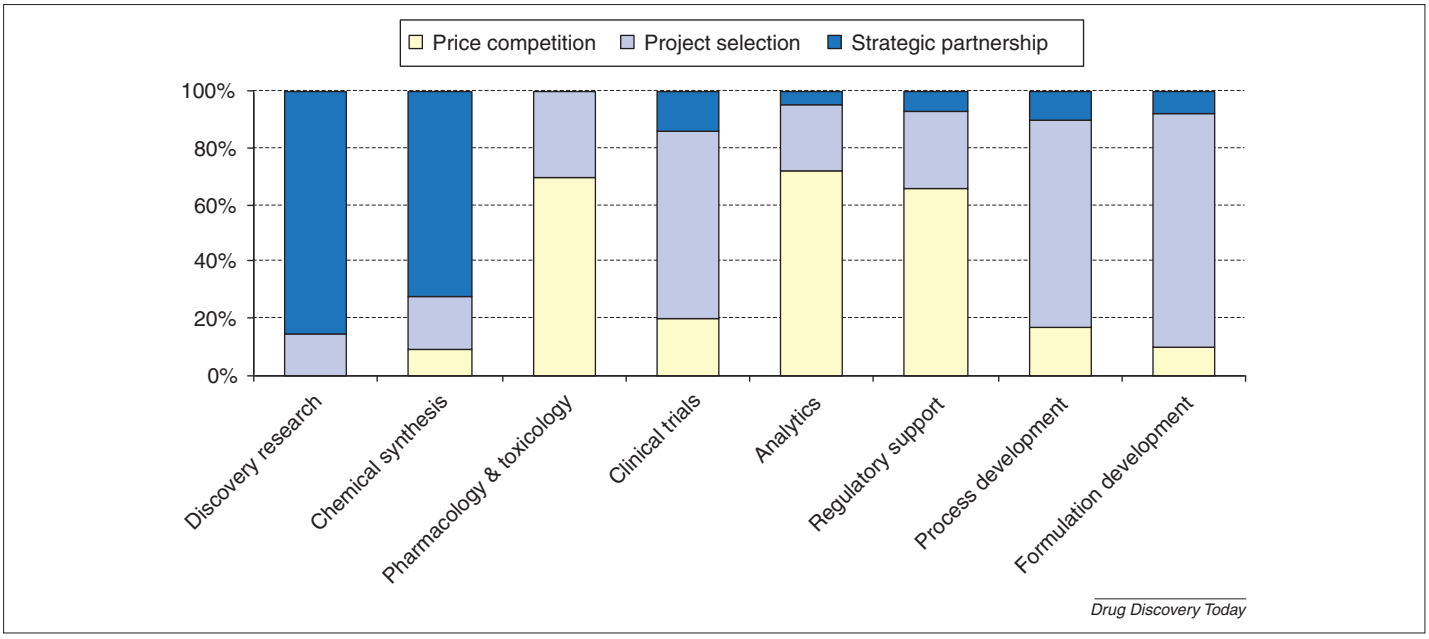

FIGURE 4

Relevance of the established cooperation models for outsourcing different R&D activities.

model is project selection (Fig. 4). The preferred partnership model is mainly used in the areas of discovery research and chemical synthesis. Price competition is mainly used for services in the areas of pharmacology and toxicology, analytics, regulatory support and logistics – fields where the deliverables are easy to control.

Focussing on chemical synthesis, the correlation of service offering and company size of the customer with the cooperation model gives interesting insights (Fig. 5 – on the left is the overall picture and on the right the details for each company size resulting from the interviews). Price competition is mainly used by large pharmaceutical companies for late-stage drug discovery and less for lead optimization, as well as occasionally by mid-size companies. The most important cooperation models are project selection and strategic partnership; the former is used more for late-stage drug discovery and/or lead optimization service offerings and the latter more for lead optimization and/or lead discovery. The reason is that these models (especially strategic partnerships) offer a high quality level and reduce management complexity caused by proven working relationships and general contract agreements. Therefore, strategic partnerships have a dominant position for offering lead discovery within large companies.

Leased competence as an emerging cooperation model

An emerging cooperation model, which is only seen in the context of small companies and lead optimization and/or lead discovery service offerings, is leased competence (Box 1 shows the leased competence model using three practice examples of lead discovery in Switzerland and the USA). External experts are integrated into internal R&D teams for a defined period to support R&D projects within pharmaceutical companies flexibly and timely. The hired experts use either their own in-house infrastructure or facilities inside the customer's organization. This could avoid the parallel installation and maintenance of research infrastructure. A project management team, for which the customer is responsible, helps to achieve good coordination and intensive information transfer. It is important to set up specific communication practices so that all parties know how the project is proceeding, when they hit a problem and how it will be corrected so that the schedule is being met. This addresses pharmaceutical industry concerns of minimizing third party activities for critical path activities through highly standardized processes.

The leased competence model forces both partners to think and act in a much more result oriented way than within existing organizational boundaries. Interfaces between customer and service provider can be reduced and redefined. This represents a switch from isolated service offerings to an integrated platform of support within the customer's processes and structures. The result is a skilful combination of in-house operations and outsourcing. Highly standardized cooperation contracts, as well as general collaboration procedures, keep additional overhead capacities for legal aspects, controlling and outsourcing management very limited. Therefore, and because of the clearly defined ownership of intellectual property, such a model enables high efficiency and flexibility. The success-based arrangements between synthesis providers and customers reflect this strong partnership and create a win–win situation: the pharmaceutical company can

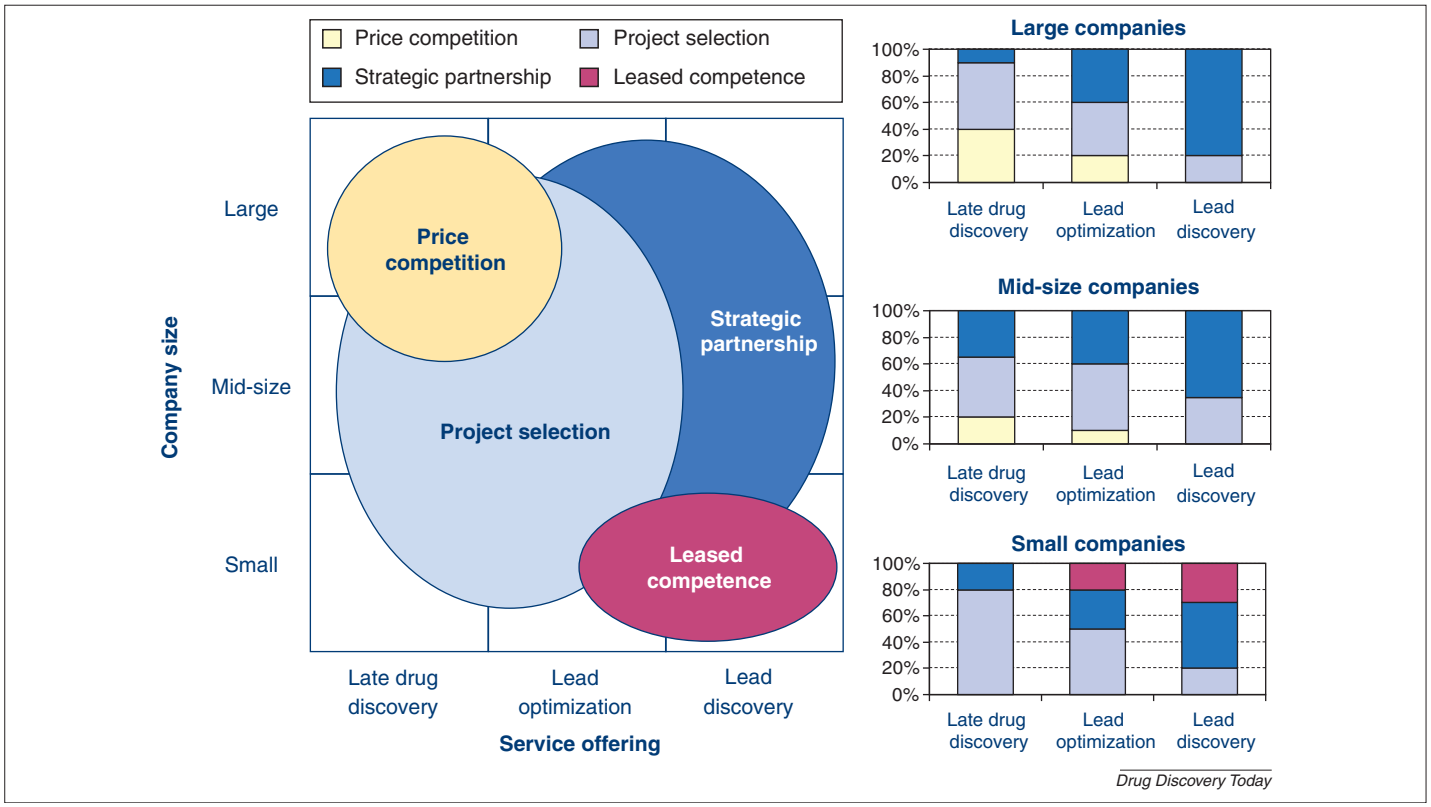

FIGURE 5

Used cooperation models within chemical synthesis outsourcing depending on service offering and company size of the customer.

BOX 1

Practice example 1

A biotechnology company develops new drug candidates with a highly sophisticated computer modelling approach. For the further development of their computer-generated leads they needed the chemical compounds in mg quantities. Because management wanted to move their compounds as quickly as possible to the next development stage they decided to outsource fully their lead synthesis activities to a specialized chemical synthesis provider. The internal build-up and maintenance of a broad synthesis technology base was not realistically possible. By using the experience of an existing and well-established synthesis team, the biotechnology company benefited from immediate access to synthesis capacity resulting in a much speedier development of the drug candidates. Even while only paying for a small number of full-time equivalents, the biotechnology company had access to knowledge and experience of ~60 chemists as well as highly specialized synthesis technology and equipment. The attention of the management could focus on core competences, because the synthesis team was fully managed by the synthesis service provider and only one project leader within the biotechnology company was in contact with that individual.

Practice example 2

A start-up ordered lead substances from a service provider for further biological screening to develop drug candidates. This was not done in the traditional way, by ordering a certain number of molecules with set characteristics and delivery dates, but by leasing experts from the service provider generating potential leads in the laboratories of the service provider under the guidelines and control of the customer. The chemical experts from the service provider worked in tight cooperation with the customer's biological experts so that additional internal competence was built up. The customer directly received every new lead candidate for biological screening. Only if the lead candidate showed the intended response in the biological assay were all essential data for further development (e.g. 'cook book', analytical data and chemical instructions) released, becoming the customer's intellectual property. Therefore, the transfer of intellectual property was well defined and acceptable for both parties. Two subproject managers, one from the customer and one from the service provider, were nominated to the project management team under the customer's control. Because the project team operated as the 'backbone' for the whole development project, reporting lines were not cut on the customer's side and no additional project management was required. This ensured that milestones were efficiently realized.

Practice example 3

A spin-out of an international pharmaceutical company, with only project management in-house, initially relied on outsourcing partners to move forward with a drug development project. The challenge was to develop a cost-effective synthesis route for the new chemical entity. The spin-out had the flexibility and risk tolerance to pursue unconventional approaches to the problem that the parent company's more-conservative internal R&D department had rejected as too risky. The spin-out's strength compared to its parent was the flexibility to select the most suitable partner for solving the synthesis problem. A chemical synthesis provider supplied special expertise in chemical synthesis and catalysis technology and follow up with analytics. With this combination of flexibility, risk tolerance and collaboration the project moved through development quickly. The spin-outs rapidly brought a product, which the parent company had failed to develop in-house, to commercialization, and did so without exhausting internal R&D resources. This case is a good example of how collaborations allow for rapid deployment of a flexible combination of skills, resources and expertise, thus accelerating the development process.

reduce its own risk in the discovery process and the chemical service provider can strengthen the partnership.

Concluding remarks

Outsourcing leads to negative effects when used only as a cost reducing strategy to improve short-term performance. The consequence could be the loss of internal knowledge and expertise as well as higher total costs in the long-term. The positive effects of outsourcing are enhanced if the supplier is used to supplementing existing core competencies (i.e. to free resources to invest in higher internal capability). Nevertheless, some aspects, such as perceived (or real) difficulties to transfer experience and issues with the intellectual property situation, are seen as major obstacles to outsourcing chemical synthesis.

Service providers should react to the concerns of pharmaceutical customers with a best practice approach that includes the following aspects.

- *Complexity and efficiency*: definition of highly standardized and transparent processes and contracts. Service providers should establish them together with their customers.
- *Cooperation and communication*: local presence with project management in close vicinity to the pharmaceutical company. Offshore lab resources alone (e.g. in China or India) are not sufficient in most cases.
- *Costs and intellectual property*: establishing full cost transparency (e.g. fixed prices attached to milestones) and cooperation agreement leaving all crucial intellectual property at the pharmaceutical company.
- *Flexibility and quality*: high flexibility regarding project execution with stringent quality control by the customers together with the service provider.
- *Exclusivity and secrecy*: clear and transparent rules regarding the engagement in projects of direct competitors as well as the highest standards regarding secrecy.

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