Gunter Festel

Getting access to new technologies

How chemical synthesis outsourcing can tweak the process of drug discovery

GUNTER FESTEL*, RUTH MAAS, MARTIN BELLOF

*Corresponding author

Autodisplay Biotech GmbH, Lifescience Center, Merowinger Platz 1a, D-40225 Düsseldorf, Germany

KEYWORDS

Outsourcing, drug discovery, chemical synthesis, biocatalysis, enzymes, cytochromes.

ABSTRACT

Outsourcing has traditionally been thought of as a short-term strategy in order to cut back expenses or to provide a company with additional capacities. This understanding has changed throughout the last few years. Today, outsourcing is seen as a method to increase performance in pharmaceutical R&D via leveraging of core competencies. Service providers are able to provide timely and efficient solutions to any given problem along the whole value chain of pharmaceutical R&D. Outsourcing enables pharmaceutical companies to gain access to new technologies such as biocatalytical reactions. Therefore, three very distinct co-operation models have been established.

INTRODUCTION

In order to improve their competitive position, pharmaceutical companies permanently reassess their mode of R&D operations, including outsourcing activities (1, 2). These activities are very common along the whole value chain of pharmaceutical R&D (Figure 1). Traditionally believed to be a short-term strategy to cut down expenses or to provide additional capacities, outsourcing today is being considered to enhance performance of pharmaceutical R&D through leveraging of core competencies (3).

In the field of pharmaceutical R&D, one of the fastest growing segments for outsourcing activities is chemical synthesis.

There, outsourcing can be used in the discovery phase (discovery chemistry to synthesise and optimise lead compounds) and the development phase (development chemistry to provide chemicals substances for clinical trials).

In 2008, the worldwide market volume of chemical synthesis services was US$2 billion, growing at a strong rate of 10% per year (4). In total, all external service providers in pharmaceutical R&D had a turnover of around US$ 30 billion in 2008.

A pharmaceutical industry's shifting focus towards the use of outsourcing has resulted in a growing number of service providers focused on chemical synthesis. These companies also partly cover process development and small-scale production. Strongly growing service providers from Asia (especially China and India) are gaining importance on a global level – a major trend, which is caused by a flourishing pharmaceutical industry and cost advantages in relation to European and North American competitors. In order to get a foothold in these markets, Asian service providers have been increasing the number of acquisitions in Europe and North America. But outsourcing does not per se lead to an improvement of a company's competitive position. Moreover, project complexity and a loss of flexibility bear numerous risks. That is why pharmaceutical companies need to assess the potential value of R&D outsourcing on a case-by-case basis, always taking the individual circumstances into account (5). If they decide to outsource services, they need to carefully plan the ideal supplier structure as well as suitable co-operation models.

REQUIREMENTS AND CO-OPERATION MODELS

In most large and medium-sized pharmaceutical companies, in-house resources for chemical synthesis are available. In these cases, an outsourcing of services does not only have the intention to reduce costs (e.g. reduction of fixed costs or reduction of the number of employees on payroll) or to acquire additional capacity.

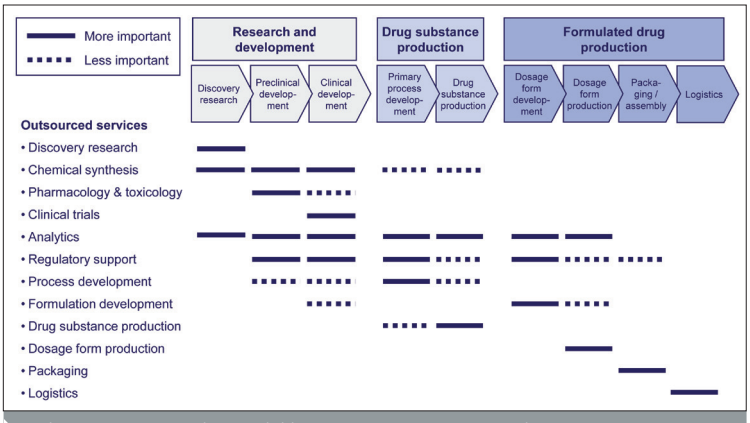

Figure 1: Outsourcing activities along the pharmaceutical R&D and production value chain

It is further aiming to enable the company to access additional, external synthesis know-how (e.g. special catalytic know-how), which is not available in-house or too expensive to build up internally.
Pharmaceutical companies prefer service providers with a clear competence profile and focus. In addition they expect leading-edge know-how and equipment while adhering to the highest possible technical standards for discovery chemistry. Another requirement is a highly standardised co-operation model framed by general agreements that precisely define the ownership of intellectual property.
In contrast to large and mid-sized companies, small companies have very different needs. In most cases, a lack of experience and expertise around chemical synthesis forces them to rely on external service providers. Outsourcing is then used as an effective method to access capacity and expertise without having to invest large amounts of money in in-house resources at the same time. Consequently, small companies usually need the full service range and know-how around chemical synthesis with capabilities for the support of project management. Service providers should also be able to easily adapt to smaller demands. In order to avoid administrative resource burdens, service providers should use flexible and transparent cost structures, similar or equivalent to small companies' in-house structures.
Three co-operation models between pharmaceutical companies and service providers have been established in the field of chemical synthesis: price competition, project selection and strategic partnership. *Price competition* aims to secure the lowest purchasing prices. A long list of service providers is systematically put into competition. The model should be applied whenever the most cost-efficient fulfilment is needed and only works, if the outcome can be easily measured.
An example for the use of this model is the purchase of standardised synthesis services for routine tasks (e.g. first quantities for toxicological studies). *Project selection* means that the selection of a service provider is based on a project-by-project basis. A list of pre-selected service providers can be used.
The service provider, whose core competencies meet the requirements for a specific project the most, will then be chosen (e.g. the choice of the best-fitting synthesis provider based on special synthesis know-how).
In a *strategic partnership* a pharmaceutical company grants few preferred service providers the preferential right of first refusal. In that case, framework contracts cover all relevant aspects such as compensation, quality control, intellectual property situation and project management (e.g. contracts with service providers to deliver new hits or leads).
Analysing the relevance of these co-operation models for different outsourcing areas shows that the most often used co-operation model is project selection. The preferred partnership model is used mainly in the areas of discovery research and chemical synthesis.
Price competition is mainly used for services in the area of pharmacology and toxicology, analytics, regulatory support and logistics, fields where the deliverables are easy to control.
Leased competence is an emerging co-operation model, which is solely used by small companies and service providers offering lead discovery or lead optimisation.
External experts are integrated into the pharmaceutical company's internal R&D teams for a defined period of time, in order to support R&D projects in a flexible and timely manner (Figure 2). Hired experts then either use their mother company's in-house infrastructure or facilities inside the customer's organisation. Thus, parallel installation and maintenance of research infrastructure can be avoided.

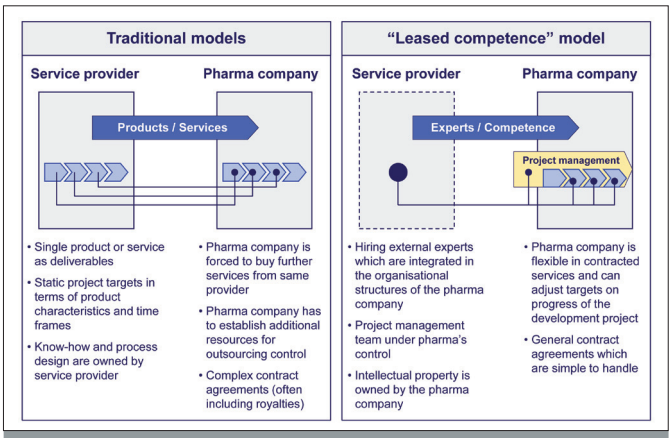

Figure 2: "Leased competence" model as outsourcing concept

The customer provides a project management team, which is responsible for coordination and intensive transfer of know-how. Specific communication practices are set up, enabling all parties to monitor the project's progress. This allows the elimination of problems as they emerge and in return ensures the meeting of deadlines.
In this setup, the pharmaceutical industry's concerns of minimising third party activities for critical path activities through highly standardised processes are being addressed.
In a leased competence model, both partners involved are forced to think and act in a way that is more result-oriented than within existing organisational boundaries. For customer and service provider, points of contact can be reduced and redefined, enabling a switch from an isolated offering of services to an integrated platform of support within the customer's processes and structures. This results in a skilful combination of in-house opertions and outsourcing.
If highly standardised co-operation contracts as well as general collaboration procedures are being used, overhead capacities for legal aspects, controlling and outsourcing management can be held very limited.
Therefore, and because of the clearly defined ownership of intellectual property, such a co-operation model enables high efficiency and flexibility. Success-based arrangements between synthesis providers and pharmaceutical customers reflect this strong partnership and create a win-win-situation: the pharmaceutical company can reduce its own risk during the discovery process, while the chemical service provider can strengten the partnership.

ACCESS TO NEW TECHNOLOGIES THROUGH OUTSOURCING

Outsourcing can also give access to new technologies to synthesize compounds. Especially enzyme catalysis will be a key technology in the future as the recent technological breakthrough has led to an enormous boost in the number of available enzymatic systems (6).
Biocatalysis today is a standard technology for the production of chemicals. The increasing knowledge of enzyme reactions in non-aqueous solution leads to a broadened spectrum of reactions and a greater number of substrates. Due to new developments in reactor and process design, the process efficiency has improved.
Thus, both novel enzymatic systems and process optimisation has led to successful applications of biotechnological processes within the drug discovery process.
Most products of biocatalytic processes are chiral fine chemicals. Hydrolases and redox biocatalysts are the most prominent classes of used enzymes (7).

The greatest impact for biocatalysis still remains on the pharmaceutical sector where the regio- and stereoselective properties of enzymes enable difficult syntheses.
The ability of biocatalysts to reach their full potential in pharmaceutical synthesis will require time- and cost-reducing techniques. This includes miniaturisation, enabling parallel experiments with small amounts of compounds, resulting in huge savings in costs and experimentation time (8). Micro-scale technologies will have an impact on accelerating screening and process development timelines. Such methods are well established for chemical synthesis but now it is crucial that these be developed for biocatalysis.
Since it is more difficult to replace a chemocatalytical step late in a process, the implementation of a biocatalytical step is most promising early in process development. This requires that the speed of the development of a biocatalytical step has to be comparable to that of chemical synthesis (9).
Although enzymes have demonstrated their potential in numerous applications, so far only relatively few reactions have been able to be established. This is due to several factors. First, the purification of enzymes still represents a significant cost factor and secondly, the purified enzymes often exhibit low stabilities, limiting their use in industrial processes. Though it was possible to improve the cost effectiveness of some enzymes by employing different immobilisation techniques, there is still need for improvement, since some enzymes do not tolerate the necessary procedures. By using new approaches, such as surface display systems, some of these disadvantages can be circumvented. Surface display means a protein expression system in which the enzymes are no longer located inside a cell (e.g. bacteria, yeast), but are displayed on the cell surface e.g. of bacteria such as Escherichia coli (E. coli). These surface display systems have several advantages compared to conventional intracellular enzyme production. Displayed enzymes exhibit a higher stability in comparison to the free enzymes and furthermore, the free accessibility of the enzyme for its reaction partner makes purification unnecessary.
A good example are cytochrome P450 monooxygenases (P450s). They represent a huge family of heme containing monooxygenases currently consisting of more than 4000 members which are ubiquitously distributed in nature (10, 11). P450 monooxygenases are involved in the synthesis of steroids, vitamins and secondary metabolites.
They also play a pivotal role in the biodegradation of xenobiotic compounds and are mainly responsible for the human metabolism of drugs, in which five P450s are involved in around 95 % of P450 derived drug metabolism (12). This class of enzymes possesses the extraordinary ability to introduce atmospheric oxygen into non-activated carbon-hydrogen bonds in a regio- and stereoselective way.
The basic reactions catalysed by P450s in the presence of oxygen, the cofactor NAD(P)H and a corresponding electron transfer system include hydroxylations, oxygenations, epoxidations, dealkylations and the cleavage of carbon-carbon- bonds (11).
However, in recent years a number of more complex P450 related reactions have also been described and these include chlorine oxygenation, aromatic dehalogenation, dimer formation, ring coupling, ring formation, ring contraction and oxidative aryl migration (12). Since P450s catalyse valuable reactions on a vast variety of substrates, they have a great biotechnological impact.
Despite their impressive synthetic potential, these enzymes have, however, so far enjoyed very limited biotechnological use due to their complexity, instability and in most cases, low catalytic activity (13).

CONCLUSION AND RECOMMENDATIONS

If outsourcing is solely used as a strategy in order to improve short-term performance through a reduction of expenses, it will lead to negative effects. The analysis of pharmaceutical companies' outsourcing in chemical synthesis proves that loss of internal know-how and expertise and higher total expenses in the long-term can be crucial consequences. Thus, pharmaceutical companies have to choose outsourcing strategies dependent on their specific situation. In addition they need to systematically evaluate all options, based on company specific criteria.
Positive effects of outsourcing can be enhanced, if service providers as strategic partners offer unique know-how. In that case, their services can be used to supplement existing core competencies (i.e. to free resources in order to invest in higher internal capability). The emerging co-operation model of leased competence offers additional access to high-level expertise: a temporary integration of external service providers into internal R&D teams supports R&D projects in a more flexible and timely manner. Examples have shown that this model boosts an efficient execution of milestones and helps to build-up a high internal competence level in the long-term, especially in small pharmaceutical companies. Nevertheless, there can be major obstacles when outsourcing chemical synthesis: for example (the perception of) difficulties to transfer know-how and issues regarding the intellectual property situation. Service providers should address concerns of pharmaceutical customers with a best practice approach including a number of important aspects: (a) reduce complexity and increase efficiency through the definition of highly standardised and transparent processes and contracts together with customers. (b) Build up trustful relationships through full cost transparency (e.g. fixed prices attached to milestones), (c) co-operation agreements that leave all critical intellectual property at the pharmaceutical company, (d) clear and transparent rules regarding participation in projects advertised by a customer's competitor and (e) set highest standards regarding confidentiality. (f) Improve the co-operation and communication process through close proximity to the pharmaceutical company and direct interaction with the pharmaceutical company's project management team. As a rule, offshore lab resources alone (e.g. in China or India) are insufficient. Last but not least, (g) ensure high quality through flexible project execution and compelling quality control that involves both parties: pharma customer and service provider. ■

REFERENCES AND NOTES

1. J.B. Quinn, *Sloan Management Review*, **40 (4)**, pp. 9-21 (1999).
2. J.B. Quinn, *Sloan Management Review*, **41 (4)**, pp. 13-28 (2000).
3. S.M. Findlay, *Pharmaceutical Technology Europe*, **19 (5)**, pp. 13-14 (2007).
4. G. Festel, *Drug Discovery Today*, **16 (5-6)**, pp. 237-243 (2011).
5. B. Achilladelis et al., *Research Policy*, **30 (4)**, pp. 535-588 (2001).
6. G. Festel et al., *Journal of Commercial Biotechnology*, **18 (1)**, pp. 11-21 (2012).
7. A.J.J. Straathof et al., *Current Opinion in Biotechnology*, **13 (6)**, pp. 548-556 (2002)
8. J.M.Woodley, *Microbial Biocatalytic Processes and Their Development*, **60**, pp. 1-15 (2006).
9. D.J. Pollard et al., *Trends in Biotechnology*, **25 (2)**, pp. 66-73 (2007).
10. D. Werck-Reichhart et al., *Genome Biology*, **1 (6)**, (2000).
11. V.B. Urlacher et al., *Trends in Biotechnology*, **24 (7)**, pp. 324-330 (2006).
12. D.C. Lamb et al., *Current Opinion in Biotechnology*, **18 (6)**, pp. 504-512 (2007).
13. R. Bernhardt, *Journal of Biotechnology*, **124 (1)**, pp. 128-145 (2006).