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Serving as a contract research organization (CRO), Endotherm Life Science Molecules is a provider of medicinally relevant compounds for the discovery and development of novel small molecule drugs. The product range includes focused compound libraries, building blocks and reagents for the development of biochemical assays (fluorescent probes). The company has an outstanding expertise in the synthesis of high-value active pharmaceutical ingredients (Vitamin D derivatives, steroids, antiviral APIs) to be used for generic drugs. Additionally, Endotherm is involved with its own original early stage drug discovery programmes within various national and international collaborations - Hepatitis C, cardiovascular diseases, antibiotics.

# Outsourcing of medicinal chemistry in the drug discovery process faces CRO's and pharmaceutical companies with challenges

**If collaborations are well-designed and properly managed, they may turn out to be highly beneficial for both sides**

It is a well known worldwide misery in the drug discovery process, that costs are increasing and overall productivity is going down.

Pharmaceutical and biotechnology companies have to make certain to get a return of their investment in R&D by launching new innovative medicines on the market more rapidly, and decrease costs at the same time.

Outsourcing is a promising and already successfully proven approach to achieve these goals, and thus led to one of the greatest changes within the pharmaceutical industry. Almost every stage of the value chain is involved. Whereas outsourcing of API production, clinical trials, regulatory issues and IT is already very well established, outsourcing of activities close to preclinical research (medicinal chemistry, including chemical synthesis and biochemical evaluation of new compounds) is less advanced. However, if the collaborations are well-designed and properly managed, they can be challenging and beneficial for both sides.

"Preclinical research is regarded as a core competence of research based pharmaceutical and biotechnology companies, and outsourcing within this stage of the value chain is thus a critical issue. In this early stage of drug discovery IP is sometimes not yet sufficiently protected and innovative companies often hesitate to reveal their potential crown jewels", says Dr. LARS KATTNER, CEO of ENDOTHERM. With regard to chemistry support of medicinal

chemistry, CRO's which provide this type of service already find themselves in a very competitive environment, but the market is still growing (Figure 1). New players from the emerging economies (China, India, Eastern Europe) arise and demonstrate that they are able to provide high quality service for moderate prices. Already 200-300 companies worldwide offer chemistry support for industrial drug discovery by providing mainly exclusive screening compounds and building blocks.

Pharma or biotech companies are looking to gain a significant added value to complement, strengthen or replace internal capabilities concerning capacity, costs, speed and technology. Even small start-up drug discovery companies often outsource their chemistry already from the beginning of their operations, because their investors force them to do so, mainly due to cost efficiency reasons. "As a CRO you have to bring something on the table if you want to get the foot in the door" says Dr. KATTNER.

Even if just additional capacity is needed, it is an attractive option to outsource, because capital costs to be spent for facilities and internal infrastructure can be saved, and pricing of chemistry work to be done can be made more transparent.

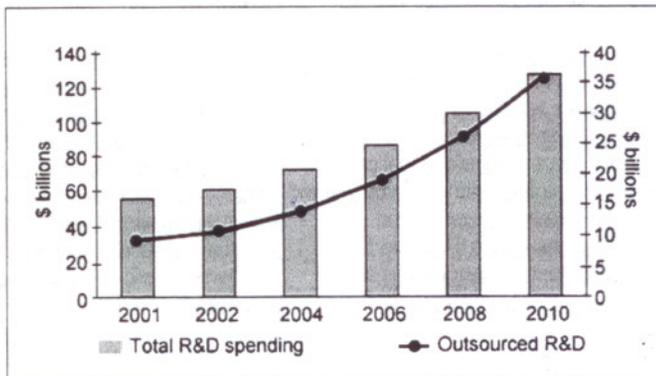


Figure 1 - Projected global pharmaceutical outsourcing market. Reuters Business Insight, Pharmaceutical R&D Outsourcing Strategies, 2002

Costs for routine work, which could as well be done in-house, can be easily analyzed and be compared with cost structures of various CRO's. This allows to choose the most cost-effective and efficient solution to save money and time in the drug discovery process. Consequently, this game may turn out for a CRO as a weak business model, and the service provider thus may get under enormous price pressure. CRO's which want to survive or consider to appear as a new player on this competitive outsourcing market should try to provide niche products, unique services or proprietary technologies.

Big pharma and small drug discovery companies are usually looking to outsource routine chemistry, mainly to achieve chemistry support for an internal biological target. In this case, not too critical collections of compounds and intermediates are outsourced, the chemistry is well defined and considered to be prescriptive. Both sides can be confident that the chemistry works.

A high demand is recognized regarding screening compounds for High Throughput Screening (HTS) to be used for hit-finding or hit-to-lead studies, the design and synthesis of small focused compound libraries and follow-up libraries in high purity for lead optimization, scaffolds, reference compounds of competitors, building blocks, intermediates, as well as various chemicals and reagents to be used for biochemical assays. Additionally, some CRO's offer assistance in library design by utilizing cheminformatics, which thus may get a chance to expand their business opportunities comparing to a sole chemistry provider. Some CRO's already operate as a fully integrated service provider covering almost every aspect of drug discovery.

To sign a deal, it has to be made clear which added value the CRO is able to provide.

A proven track record may help to gain the clients trust. Inquiries should be answered after 3-5 business days. The main criterion from the viewpoint of the client is a high scope of resources to be found concerning equipment and staff.

Highly skilled scientific personnel including the management, state-of-the-art facilities and a high safety standard are prerequisites. Additionally, the CRO should provide access to expertise or particular problem solving skills which may not be available in-house. A professional project management, a commitment to quality and high confidentiality concerning the protection of the clients IP should be guaranteed. Contract negotiations should be done speedy and pragmatically.

Usually all the IP generated by the CRO belongs to the client. If a quality management system such as ISO 9001 or GMP is not implemented in the CRO, which may not be essential in preclinical

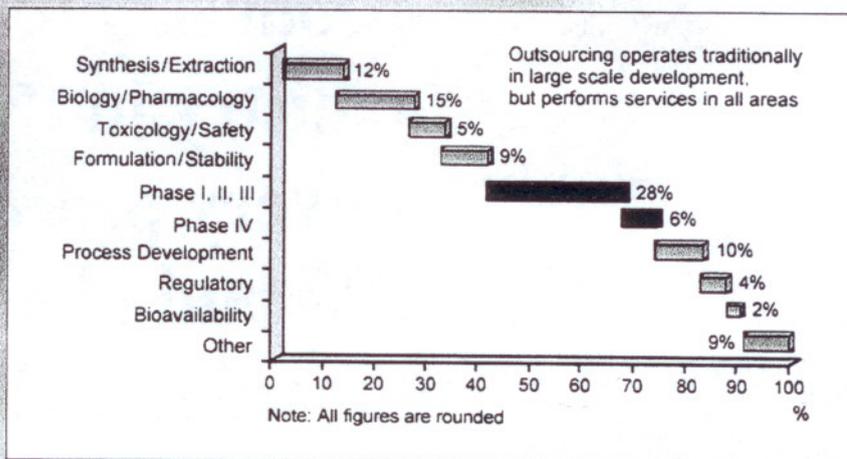


Figure 2 – Drug discovery outsourcing market: Global R&D spending breakdown (Europe, 2004).

Source: Frost & Sullivan

research, the lab of the CRO should have at least the same industry standards under which the client is operating in-house. Additionally, a critical issue is an understanding that expectations on both sides match on a realistic basis and are focused on timelines. Professional communication and reporting is essential. This includes quick response to comments and questions, immediate feedbacks if problems or hurdles arise, high flexibility and the ability to respond quickly to

to be spent on the project to solve unexpected problems.

The FTE rates (in €/year) vary dramatically worldwide between € 150,000 (US) and € 30,000-50,000 (China, India) for a comparable service. Indian firms pay a chemist commonly € 300-500 a month, versus € 3000 in the UK and € 5000 in the US or Germany. In the Asian countries there are many highly skilled scientists around, partly even trained in the UK or US, because it is more trendy there to go in university and study chemistry than in the US or Europe. Additionally, new lab facilities to be build which cost € 1 million in India or China may cost 10 times more in Western Europe or in the US. Consequently, the number and size of chemistry service providers in Asia has grown dramatically over the past few years and have become a viable alternative to service providers in the West.

However, many pharma companies realize that FTE costs are not necessarily the main factor, and they still prefer local partners where reliability, protection of IP and flexibility can more likely be

expected. Also communication can be difficult – English is often only spoken by the management, no time zone overlap, travel time – cultural differences and political uncertainties, unreliable infrastructure and tricky customs may cause problems with partners from overseas. Finally, the risk of damage to the reputation of the client, a critical issue in the pharma industry, cannot rigorously be excluded if the CRO does not meet the western environmental standards.

In conclusion, the success of a collaboration, no matter where in the world the partners are located, is dependent on frequent, honest and open communication and the dedication of well-trained staff on both sides. The partners should develop trust in each other by managing the relationship as an asset.

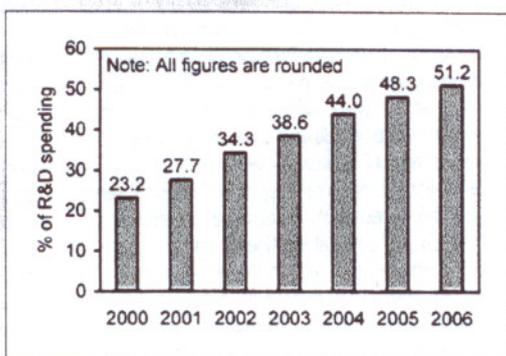


Figure 3 – Drug discovery outsourcing market: Percent of R&D outsourced to CRO's (Europe, 2000-2006).

Source: Frost & Sullivan

changing conditions. "The client wants to know first if anything goes wrong", says Dr. KATTNER.

Finally, these factors of added value have to be realized at moderate costs and offered to a client for a competitive price. Two models are established. Usually the CRO provides laboratory capacity including staff for a defined period of time, and charges for Full Time Equivalents (FTE's). The FTE rate usually includes one Ph.D., M.S. or B.S. chemist, basic chemicals and the related analytical instrumentation. FTE contracts typically last six month to one year. Another price model is to charge on a fee-per-project basis. This model implies the risk for the CRO to be confronted with expanding costs in the case of failure or if additional time has