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Feature Article

Outsourcing in Pharmaceutical Research and Development. Opportunities and Challenges*

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Outsourcing of drug discovery processes offers a vast opportunity to scientists to develop and commercialize new and innovative methods and technologies as well as other discoveries that could be of use to pharmaceutical industry. Specifically, this is of special value for investigations that are either too complex or too infrequent to be performed in-house and can be carried out faster and at less overall cost by outsourcing.

INTRODUCTION

In the last few decades, R&D costs have skyrocketed and it is becoming increasingly harder to put a new drug on the market (Figure 1).[1] The reasons for this are numerous. Regulatory requirements are more rigorous, asking for more detailed non-clinical and clinical data before approving a new drug. Product and production quality is more demanding. Genomics and proteomics together with new technology platforms have increased the cost of the early discovery phase. All of this has raised the cost of drug development by about 250 % in the last ten years.[2]

On the other hand, many best-selling drugs that are the main source of R&D expenditure will be losing their patent protection within the next few years. In this environment, pharmaceutical companies are trying to cut costs and speed up the drug discovery process either by acquiring other companies and thus overcoming the lack of expertise and knowledge and/or by outsourcing part of their activities. At the same time, Contract Research Organizations (CRO) have emerged that offer activities within the drug discovery process with great expertise and specialized knowledge in specific areas at a competitive price. The CRO industry is growing rapidly and this is expected to continue in the years to come.[3]

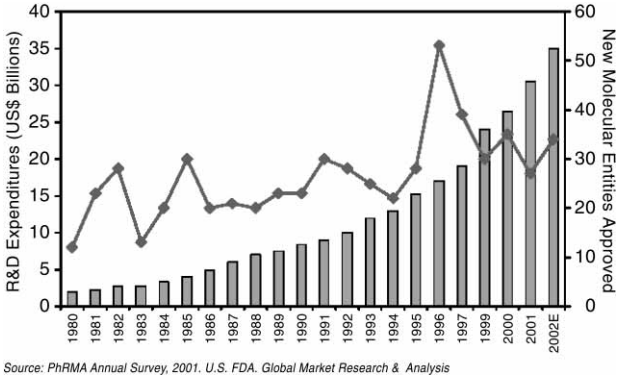

Figure 1. Growth in R&D expenditures is not followed by the number of new chemical entities on the market.

* Dedicated to Professor Željko Kućan on the occasion of his 70th birthday.

What Activities Are Outsourced, When and Why?

First of all, a strategic decision has to be taken as to what will be outsourced and what will remain in-house. Scientific methods and technologies are developing and improving every day; they are expensive, sometimes complicated and it is impossible to implement all of them in-house, hence CROs represent a perfect solution to overcome this gap. Skills or activities that are needed rarely or for a short period of time are better outsourced than developed in-house, thereby lowering the cost. When there is internal lack of knowledge, time, people or equipment, outsourcing is also the best option. CROs are usually highly qualified and experienced in their field since they have a team of people working within a narrow range of activities, which make them sometimes unbeatable competitors.[4]

Many pharmaceutical companies have established whole departments that organize and deal with contract research as part of their outsourcing. The main reason for this is to sort out and control an increasing number of contracts and to lower the costs by finding the best partner companies for their needs. The task of the outsourcing specialist is to support the goals of programs and projects by facilitating collaboration with outsourcing providers. Searching and selecting the CROs, negotiating the prices and other contract provisions, such as liability, intellectual property rights, confidentiality issues, *etc*., and establishing and maintaining good relationships with CROs through meetings and other means of communication are some of the tasks that outsourcing specialists perform.[5]

Relationships between »sponsors« and »vendors« are changing all the time. The first generation of collaborations was a classical »sponsor/vendor« relationship, but nowadays this is becoming more and more a partnership, which assumes a joint spirit and risk-taking that brings more value to both parties.

What Do Contract Research Organizations Do, Who Are They?

There are a number of small to large CRO companies, from one-activity laboratories in some specific fields to the global multiple activity companies able to cover a large part of the drug development process. Classical CROs that perform clinical trials get the most money from the pharmaceutical industry since clinical trials are large and complex studies involving enormous numbers of patients and data. These CROs (also called »Clinical Research Organizations«) select and coordinate investigation sites and physicians involved in the studies, collect and manage the data and together with the sponsor generate a study report. Other CROs perform non-clinical studies consisting of safety/toxicology testing; pharmacology (pharmacokinetics, pharmacodynamics) and other *in vitro* and *in vivo* tests required by regulatory agencies and satisfying all of their quality requirements. In addition, there are companies that up-scale the laboratory synthesis of compounds that need to be tested in clinical trials and produce the required quantities of the active compound; analytical labs, which are able to perform analyses in accordance with strict regulatory and quality requirements (GLP – »good laboratory practice«); companies that package and prepare clinical trial material (new compound, reference compound and placebo), *etc*.[6]

Among CROs, there are also a large number of new innovative and science-based companies, founded by one or a few scientists that have made their own or have applied somebody else's discovery, developed it into practical technology and finally established an innovative company – a combination between knowledge and application. There are many examples of such innovative companies that usually start as »spin-offs« from the universities or big pharmaceutical companies. One such university spin-off is »Dual Systems« in Switzerland, whose co-founder is the Croatian molecular biologist Igor Stagljar. The company uses a yeast two-hybrid system to study the influence of a drug on the interaction between two proteins. Another such company is »CXR biosciences« in the UK that developed a transgenic mouse model, based on inactivated hepatic P-450 enzymes which are involved in the metabolism of many drugs. By testing drug candidates in their proprietary model, it is possible to check toxicity and bioavailability of the intact compound and distinguish it from the effect of its metabolites. »Ifcos«, a Canadian/German company is trying to develop »*in silico*« models for simulation of intracellular interactions and pathways that would enable clients to check the influence of up- or down-regulation of any gene within the cell on its interaction with upstream or downstream proteins. Big pharmaceutical companies' spin-off examples are »Rosseta Inpharmatics«, a wholly owned subsidiary of Merck that develops and implements technologies for improvement of drug discovery and Pharmacia's »Biovitrum«, a biotech company that combines the experience of a big pharmaceutical company with the flexibility of modern biotechs. RNAi (small RNA interference) is becoming a hot topic not only for target determination and validation, but efforts are being made to develop it as a therapy, especially for »undruggable« targets. New companies have appeared based on this new discovery as producers of kits for using the technology in research or for the development of an RNAi as a therapeutic. There are a number of other examples of the transfer of a scientist's discoveries and knowledge to successful companies; a pool of companies in Cambridge Science Park, UK, is an excellent representative of this approach. Many of these companies were established as a consequence of discoveries closely related to the needs of the pharmaceutical industry.

What Determines the Selection of a Particular CRO?

Selection of a CRO is the most challenging task in the outsourcing process. There are many parameters specific to each study that have to be taken into account.

The CRO should work in compliance with the quality standards required by regulatory agencies (GLP, GMP, *etc*.) and demonstrate ability and willingness to perform the requested activity. Their experience is often a good reference. A further criterion is cost-effectiveness (comparison between quality and price). For some studies the price is crucial and for the others quality or timing is more important.

If the CRO offers completely new and unique ideas and the expected outcome of a study can bring added value to the project, this may be a unique decision-making criterion.

Finally, it is very important to establish a friendly and »easy-going« relationship between the partners and definitely the best reference for the CRO is its own experience and track record. Performance metrics introduced by relevant experts in the field have shown that strong working relationships bring about 25 % higher value than poor relationships between partners.[7]

PLIVA and Outsourcing

PLIVA, as a global company, has developed a wide network of outsourcing partners. In terms of R&D, the outsourcing money is spent predominantly on clinical trials and non-clinical testing of drug candidates that, due to regulatory requirements, cannot be performed »in-house«.

PLIVA has always, since its very beginnings, had good collaboration with its surrounding scientific community. This policy has not changed during the, sometimes turbulent, recent past for industry and science in Croatia. Nevertheless, the development and strengthening of PLIVA's R&D and the increasing use of outsourcing that has followed global trends, has not been matched sufficiently by the development of Croatian science towards innovation and applicability. There are a number of reasons for this. Our scientists were educated in an environment that did not pay enough attention to protection of intellectual property rights or the possibilities of commercializing their discoveries. There is no doubt that fundamental research is very important to all aspects of life, but there should be a balance between basic and applied research. The Croatian Ministry of Science started a few years ago with »RAZUM«, programs that encourage the establishment of small businesses based on knowledge, innovation and new technologies; but in natural sciences, biotechnology and non-clinical discovery phase there is a lot of space for the formation of small biotech companies which would provide services to the pharmaceutical industry within Croatia, and also to the industry in neighboring countries, as exemplified by developments in Hungary, Slovenia and the Czech Republic. If this were the case, PLIVA would be able to improve the ratio between its spending on outsourcing in Croatia and in other countries that now amounts to only about 3–4 % (Figure 2).

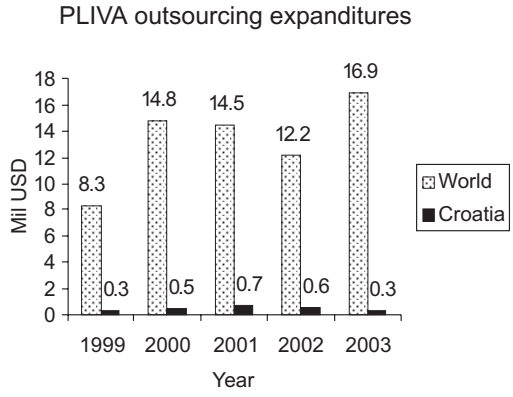

Figure 2. The relationship between PLIVA R&D spending for outsourced activities in Croatia (black columns) and abroad (patterned columns) in millions of US $.

PLIVA will continue its fruitful and good collaboration with its scientific surroundings, in particular with the Rudjer Bošković Institute, Medical Schools of Zagreb and Rijeka, Faculty of Pharmacy and Biochemistry, Zagreb, Faculty of Science, Zagreb, and is willing to extend that collaboration considerably if the services offered are competitive with those found in other countries.

CONCLUSION

Outsourcing, collaboration and partnership are relatively new, but overwhelmingly accepted approaches in all modern industries and as a part of the globalization process, represent a cost-effective opportunity for developing countries to participate and become competitive. Outsourcing of the drug discovery process is a challenge to scientists to develop and commercialize their new and innovative methods and technologies along with other discoveries that could be used by the pharmaceutical industry.

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SAŽETAK

Uporaba vanjskih usluga u istraživanju i razvoju u farmaceutskoj industriji. Mogućnosti i izazovi

Smiljka Vikić-Topić

Uporaba vanjskih usluga u procesu razvoja novih lijekova pruža brojne prilike znanstvenicima za razvijanje i komercijalizaciju inovativnih metoda i tehnologija te otvara put k novim otkrićima, koja se mogu upotrijebiti u farmaceutskoj industriji. To je osobito dragocjeno u istraživanjima koja se u farmaceutskoj industriji rijetko provode ili su presložena da bi se isplatilo njihovo uvođenje u vlastitome laboratoriju. Uporabom vanjskih usluga znanstvenika mnoga se farmaceutska istraživanja mogu provesti brže i djelotvornije.