

Full Length Research Paper

The increasing role of contract research organizations in the evolution of the biopharmaceutical industry

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The role played by contract research organizations (CROs) in the last decades has been almost completely neglected by the economic and managerial literature, which at most presents an outdated and misleading portrait, of firms performing routine clinical tasks. This study aims at filling this knowledge gap, by describing the evolution of the CRO segment of the biopharma industry in the last two decades, discussing the foundations of CROs' comparative advantage and underlining the consequences of their growth for the effective functioning of the whole industry. Importantly, this study argues that the increased role of CROs in performing fundamental phases of R & D has made the anatomy of the biopharma system more functional: in fact even if the turbulence and mortality of IP-based biotech firms is extremely high, if they rely to a great extent on CROs, the experience acquired to carry out their projects - which mostly fail - does not get lost but cumulatively enhances CROs' capabilities.

Key words: Evolution of industries, R & D outsourcing, tacit knowledge, learning, biopharma industry.

INTRODUCTION

It is curious that the enormous economic and managerial literature on the biopharmaceutical industry has almost completely omitted the role played at least in the last two decades by contract research organizations (CROs). In the absence of official data, the importance of this segment of the industry is brought to light only by some analysis and discussions in the medical literature and some managerial contributions mainly neglected by the mainstream literature.

The biopharma industry is in fact generally depicted as embedded in a tripartite vertical alliance network (Stuart et al., 2007), where biotech firms typically in-license new

ideas from universities, further develop and ultimately transfer this intellectual property to larger firms that possess the resources to perform clinical trials and commercialize the technology. At most we find some hints at CROs, which portray them as specialist firms performing routine clinical tasks.

According to this study, it is this representation of CROs' role that must be questioned, since though it may have been appropriate until about two decades ago, the subsequent evolution no longer justifies it. Moreover, the few contributions in the managerial literature focusing on CROs' activities mainly examine their role with respect to

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their big pharmaceutical clients.

Thus, a blatant gap in the literature regards the importance of CROs for smaller biotechnology firms. Not less important, an updated picture of the overall evolution of CROs is missing, as well as a discussion of the consequences of CROs' growth for the effective functioning of the whole biopharma system.

This research aims at bringing to light the role played by CROs in the last twenty years in the biopharma industry, in order to fill the literature gaps and to address the issues mentioned earlier. More precisely, the study focus is mainly on describing the broadening of CROs activity from the clinical into the preclinical field and on highlighting the importance that CROs have consequently acquired as providers of the entire range of R&D services to young biotech firms.

In fact the latter usually start their business with the project of a new drug or medical device, but lack to a great extent the capabilities to realize it. In particular, we concentrate the study attention on

1. The main reasons underpinning the competitive advantage of CROs vis-à-vis IP based small biotech firms in the execution of R&D tasks, stressing the importance of learning by experience and of tacit knowledge.
2. The importance of collaborations between CROs and their biotech clients, since the knowledge of the molecules (possessed by IP based biotech firms) and the knowledge about how to perform the development tasks must be integrated.
3. The contractual forms (open contractual arrangements) put in place in order to keep under control transactional hazards, which are particularly high in the provision of an activity whose results are intrinsically uncertain.

Finally, we reflect on the consequences of the increased role of CROs with regard to the sector cumulative learning, which, according to Pisano (2006a) analysis of the 'anatomy' of the biopharma industry, is one of the main challenges the sector has to cope.

WHAT WE KNOW ABOUT CROS

The CRO business model

CROs may be defined as 'portfolio of expertise' organizations, whose main goal is to attract clients (big pharmaceutical firms, biotech start-ups up to university scientists) needing to access their know-how and facilities for the execution of some (or even all) of the complex and numerous phases of development (Figure 1). The initial phases of development, preceding clinical trials, comprise discovery and preclinical characterization. Discovery in turn can be subdivided into two stages, lead selection and optimization followed by drug candidate confirmation. In the first phase several compounds are screened and selected for efficacy and basic drug-like characteristics. Tests are designed to be relatively low

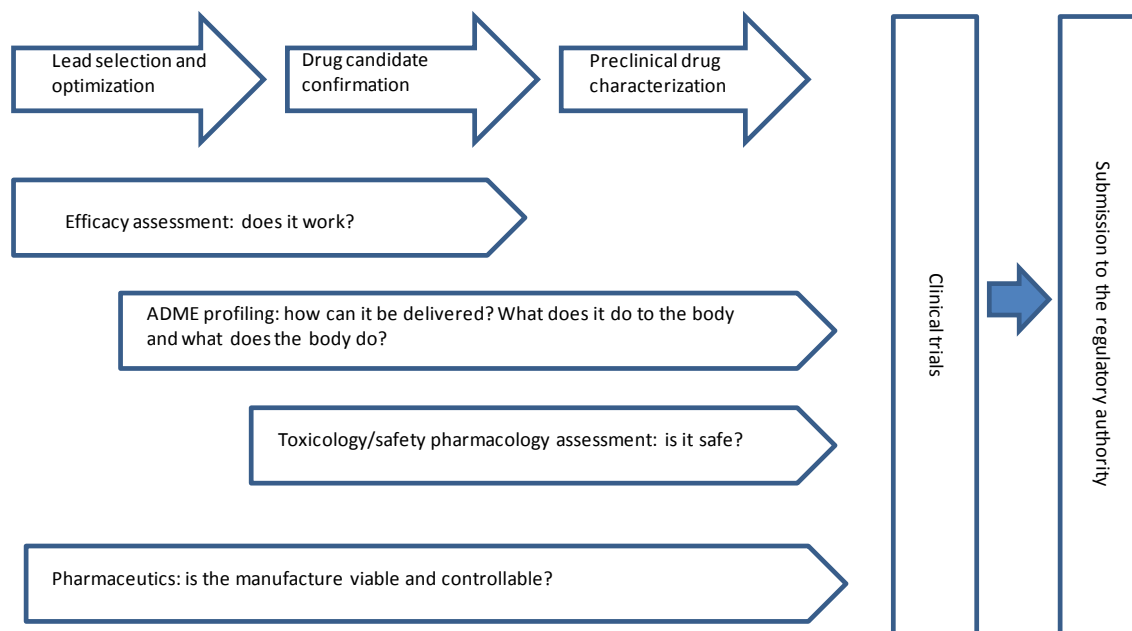
cost, using in vitro and in vivo models. In particular, early absorption, distribution, metabolism and excretion (ADME) pharmacological profiling (pharmacodynamics and pharmacokinetics) is realized by performing the tasks of in silico profiling, developing simple analytical methods, measuring membrane permeability and plasma stability. The best compounds are then assessed against more detailed criteria in the following phase of drug candidate confirmation, whose main objective is confirming that a compound is worthy of further development without incurring large costs. This involves a more in-depth application of the tests from the previous stage and adds a broader panel of tests, including some that may be 'show stoppers'. The data generated here is commonly used to meet investment milestones. The tasks and methods comprise preliminary CMC (chemistry, manufacture and control), validation of in vivo models, more advanced ADME profiling and preliminary toxicology.

Preclinical drug characterization has the objectives of providing highly accurate, reliable data that will be used to justify the conduct of clinical trials. It requires a high level of evidence and documentation to meet the demands of government regulations (e.g. GLP - good laboratory practices - accreditation) or pharmaceutical companies, and is therefore relatively expensive to conduct. The tasks and methods include detailed preclinical CMC, comprehensive ADME and a toxicology package.

A great number of CROs exist, with different specializations, both in terms of field of activity (ranging mostly from the preclinical phases of toxicology, analytics, pharmacodynamics, pharmacokinetics etc. to the various clinical phases) and therapeutic area. Their specialised capabilities are based to a large extent on static and dynamic economies of scale (a point that we shall develop later) and are continuously enhanced over time through learning.

In general, they are subject to a normal commercial risk, since their success does not depend on any one of the projects to which they add value: even if the results of some studies fail to meet expectations, CROs are paid for their work by their clients (fees for service), who instead bear the risk of the failure. Due to their expertise in the latest technologies, they are increasingly considered as strategic partners by clients (usually called sponsors) and have a growing impact on the overall research direction and success (Colin, 2015)¹. However,

¹ For example, the biopharma industry is currently extensively engaged in the development of ADCs (antibody drug conjugates), a breakthrough cancer treatment that can deliver cytotoxins directly to cancer cells without the collateral damage of traditional chemotherapy. These are complex molecules that need careful development of a bioanalytical strategy. Bioanalysis requires highly specialized equipment and expertise that are often only found at a CRO. Therefore, assembling a collaborative development team with diverse knowledge and technical expertise comprising members from the pharmaceutical company and the CRO has become crucial, in this as in other fields (Spriggs et al., 2015).



Source: Simon (2009)

Figure 1. Tasks performed in the phases of discovery and preclinical development .

there are also CROs with a hybrid business model, who devote some resources to pursue their own R&D projects.

Finally, many CROs also provide manufacturing services to their customers, who need small amounts of different bio drugs (cells, proteins, immunological products, plasmids for DNA-based vaccines etc.) for preclinical R&D and larger volumes for clinical trials. The batches used for clinical trials must be manufactured in facilities authorized by the regulatory authority and must comply with good manufacturing practices (GMP) guidelines. Firms offering manufacturing services are called contract manufacturing organizations (CMOs), so in many cases CROs are also CMOs.

The economic and managerial literature on CROs

To the best of this study knowledge, the first contribution on the topic is the work of Piachaud (2002). According to this author 'what was once a cottage industry of consultants and independent laboratories' grew significantly since the 1960s after the approval of the Kefauver-Harris Act in the United States (a consequence of the high incidence of birth defects resulting from the use of thalidomide), which required companies to provide proof of efficacy in addition to proof of safety.

Thus, the quantity of work in clinical trials increased substantially, inducing pharmaceutical firms to resort to the external expertise and resources of CROs. Piachaud

(2002) stresses that over the years CROs' activities expanded beyond clinical phases to include early stage research, preclinical development (pharmacokinetic, pharmacology, toxicology studies etc.), regulatory services and clinical manufacturing, even though by the year 2000 clinical trials still constituted about 60% of their revenues. Among about 1,300 active companies, some had annual sales exceeding \$500 million (for example, covance, quintiles, transnational corp. and parexel) and R & D departments pretty similar in size to those of their big pharmaceutical sponsors.

Piachaud (2002) mentions that also biotechnology and device industries were increasingly resorting to their services, but his focus is on big pharma companies. Through a questionnaire survey of multinational pharmaceutical organizations, he identifies the major advantages/disadvantages of collaborating with CROs as opposed to hiring, training and organizing R&D internally. Lack of resources - facilities and capabilities - turns out to be one of the primary drivers of collaborations. In fact due to the expansion of the knowledge base of the industry and the emergence of a number of novel research techniques, even the largest firms could no longer afford to keep in-house all fields of expertise. By outsourcing phases of development, they could strengthen their focus on core capabilities and broaden their research scope (in term of therapeutic targets) avoiding long-term commitments, thus increasing flexibility and diminishing risks. However, this growing reliance on external agents also raised concerns about the loss of control over the

Table 1. A decade of contract research organizations.

Variable	1992	2001
CRO market size	US\$ 1.0 billion	US\$ 7.9 billion
Top 20 CRO revenues	US\$ 0.5 billion	US\$ 4.6 billion
# CROs ≥ US\$ 100 million	2	16
CRO employees	12,000	94,000
# Publicly traded CRO	2	19
# Enrolled research subjects	7 million	20 million

Source: Mirowski and Van Horn (2005).

outsourced activities.

Mirowski and Van Horn (2005) showed some interesting data on the growth of CROs in the 1990s, which they acquire from industry sources (Table 1). CROs' expansion is remarkable, with an increase of the market served by about 8 times. They also emphasize the undeniable success of CROs in capturing the bulk of industry-sponsored clinical research away from Academic Health Centers (AHCs), whose share fell in a decade from about 70/80 to 35/40%.

They argue that in a period when the duration of the clinical developmental cycle was lengthening and its cost soaring, pharmaceutical firms as a remedy were looking for a new breed of scientific researchers who was more comfortable with deadlines and cost containing innovations; they also needed full-service providers, able to coordinate clinical research across national boundaries. Thus, CROs expanded due to the ability of far-sighted entrepreneurs to respond to these requests, by introducing 'a set of research practices that more effectively adjusted to the traffic and rhythms of corporate privatized science'.

Howells et al (2008) presented the results of a survey of 105 research-based UK pharmaceutical firms conducted in the period 1998 to 2003. The outcomes are similar to those of Piachaud (2002). The reasons to outsource rated most highly are accessing expertise not available in-house, followed by the ability to reduce development time and costs. In the activities not considered core by pharmaceutical firms, CROs could perform better due to 'more experience and scale and scope benefits' (p. 216): clinical trials rank first, followed by R&D software and applied research. Finally, in partner selection the most appreciated factors are capability, timeliness and trustworthiness. As to 'constraining' factors, Howells et al. (2008) highlight the absence of modularity in some tasks.

Lowman et al. (2012) focused exclusively on the increasing role of CROs in clinical development. While initially CROs provided only a limited service in clinical trials management, they gradually extended their expertise 'across a range of therapeutic areas, benefiting from working with, and learning from, multiple clients'.

Hu et al. (2007) proposed a more comprehensive view

of the CRO industry, in a working paper never published by refereed journals. According to these Authors, the model of outsourcing of big pharmaceutical firms was initially based on the need to save resources spent in labour intensive and routine tasks. 'CROs were traditionally seen as a necessary evil: while in-house teams allowed better oversight and typically had more experience, outsourced teams were more cost efficient'.

Over time, however, *the emergence of biotechnology radically changed the outsourcing landscape*. In fact biotech startups, distressed by scarcity of funds and lacking capabilities, found in outsourcing the natural solution to develop their ideas. In extreme cases, 'virtual companies' started to flourish, managing relationships with multiple CROs to complete all the preclinical and early clinical testing before looking for a more long-term partnership with a pharmaceutical firm.

In parallel, the pharma industry discovered not only that the external service providers could do all steps in the development process, but also that quality was no longer an issue. 'Because CROs began to specialize in certain steps of the development process or specific therapeutic fields, they became the experts in those areas'. Finally, by outsourcing to CROs that served many clients, each one client did not incur the risk of intermittent utilization of resources.

A brief overview of the recent evolution of the CRO industry

In order to update the picture of the CRO industry, in the absence of official data, we have relied on the reports written by the most important industrial advisors and consulting companies, publicly traded CROs' annual reports, CROs' directories and websites, specialized biopharmaceutical journals and industry magazines.

We present in Table 2 the main estimates of the global growth of outsourcing of preclinical and clinical development to CROs in the period 2005 to 2013, and forecasts until the year 2020.

According to most sources, CROs' market size (measured by revenues) reached about 23/25 billion dollars in 2013, a value which compared to that of about

Table 2. Outsourced preclinical and clinical development to CROs in 2013 and 2020: various estimates

Source	Global CRO market size 2013 to 2020 (\$b)	Global Biopharma R&D spending 2013 to 2020 and CROs' potential market (\$b)	Estimated future CROs' CAGR	Segmentation of CRO services 2013		Penetration rate of global biopharma R&D spend by CROs
				Preclinical (%)	Phase I-IV clinical (%)	
Brocair Partners (2014)	-	-	To 2018: 8.7% overall. Preclinical growth higher than clinical	21	79	-
Harris Williams & Co (2014)	25.3 (2013)	-	To 2018: overall 6.6%; preclinical 7.4%, clinical 6.4%	21	-	-
IMAP (2014)	25 (2013)	Global biopharma R&D spend 139 (2013)	Slower growth compared to the past	13	-	10% 2001 18% 2013
Innoaction (2014)	25-30 (2013)	-	To 2020: 7-9% overall	25	75	-
Results Healthcare (2014)	23-25 (2013) 30 (2018)	2/3 of the global R&D spend by the top 500 biopharma companies is CROs potential market (about 90/95b)	To 2018: 5-6% overall	Early stage (including phase 1 clinical services) 25%	Late stage: including phase 2-4 clinical trials and central lab services: 75%	24/28% 2013 35% 2018 more than 60% long term (penetration of the potential market)
William Blair and Company (2014)	23.5 (2013) 42.3 (2020)	Preclinical and clinical only global spend: 65.1 (2013) 87.1 (2020)	2013-2020: overall 8.8%; preclinical 7.8%; clinical 8.9%	12	88	36% 2013; 49% 2020
Zion Market Research (2015)	34 (2014) 59 (2020)	Global biopharma R&D spend 142 (2014); 160 (2020)	2015-2020: overall 9.8%; early stage 5.5%; late stage 11.2%	Early stage (including phase 1 clinical services) 28 (2014)	Late stage: (including phase 2-4 clinical trials and central lab services): 72 (2014)	24% 2014; 37% 2020

Source: The study elaborations from the cited industrial sources.

8 billion presented by Mirowsky and Van Horn (2005) produces a CAGR of about 19% over 12 years (in current dollars).

Relatedly, the penetration rate of the global biopharma R&D spending increased from 10% in 2001 to 18% in 2013 (IMAP, 2014) and is expected to grow further. The estimates of future CAGR to 2018/2020 vary within the range 6 to 9%, and those of future penetration differ mainly according to what is considered as potential market (since not all global R&D biopharma spending is conquerable by CROs), in the range between 40 to 60% in 2020. Even the lower bound is quite impressive. The value of clinical services offered by CROs in 2013 is generally considered about 4 times higher than preclinical,

but we find no consensus on whether clinical or preclinical activities will grow faster in the future. Given these figures, it is obvious that the largest CROs are those firms that keep a leading position in the clinical phases.

These forecasts reflect more than one evolutionary change. First, biopharmaceutical companies not only continue to reduce their R&D infrastructure and to search for more efficient and cost-effective modes of drug development, but they have also started to outsource drug discovery research, an area which historically was considered a core competence. Second, an increasing number of emerging specialised biotechnology companies have limited or no internal capabilities at all. Third, even academic

institutions, many of which are benefiting from funding by global biopharma companies, increasingly rely on CROs' assistance to navigate the drug discovery and development pipeline (Charles River Laboratories, Annual Report 2013) (Table 2).

According to common estimates, the number of companies active at the world level is currently more than 1,000. The share of the top four companies, which are all headquartered in the US, accounts for about 43% of the market (estimated at 25 b\$), with a growth in recent years (Table 3). Overall, the players are essentially segmented into three groups according to size: few top tier companies, several midsized firms, and several-hundred small, niche service-

Table 3. Largest CROs' revenue growth (2000-2013).

CRO	Revenues 2000 (M US \$)	Revenues 2013 (M US \$)	CAGR 2000-2013 (%)	Market share 2013 (%)
Quintiles	1,660	3,886	6.8	16
Covance	868	2,442	8.3	10
PPD	345	2,000	14.5	9
Parexel	378	1,892	13.2	8

Source: Mirowsky and Van Horn (2005) and Paine (2013).

Table 4. Main services offered by key-players (2013).

Name	Revenues 2013 (Millions US \$)	Global headcount (thousands)	Country	Ownership	Early stage					Late stage			Other		Central lab
					Pre-clinical					Clinical			Peri-approval		
					Research models	Discovery services	chemistry	Bio analysis	Toxicology	Phase 1	Phase 2	Phase 3	Phase 4	Consulting	
Quintiles	3,886	27.412	US	Public				√	-	√	√	√	√	√	√
Covance	2,442	11.800	US	Public	√	√	√	√	√	√	√	√	√	√	√
PPD	2,000	12.500	US	Private	-	√	√	√	√	√	√	√	√	√	√
Parexel	1,892	12.700	US	Public	-	-	-	√	-	√	√	√	√	√	√
Icon	1,369	9.500	Ireland	Public	-	-	√	√	-	√	√	√	√	√	√
Inventive health	1,300	13.000	US	Private	-	-	-	√	-	√	√	√	√	√	-
Charles river laboratories	1,174	8.000	US	Public	√	√		√	√	√	√	√	√	√	-
Wuxi Pharma.Tech.	593	7.000	China	Public	-	√	√	√	√	√	√	√	√	-	-
Inc research	550	5.000	US	Private	-	-		√		√	√	√	√	√	-
CMIC holdings	497	3.500	Japan	Public	-	-	√	√	√	√	√	√	√	√	√

Source: Authors' elaboration from BofAML CRO Industry report (2013), Credit Suisse CRO Industry report (2013), Brocair Partners, CRO industry perspective (2013).

providers, that have arisen, especially to supply small biotech companies. A spur to new entries can be attributed to the preference accorded by the larger CROs to their big pharmaceutical customers, which leaves biotech companies under-prioritized for these same services (Results Healthcare, 2014).

On the whole, the CRO industry is highly competitive, since CROs not only compete for business with other CROs, but also with in-house discovery and development departments of their larger clients, and, to a more limited extent, with

universities and teaching hospitals (Covance Annual Report, 2013; Quintiles Annual Report, 2013).

Quintiles, the world's largest CRO (Table 3), is particularly strong in the clinical phases. Both Covance, the second largest, and PPD deliver a wider range of services, also covering early stage development, while Parexel is more focused on clinical research, technology and consulting services. Behind these major players, Table 4 shows a group of large/mid-sized CROs offering more specialized services, such as Charles River

Laboratories (with sales of \$1.17 billion in 2013) and Wuxi Pharma Tech, particularly focused on the preclinical stages (including both discovery and development).

Recently, the major CROs made important steps to consolidate the fragmented structure of the industry by a number of acquisitions and by extending their global networks to run multinational clinical trials with sites in dozens of countries (Miller, 2015; Korieth, 2014; IMAP, 2014; Brocair Partners, 2014). The broader range of services offered and the extended geographic

Table 5. Affiliation of key informants: Type of firms.

Variable	Number of companies	Type of company
Pure CROs ¹	2	Public
Hybrid CRO also CMO	1	Private
Partnership broker in drug development	1	Private
Pure DBFs	5	Private
Hybrid biotech company ²	1	Public
Biopharma midsize company ³	2	Public
Diagnostics midsize company	1	Public
Total number	13	-

¹ One pure CRO is the Italian subsidiary of a company headquartered in the USA; ² By hybrid biotech company we mean a biotech company that works mainly on his own projects but also provides (extremely complex) research services to a single client; ³ One biopharma midsize company is headquartered in France. All the remaining companies are Italian.

coverage are the factors which enable a full-service and strategic partnerships relation with major pharma clients, who can streamline vendor management by an integrated support over the various development phases. Thus, many large biopharma companies transferred substantial portions of their clinical research operations to just two strategic partners, who were able to absorb hundreds of staff from their sponsors.

On the other hand, some big CROs have become interested in serving the market of biotech start-ups and are stepping in to help make starting new biotech projects a safer endeavor. Quintiles, for example, now directly co-invests in some projects with its clients (Quintile Annual Report, 2013). Among the study interviewees, Aptuit launched a biotech incubator in Verona, to help develop its potential future clients.

A final observation regards intellectual property rights. It seems that although patents are considered valuable by CROs, 'such factors as the technical expertise, proprietary know-how, ability and experience of our professionals are more important'². Moreover, where considered appropriate, proprietary know-how is protected through confidentiality agreements and registrations.

The relationships between biotech firms and CROs: The main insights from our survey

Methodological notes

In this section, we focus on the relationships between biotech firms and CROs in the phases of discovery and preclinical development, seeking to highlight the economic logic that drives their cooperation.

To get a first-hand knowledge of the phenomenon under investigation, we relied on interviews with key

informants (Kumar et al., 1993). The key informants approach has been widely used in empirical studies (Sen and Egelhoff, 2000; Stump and Heide, 1996) because of their access to strategic information and familiarity with the sector environment (Aguilar, 1967).

The study key informants included founders, CEOs and senior scientists, all individuals with direct knowledge about the R&D strategy of their firms. Most of them had previously worked for other companies and all had a deep knowledge of the international landscape.

After mailing a questionnaire to potential key informants and a letter explaining the purpose of the study, we were able to do 18 semi-structured interviews with 20 respondents affiliated to 13 firms (Table 5). The interviews were conducted face-to-face at the firms' head office, except 3 via Skype. Overall, approximately 25 h of interviews were tape-recorded and transcribed. The questions revolved around the R&D collaborations the firms engaged in, the main reasons for outsourcing development tasks and the type of contractual arrangements that framed the collaborations.

Superior CROs' capabilities lead DBFs to outsource R&D tasks

Dedicated biotechnology firms (DBFs) can be considered 'portfolio of IPs' organizations³. As it is well-known, they are the sponsors and developers of certain patented substances with therapeutic potential (molecules, antibodies etc.), which they often import from a university. Their activities, which are mainly funded by venture capital or big pharmaceutical firms, consist in planning and conducting the phases of discovery, preclinical development and in some cases also clinical development.

According to industry sources, the probability of

² This same claim is made in Charles River Laboratories, Annual Report 2013, p.12, and in Covance, Annual Report 2013, p.8. Similar views were expressed by our informants.

³ The IP portfolio of startups may be very limited, at the extreme to one or a couple of patents/licences.

Table 6. Biopharmaceutical drug development: the rate of attrition.

Phase	Drug discovery	Preclinical	Industry submitted	Clinical trials phase 1, 2, 3	NDA submitted	FDA review	Large scale manufacturing/ Phase 4
Phase cycle time	5 years	1.5 years		6 years		2 years	2 years
Number of compounds	From 10.000 to 250			From 250 to 5		1 FDA approved drug	1 FDA approved drug

Source: Simon (2009)

transforming a compound into an food and drug administration (FDA) approved drug is about 1 in 10 thousand (Table 6), in a field where the know-ledge base is extremely complex, many disciplines (such as biology, chemistry, pharmaceuticals, medicine and increasingly molecular biology and immunology) must be resorted to and many tasks must be performed. Thus, they face a very risky bet.

Usually a DBF starts its operations with a small team of researchers, a lean laboratory structure and the intellectual property (a patent or an exclusive license on a university patent) over the molecule(s) it bets on. Since it would be impossible to realize internally all the experiments and analysis which must be performed in order to fully understand the characteristics of their molecules and test their validity for curing a disease, a *crucial decision for a DBF is to choose which tasks to realize internally, and which to externalize*. According to the study interviewees, the decision must take into account a number of factors.

First, it must be considered whether the know-how needed to perform a given task is strategically or rather occasionally important⁴. Second, the costs of realizing the tasks internally must be compared with the cost of outsourcing their execution. Economies of scale are crucial with regard to this factor. Third, and most important, it must be considered whether *the degree of skill in performing the tasks mastered by an external specialized supplier could ever be emulated internally, in a long run perspective*. Thus, the issue is not simply one of relative costs and of efficiency (in a williamsonian perspective), but rather one of capabilities and their possible evolution over time. It is to this aspect that we devote the study attention, seeking to understand what determines the durable *gains from trade* (Jacobides and Hitt, 2005) that can be captured by biotech firms by resorting to specialised suppliers.

Tacit knowledge underpins capabilities

A particularly important form of complexity that must be

⁴ However, even if a certain know-how is deemed strategic, a newly born firm with tight resource constraints might not be in the condition to build it, at least in the short run, since it might not afford the investments which are required. Regarding the implications of cash constraints on entrepreneurial decisions about firm scope, see Jacobides and Winter (2007).

addressed in building a capability is the degree of tacitness of the know-how. According to the R&D managers we interviewed, tacit knowledge is extremely important in biotech R&D:

Firm A: It is important to evaluate to what extent experience, feeling and intuition matter for performing a task, as opposed to hard, transferable elements. In my case, I have a great experience on cells, which I cultivated for 12 years. Literally, from 1 cell 2 can be obtained, from 2 cells 4 etc. They are not chemical stuff and are more complex than chemical molecules. Cells must be cultivated like plants. When one observes plants, one sees how healthy they are: if they suffer or have aphids, if the leaves are yellow...cells are the same thing, one must look at them and understand their condition. It is very difficult to teach someone to understand the face of a cell at the microscope. No handbook teaches it.

Firm B: Cellular biology is an art, not only a science. When you look at cells at the microscope, apparently they are all equal. You must have a very keen eye, to discover differences. This depends on personal sensitivity and experience.

Firm C: We collaborate with a group of Quebec City that works with monkeys since 25 years...they know that if monkeys move a finger this means something...How can we compete?

Also: The experts in a field know how to interpret the data... we might become very excited for data we did not expect, but those who can locate it in a wide context, due to their experience, know whether those data are really interesting or not.

A *high level of tacitness* (Pisano 2006a, 2006b⁵; Balconi 2007) not only involves a long time to acquire

⁵ According to Pisano (2006b, p.151), despite the advances in science and the growing use of bioinformatics and computer-aided drug discovery, biotechnology still contains a strongly tacit dimension: 'what is known about a target or a molecule or the behavior of a drug inside the body cannot be fully codified or reduced to precise rules (if X, then Y). Data from experiments are subject to a high degree of interpretation and differences of opinion. What constitutes a strong signal of potential efficacy for one researcher may give pause to another, based on idiosyncrasies in their training and experiences.... posed differently, there is still an 'art' to drug discovery that relies on judgment, instinct, and experience'.

knowledge, since learning is based on experience, but it also confers a great weight to the intensity of use of this knowledge over time. Since tacit know-how is continuously improved through its intense application to a variety of problems, if the internal use is lower than the use made by external suppliers, internalization over time is bound to lead to an increasing and insurmountable competitive disadvantage. Any form of fixed investment with a low level of utilization creates a cost burden, but in the case of tacit knowledge the issue is compounded by the inability to keep abreast of competitors. This aspect, which was repeatedly emphasized by the researchers we interviewed, weighs heavily in determining the choice of DBFs in favor of accessing external expertise and buying the services of a CRO.

Integrating different capabilities requires collaboration

It is also worth noting that when DBFs work on big, complex molecules, they need *to collaborate* with the CRO to which they outsource a development task, since the knowledge of the molecule (possessed by DBFs) and the knowledge about how to perform the task must be integrated.

Outsourcing the task cannot be done at arm's length. These partnerships do not tend to be jeopardized by the possibility that the parties learn from each other and then become competitors. In fact, learning simply as a byproduct of a collaboration is impossible for complex tasks. One should here distinguish between learning about previously unknown characteristics of the molecule, which is a typical and important result for a DBF of the collaboration with a CRO, and learning in the sense of acquiring the know-how of the specialised collaborator. This much more engaging form of learning can be accomplished only by means of a deliberate and long lasting training. It involves learning certain techniques and methodologies of analysis and how to use some specific instruments and facilities with the active assistance of the trainer, besides acquiring a theoretical knowledge. Only very simple techniques can be learned just by looking, at times, at what the expert is doing during the collaboration. According to the R&D manager at firm D:

Learning is very difficult. In order to learn through a collaboration, you need a completely different approach from that you put in place in order to obtain a precise specific result. For example, we went to AAI (Applied Analytical Industries) since we needed an analytical test on a very complex protein. They had never done it before, but they possessed the resources/competences to do it. So we met, we discussed, our scientists explained the specifications and how we worked with this protein and we came up together with the methodology for the test. They could have developed the test

autonomously, but it would have taken too much time. We have been working on these kinds of proteins for 15 years, so they have learned something new from us. We have learned as well, since we saw how they performed the analytical method. However, to be able to perform it ourselves would have implied too costly investments. Moreover, there is a 'small' problem. They were doing about 20 projects of that type, and before those other 20, and in the future they would have done other 20, so that they have hundreds of different cases and they accumulated know-how on that topic that we do not have and will never have. We address only one problem, that associated is to our protein. This is the great difference.

Open contractual arrangements harness transactional difficulties due to uncertainty

As explained by Jacobides and Hitt (2005), the condition that must be met for vertical specialization to take place is that the gains from trade arising from accessing the superior capabilities of a vertical specialist are not offset by high transaction costs - *the net TC tax* - which is the difference between external and internal governance costs.

Transaction cost theory (Williamson, 1975) claims that the cost of market governance is high when the terms of exchange are surrounded by uncertainty and when a party needs to invest in transaction-specific assets. Contracts made in conditions of uncertainty are necessarily incomplete and may require renegotiation when unexpected contingencies occur.

Referring to the issue of sourcing external R&D capabilities, Pisano (1999) stressed contractual difficulties caused by small-numbers-bargaining and the appropriability problems that arise if the R&D contractor is able to sell the know-how created during the project to the sponsor's product market rivals.

Howells et al. (2008) discussed the issue of asymmetric information between the client and the knowledge provider concerning the quality of the knowledge transferred. They argue that contractual incompleteness in a research contract arises because the supplier of the knowledge himself does not know *a priori* the results of his experiments and their duration before the project demanded by the client is performed. These contractual difficulties are likely to be greater for more complex research projects, to a point where market exchanges might be precluded. As to the possibility that the supplier could provide the knowledge created for a client to other clients, they emphasize the importance of the confidence accorded to the supplier. The arguments aforementioned could be synthesized into two main points, namely that exchanges might be hindered by:

1. The need of renegotiating contracts over time, due to initial incompleteness, in a setting of high uncertainty
2. The risk of misbehavior of the R&D supplier.

As to uncertainty and contractual incompleteness, it is not relevant in the case of the externalization of simple and repetitive tests, which is easily accomplished through contracts based on fees for services. In contrast, when complex and long-lasting research projects are externalized, *the unexpected is the norm*, and the question of contractual incompleteness, as put by transaction costs theory, seems even to understate the purport of the problem. The issue, more than the possible occurrence of 'unexpected contingencies', is rather that of framing the provision of an activity whose results are intrinsically uncertain (Pisano, 2006b).

Relatedly, the problem is not that of *renegotiating* inflexible contracts, to address unanticipated deviations from a predetermined path. Rather, the path can be defined only over time, step by step, through a process of *successive negotiations*. Interestingly, the solution devised and generally applied are *open* contractual arrangements, explicitly designed *to be completed over time*, in steps scheduled according to the sequence of experiments, after their results have been known. According to firm A's manager:

'A contract is written, inflexible, while R&D activity is flexible by nature, since it is unknown where it will lead. The idea is to make the two things compatible'.

Compatibility is attained by grafting flexibility into the contracts through open clauses, to be written at the completion of each phase of the R&D process. Thus, uncertainty is unpacked and reined in by subdividing an uncertain long-lasting process into sequential steps, where the completion of each step, by transforming into known what was previously unknown, sets the stage for the contractual definition of the next.⁶

A contractual arrangement that we have found put in place is the following. The parties sign a Master Service Agreement, a long-term framework contract which sets the rules of the collaboration between the client and the R&D service provider, defining the objectives of the research project and the route to realize them.

A joint operating committee (JOC) and a joint steering committee are created, with equal participation of both parties, with the aim of monitoring and managing the development of activities. Then the so called Work Orders (WO) are introduced in the course of time, each defining what is to be realized in a certain phase and how. When each phase is completed, the results are evaluated by the JOC and the successive WO is defined. A WO itself is not fixed, since over time various amendments - the so called Change Requests - are introduced, which define technical details and their

prices. For example, a WO states that after activity A activity B will start, but if A does not yield the expected results, B must be postponed.

Therefore, a change request amends the unfulfilled WO. This system is deemed very effective, since the needs of amendments are fully understood by the client, due to the continuous interactions between the research staff of the two parties and the supervision of the JOC. Overall, the externalization of complex R&D projects amounts to a long-lasting collaboration based on intense relationships among the parties, rather than an arm's length provision of a service.

This form of collaboration might also evolve into a true partnership, formalized through a risk sharing agreement. This contractual form states that the activities undertaken by a CRO are not paid as the work develops, but at the end of the project when its value is monetized in the market (that is, a big pharma company buys the product/therapy developed).

This more risky business model has spread recently. It helps resource-constrained biotech firms to fund their projects and it is expected to increase CROs' profitability, by rewarding risk. However, most CROs' business is still based on fees for services, a model which ensures their basic economic viability, while risk sharing agreements tend to cover a minor part of their activities.

CROs might also prefer, instead of receiving only fragmented orders by many clients, to undertake integrated projects with them. In this case, the CRO's project team might include researchers of the client firm, and the form of payment becomes based on the number of researchers allocated to the project (Full Time Equivalent payment model). Some risk sharing might also be introduced, by reducing the FTE payment by an amount to be due at the end of the project in the form of a (higher) bonus in case of success.

The problem of small-numbers-bargaining seems to rise only in very particular cases, of extremely advanced research projects, such as tailor-made services for cell and gene therapy projects. An example of this sort is the collaboration between the Italian hybrid biotech company Molmed and Glaxo SmithKline. In order to provide GSK with the productive capacity required to develop gene therapies for some rare diseases, Molmed - already possessing the specialized know-how and the theoretical knowledge brought by its founder, a star academic scientist - had to make important investments, which tied it to GSK.

However, it would have been difficult for GSK to transfer the good manufacturing practices (GMP) methods developed by Molmed to the facilities of another firm. On both sides of the relation, the possibility of changing partner was very limited, due to the very small number of actors at the world level working on similar projects, and it would have involved significant costs, but it remained a potential threat. Thus, a delicate balance between the contractual strength of the partners had to be maintained day by day, through a process monitored

⁶ Clearly, 'unstructured technical dialogue' is a fundamental aspect underpinning contractual agreements in our case. The capability of commercial partners to manage this issue successfully stands in contrast with much literature (among others, Monteverde 1995, Christensen et al. 2002), according to which markets are inefficient coordination mechanisms 'across interdependent interfaces' (Helfat 2015).

and governed at the top level between Molmed's CEO and GSK manager responsible for the therapeutic area.

Cases of this sort are the exception, while the rule is that the market for R&D services is quite competitive - there are a multitude of CROs in most segments of the market - and in order to meet the demands of their clients CROs do not need to make relevant specific investments. The force of competition and the importance of reputation also diminish the risk that a CRO might provide services of unsatisfactory quality. And with regard to the risk that a CRO might transfer the knowledge acquired from one client to other clients, it is kept low by the fact that client firms always patent their discoveries before approaching a CROs for their services. Moreover, there is a widespread awareness that 'fairness' in contractual relations with R&D partners is fundamental.

The self-reinforcing dynamics of vertical specialization: A framework consistent with the study insights

The heterogeneity of firm capabilities is widely acknowledged, as well as its importance to determine the division of labour among firms (Jacobides and Hitt, 2005; Jacobides and Winter, 2005). Recently, Jacobides and Winter (2012) underlined that initial divergences among actors are sustained by a variety of mechanisms, both rational and behavioral, so that over time they tend to increase.

The focus of this study is not on the heterogeneity among single agents, but rather between IP-based firms (DBFs) and expertise-based firms (CROs). According to this perspective, once a process of vertical disintegration starts, and specialist firms arise (specialised in various stages/tasks of the R&D value chain) capabilities become *divergent*, not simply heterogeneous.

Moreover, specialists increasingly attain a competitive advantage over integrated firms as a consequence of specialization itself. We suggest that dynamic economies of scale are particularly salient⁷. In fact, specialists engaged in many projects are able to develop superior capabilities over time through a learning process which takes place more rapidly and deeply than it is possible within vertically integrated firms. If tacit knowledge is important - as it is in the R&D process in the biopharmaceutical industry - the scope and variety of experiences of specialists translate into a deep-rooted superior capability. This perfectly resonates with Jacobides and Winter (2005) contention:

Changes in vertical scope at the firm and especially at the industry level can and do affect the nature of the

knowledge accumulation and capability development process; indeed, such changes may be among the most pervasive and least studied drivers of capabilities over time. To the extent that the specialized production leads to faster knowledge accumulation, vertically specialized firms may be able to improve more quickly than the integrated ones.

The generated capability gap feeds back into an acceleration of the disintegration process, since it becomes increasingly advantageous to resort to specialised know-how. Thus, a self-reinforcing dynamic of specialization takes place. Moreover, the existence of an *industrial infrastructure of specialist capability carriers* at various stages of the R & D value chain facilitates entry by IP-based start-ups, which have the opportunity to choose even a virtual business model. Barriers to entry are low due to this infrastructure. The entry process further contributes to increase the degree of disintegration of the industry.

Finally, the study focus on capability gaps does not imply that other factors⁸ should be considered negligible to explain a disintegrated industrial architecture, such as the quest by firms of *velocity*, and *flexibility* and their tendency to concentrate resources on core strengths. The pursuit of flexibility is especially emphasized in the literature on the increasing reliance on CROs by big pharmaceutical firms, seeking to *streamline their structure and reduce risks* (Piachaud, 2002; Howells et al., 2008). Note that this process of reorganization which implied the expansion of CROs' market (disintegrating firms becoming their new clients), at the same time enabled CROs' growth, since they could absorb the experienced research teams that big pharmaceutical firms were disbanding. An interesting example we came across is the agreement of Aptuit with GlaxoSmithKline (GSK).

In February 2010 GSK announced its decision to cut its research center of Verona (Italy), staffed with about 500 scientists, in the context of its exit from the field of research on central nervous system. Aptuit, a CRO founded in 2004 and headquartered in Connecticut (USA), decided to acquire it, greatly increasing the scope of its capabilities. Hence an important scientific team was not dispersed, but became part of the global infrastructure of knowledge carriers to which IP-based firms can resort to, in their search for flexibility. And again, the process of streamlining R&D by big pharmaceutical firms feeds-back into strengthening the capabilities and resources of vertical specialists. The dynamics of the increasing division of R&D labour in the biopharmaceutical industry could be summarized as follows:

Phase 1) Initial state: The biopharmaceutical industry is

⁷As is well known, the importance of static economies of scale as a source of competitiveness for independent supplier firms was originally proposed by Stigler (1951), since their scale of production is not limited by the extent of in-house demand.

⁸According to Jacobides and Hitt (2005) a 'panoply of different factors can come into play in explaining vertical scope'.

populated by big integrated firms; also the first biotech firms are integrated in all phases of R&D (no external carriers of new biotech methodologies and techniques exist).

Phase 2) Transformation: The increase of R&D costs and complexity prompts vertical specialization, as disintegration drivers acquire importance. A population of consultant and small independent laboratories undergoes a major transformation: the CRO segment of the biopharma industry emerges starting in the field of clinical trials, statistical analysis and database management and it grows (by expansion of incumbents and new entries) by expanding capabilities in the area of preclinical development (in fields such as pharmacokinetic, pharmacology, formulation and toxicity studies etc.) besides manufacturing of small batches in GMP. Transaction costs are kept low by devising contractual forms suited to address uncertainty, by competition among CROs and by the importance of reputation (both scientific/technical and moral) to attract clients. Barriers to entry for IP-based start-ups are lowered.

Phase 3) Self-reinforcing dynamics: The emerging division of R&D labour shapes capabilities. A self-reinforcing dynamics of specialization takes place. CROs increasingly become a sort of industrial infrastructure of R&D capabilities which IP-based firms (both incumbent firms and start-ups) and universities can tap.

CONCLUSIONS

The main contribution of this study is shedding light on a phenomenon which has been well known by practitioners already for many years, but scarcely studied and appraised by the economic and managerial literature: the role attained by CROs in the biopharma industry.

In particular, after presenting the breadth of their development by relying on industrial secondary sources, we develop a novel interpretation of the basis of their competitive advantage, delving into the mechanisms of R&D capability building. We also highlight how new open contractual forms make it possible to harness transactional difficulties in a context of extreme uncertainty.

Depending on the sources, the CROs' market size in the biopharma industry has reached about 25 to 34% in the years 2013 to 2014, and should increase to about 43 to 59% in the year 2020, with a CAGR of about 9 to 10% over the whole period. The major part of CROs' revenues (about 80%) will continue to be obtained at the clinical stage (as one can expect since clinical services are much more costly than preclinical ones), even though, according to various sources, preclinical growth will be higher. For a great part of small biotech firms the importance of CROs' both preclinical and clinical services has become paramount, but unfortunately no data are available and this appraisal relies mainly on the

witnesses that we have collected and on the contributions found in the medical/pharma literature.

The growth of CROs, specialised knowledge carriers capable of accomplishing the development tasks with higher expertise than most IP-based firms, has changed the vertical structure of the biopharma industry. Based on the interviews of a number of key informants, we propose that the higher scope for learning is the main factor underpinning CROs competitive advantage which drives their expansion.

In fact given the importance of tacit knowledge, the variety and the multitude of experiences are a fundamental lever for acquiring superior capabilities: this condition favors specialised actors working for many clients compared to those that can deepen their experience only by executing their own projects. Hence IP-based small and middle-size biotech firms (as well as big R&D streamlining pharmaceutical companies) can carry out their projects by leveraging this external infrastructure of specialised capabilities, supposed they are endowed with the human capital required to build a collaborative dialogue with them.

This infrastructure is very important for an effective functioning of the biopharma industry. The existence, as underscored by Pisano (2006), of many inexperienced firms in the industry, due to the high rate of IP-based firm formation and early demise, no longer means that 'much of the tacit technical and organizational knowledge needed to do R & D well is not accumulating in the industry' (Pisano 2006a). While it remains true that IP-based biotech firms, with the exception of established actors like Genentech, Amgen and few others, are not organized to learn from experience, at the level of the industry this weakness has been to a large extent made up for by the role acquired by CROs.

In other words, the emergence and expansion of CROs is functional for the industry, since a sort of backbone of stable capabilities has been created. Even if the turbulence and mortality of IP-based firms is extremely high, if they rely to a great extent on CROs, the experience acquired to carry out their projects - which mostly fail - does not get lost but cumulatively enhances CROs capabilities, a resource that remains available for an effective execution of further projects sponsored by other actors.

Finally, some interesting managerial implications can be drawn from the study analysis. First, we stress the importance, in the managerial decision regarding whether to outsource R&D, of taking into account not only static sources of competitive advantage (such as economies of scale), but also the likely dynamics of capabilities over time, on a comparative basis with external R&D providers. In a knowledge-based field of activity this aspect is crucial. Second, we suggest decision makers not to consider transaction costs as a given: innovation in contractual forms might lower them to acceptable levels, even if uncertainty is very high. In particular, in a

collaborative relationship between client and supplier, open contractual forms, with clauses to be defined over time as an R & D project reaches new milestones, might be very effective. The main limitation of this study is the absence of first-hand quantitative data and the reliance of secondary sources.

Thus, a very interesting direction for future research would be the collection of data on the diffusion of CROs at a global level, or at least within a wide geographic area, such as Europe or North America. This could be done only through a research project lasting a few years and based on a great number of interviews to biopharma firms, aimed at uncovering their real nature, whether of process-based firms or rather of product/IP based. But many other interesting questions could be addressed: for example, what is the relative competitive force of big CROs versus small ones? What tasks can be automated over time and thus would no longer rely on tacit knowledge? Accordingly, how would processes of capability development change?

These and many other possible questions are suggested by this study, that we hope can open a breach in a field that is both very interesting and largely unexplored.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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