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MEASURES THAT MATTER –
VENDOR PERFORMANCE IN OUTSOURCED BIOEQUIVALENCE STUDIES

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ABSTRACT

Outsourcing clinical research (R&D) and development to specialised contract research organisations (CROs) is common in the pharmaceutical industry and while these practices and characteristics of sponsor-vendor relationships have been widely studied in the context of new drug development, little has been presented about outsourcing activities of generic pharmaceutical companies. Outsourcing brings the need to monitor vendor performance through meaningful measures in an effective manner. The paper presents a case study of a multinational generics company that outsources all clinical research activity, either to a wholly-owned subsidiary CRO or to different external CROs. Clinical R&D managers were interviewed in order to establish the context and areas of focus for vendor performance measurements for the case company. The study briefly explores whether differences exist in how the company handles evaluation of its external and internal vendors. Although specific to the case company, the results may be relevant to other generics developers.

Keywords: Clinical research, outsourcing, performance measurements, quality

ÁGRIP

Útvistun klíníska lyfjarannsóknaverkefna til sérhæfðra þjónustufyrirtækja (s.k. CRO) er algeng í lyfjaiðnaði. Allmikið hefur verið rannsakað og ritað um útvistun og eiginleika viðskiptasambands bakhjarlsins (þ.e. lyfjafyrirtækisins) og birgjans (þ.e. CROsins) í tengslum við frumlyfjaþróun. Minna hefur verið fjallað um útvistun innan samheitalyfjageirans. Útvistun kallar á skilvirka vöktun á frammistöðu birgjans með viðeigandi mælingum. Hér er kynnt tilviksrannsókn þar sem viðfangsefnið var alþjóðlegt samheitalyfjafyrirtæki sem útvistar öllum klínískum rannsóknum, annað hvort til eigin dótturfyrirtækis eða til mismunandi ótengdra CRO-fyrirtækja. Tekin voru viðtöl við stjórnendur klínískra rannsókna til að draga fram áherslusvið fyrirtækisins fyrir mælingar á frammistöðu birgja. Kannað var hvort einhver munur sæist á birgjamati á eigin dótturfyrirtæki eða öðrum þjónustufyrirtækjum. Niðurstöðurnar eru fyrst og fremst lýsandi fyrir fyrirtækið sem skoðað var, en kunna þó að hafa almenna skírskotun innan samheitalyfjageirans.

Lykilorð: Klínískar lyfjarannsóknir, útvistun, árangursmælikvarðar, gæði

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1. INTRODUCTION

Pharmaceutical companies are under constant pressure to increase productivity and bring medicinal products to market within shorter timelines, operating in an environment of intense competition, changing technologies, ever increasing regulatory requirements for the amount and quality of data needed to support marketing authorisations, and an economic climate that forces them to do more research with less headcounts and smaller budgets.

One of the approaches adopted by pharmaceutical companies to respond to these pressures has been to outsource some of their research and development (R&D) operations to specialised service providers or vendors, so-called contract research organisations (CROs), in order to reduce costs, accelerate development speed and increase organisational flexibility (Lee, 1998; Piachaud, 2002; Winter & Baguley, 2006). Outsourcing brings the need to monitor vendor performance in a consistent and economical manner. Although this is an accepted reality, a recent survey of pharmaceutical companies that outsource clinical research activities revealed that only about half of the respondents employed measures of performance and relationship quality, whereas overall the companies rated better performance measurements as one of the most important areas to improve to achieve greater outsourcing efficiency (Calaprice-Whitty, 2010).

Much has been written about clinical research management in new drug development, including outsourcing to CROs, however, the literature on outsourcing activities of generic pharmaceutical companies in particular is sparse. As discussed later, there are certain key differences in the characteristics of outsourcing of clinical research for generic versus brand pharmaceutical companies, in part explained by the nature and scope of the projects being outsourced and in part by their operating environment. This manuscript presents a case study of an international generics company that outsources all clinical research conduct (i.e. conduct of bioequivalence studies) through either of two routes; true outsourcing to independent CROs, or; commissioning work from a wholly-owned subsidiary CRO that also conducts business for third parties. Qualitative interviews were conducted with key informants of the case company and its subsidiary CRO to draw out their experiences, insights and perceptions in order to answer the following questions:

- What are relevant measures of quality of clinical vendor performance for generic companies?
- What are the benefits of owning a CRO?
- Are there differences in how the case study company handles evaluation of its external or internal vendors?

The paper is structured as follows: The literature review in section 2 provides a brief overview of the drug development process for new drugs and generic development; the outsourcing practices of the pharmaceutical industry in general and of the generic sector; and introduces the principles of performance measurements. The research approach is explained in section 3. Section 4 contains interview results and analysis of the case company's quality audit data. The discussion in section 5 allows conclusions to be drawn in section 6 that are primarily applicable to the case company but can be of relevance for the generics industry as a whole.

2. LITERATURE REVIEW

2.1 Drug development

Pharmaceutical development is a long and costly process. It involves the identification of new molecular entities (NMEs) with promising activity towards a specific disease target and bringing that compound through laboratory, animal (or pre-clinical) and human (or clinical) testing, collecting evidence on its physicochemical properties, safety and therapeutic efficacy along the way to eventually support a marketing authorisation by regulatory bodies and subsequent marketing of a drug (see schematic representation in Figure 1).

The full R&D process requires on average 13.7 years to complete (Pharmaceutical Benchmarking Forum, 2012). Published estimates of the time and cost of development of a new drug span substantial ranges (Morgan, Grootendorst, Lexchin, Cunningham, & Greyson, 2011). A recent analyses estimates the capitalized cost of developing an NME to a marketed drug at 1778 million USD (1929 USD adjusted for inflation from 2009 to 2013 (Bureau of Labor Statistics, n.d.)) with clinical development accounting for approximately 63% of the costs (Paul et al., 2010). Clinical drug development progresses through four temporal phases (phase I-IV, see Figure 1) from small first-in-man studies in phase I through to large, multinational studies involving thousands of patients in phase III and a large number of investigative sites. Safety and effectiveness of the drug must be demonstrated in diverse populations (e.g. elderly, children, different ethnicities, pregnant and lactating women). Subsequent to marketing authorisation, even larger phase IV post-marketing studies are conducted to collect data about the drug's safety and effectiveness when large populations of patients have been exposed to its use over a period of time.

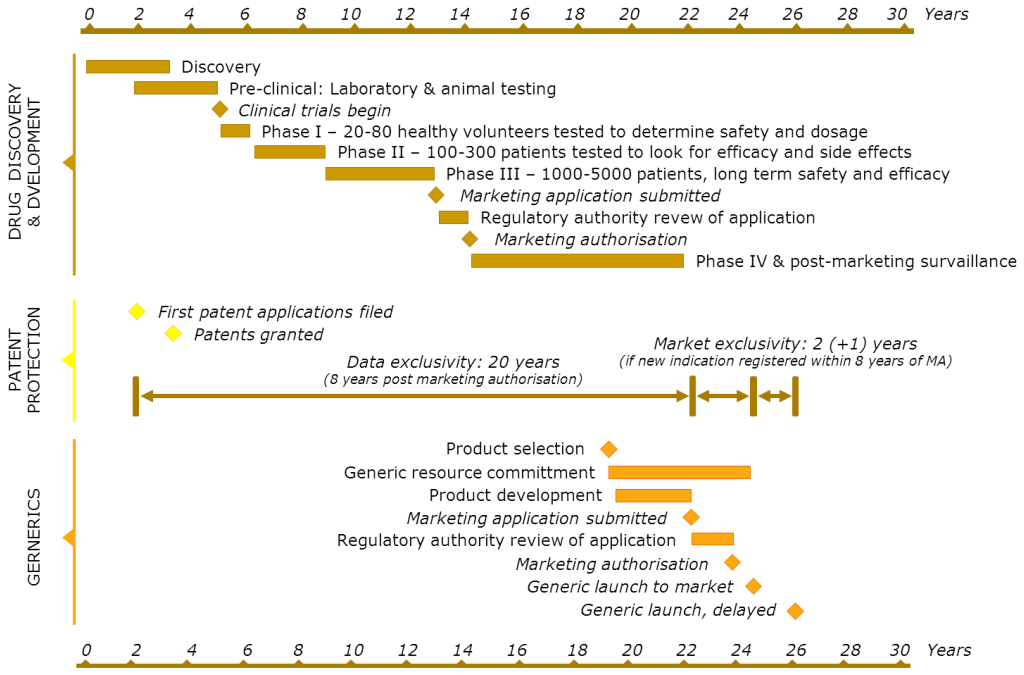

Figure 1 – New drug development, periods of patent protection and generic medicines

Productivity in pharmaceutical R&D is low. In 2011, the US Food and Drug Administration (FDA) approved 24 NMEs and 6 new biologics drugs, the most since 2004 (Mullard, 2012) and more than approved by the European Medicines Agency (EMA) in that year. Aside from this slight increase in 2011, the number of NMEs reaching the market has declined by 20% over the last decade (Paul et al., 2010).

At the same time, the global pharmaceutical and biotechnology industry spends more on R&D than any other industrial sector (European Commission, 2012).

The drug development process is highly regulated and the level of regulatory authority governance and scrutiny is ever increasing. Regulatory bodies and industry associations in Europe, USA and Japan have collaborated since the 1980s to harmonise requirements for development and registration of drugs through the foundation of the International Conference on Harmonisation (ICH). The guidelines developed by ICH are then adopted into law in the ICH countries, however, local and regional requirements outside the ICH region, and even within the region, remain disparate, calling for certain multiplication of development efforts and expert knowledge of many different requirements that all must be fulfilled at the appropriate stages throughout the development process. Regulatory compliance – and thereby, quality management of the development process – is of paramount importance with the ultimate objective of ensuring patient safety and data integrity.

2.2 Outsourcing in pharmaceutical R&D and its advantages

Pharmaceutical companies have, since the late 1970s, relied on outsourcing to manage within the constraints described above. Outsourcing has be defined as "a predetermined means of externally obtaining goods or services previously provided by the organization itself" (Kakabadse & Kakabadse, 2000). The decision to outsource has through history been considered around the question to "make or buy", the original reasoning for outsourcing being that a company should not make on its own what it can reasonably obtain from outside sources at a better price, i.e. cost motivation. Piachaud (2002) summarised the factors driving the use of CROs in the pharmaceutical industry as the following:

- Convert fixed costs into variable costs – Service agreements with CROs do not bind the company in long-term obligations in hiring, training and maintaining a talent pool
- Reduce the number of employees – Consolidation and downsizing in the pharmaceutical industry has continued over the last two decades and CROs represent just one available source of contractors
- Lack of capacity – In times of peak activity or large projects exceeding in-house capacity, excess work can be contracted out
- Accelerate speed to market – The combined effect of expediently accessing resources and expert therapeutic area knowledge. Research has shown that CRO usage is associated with faster development speed at comparable quality between low and high CRO use (Getz, 2006)
- Terminate weaker projects – More straightforward for outsourced projects than concluding an in-house project
- Global drug development – A multinational CRO or different local CROs can provide the reach and local knowledge to aid the process
- Access to knowledge and skills – Contractors can fill gaps in a pharmaceutical company's competence, relating to innovation and specialist expertise, including regulatory knowhow
- Access to technology – A segment of the CRO market offers primarily technological solutions for pharmaceutical development

In their review, Kakabadse & Kakabadse (2000) summarised the above as the advantages offered of greater capacity for flexibility, decreased cycle times, full utilisation of external suppliers' investments, innovations, and specialised professional capabilities than otherwise would have been the case, which for any one organisation would be prohibitively expensive to replicate.

The first CROs offered specific tasks for pharmaceutical companies, such as identifying investigator sites, monitoring data processing and protocol compliance at sites, statistical analysis and regulatory support (Lee, 1998). The service offering has developed significantly and in addition to specialised contract manufacturing organisations, various niche and full-service CROs now offer an array of services that extends both upstream into early development and downstream into regulatory submissions, post-authorisation pharmacovigilance and marketing and sales (Winter & Baguley, 2006).

In 2011, the total global market for all contract services supporting prescription drug R&D (see Table 1) has been estimated at 90-105 billion USD (Getz, Lamberti, Mathias, & Stergiopoulos, 2012). Clinical research outsourcing was estimated at between 12.4-16.2 billion USD and the growth of clinical outsourcing continuing to exceed that of the overall R&D spend(William Blair & Company, 2011), a trend observed since 2001 (William Blair & Company, 2011; Getz & Vogel, 2009). In light of the above, it is surprising still only about half of sponsors[3] monitor performance of these vendors in a systematic manner.

Table 1 – Global pharmaceutical sales, R&D spending and outsourcing 2011

	Total (billion USD)	Growth from previous year
Prescription drug sales, total	716	5.9%
Prescription drug sales, generics	65	10.2%
R&D spending, total	135	4.9%
R&D spending, clinical development	85*	N/A
R&D outsourcing, total	90-105**	N/A
R&D outsourcing, clinical development	12.4-16.2**	10%***

Prescription drugs only, over-the-counter and nutraceuticals excluded; N/A = not available
Sources: *World Preview 2018 – Embracing the Patent Cliff* (EvaluatePharma, 2012)
Industry sales based on Top 500 pharmaceutical and biotech companies
* *How to improve R&D productivity* (Paul et al., 2010)
Clinical development costs account for 63% of total R&D cost
** *Resizing the Global Contract R&D Services Market* (Getz, et al., 2012)
*** *CRO Industry Update - Results from Fifth Survey of Pharma and Biotech Sponsors* (William Blair & Company, 2011)
Projected growth rate over the period of 2010-2015

2.3 Drawbacks or disadvantages

Outsourcing clinical R&D carries risks and one of the first important disadvantages mentioned may be dependence on the supplier and loss of control over critical functions (Kakabadse & Kakabadse, 2000; Piachaud, 2002). Laws and guidelines are explicit regarding the sponsor's responsibility for conduct of clinical trials in that the sponsor is ultimately responsible for ethical study conduct and scientific integrity of the data, even though all of the sponsor's trial-related duties and functions are being contracted to a CRO and the CRO must follow the same regulations and guidances as the sponsor (European Commission, 2004; International Conference on Harmonisation, 1996)[4]. This means that non-compliance with regulatory requirements at any level in the supply chain may lead to sanctions towards the pharmaceutical company or its executives. Ethical questions raised about the practices of a subcontractor will be reflected upon the sponsor with potential loss of reputation, lack of public trust and damage to business objectives. These risks must be mitigated through effective vendor management activities by the sponsor and such requirements are recognised in

[3] An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial (International Conference on Harmonisation, 1996), i.e. the pharmaceutical company developing the drug.

[4] The ICH Guideline for Good Clinical Practice (ICH GCP) is, along with the Declaration of Helsinki, the principle guideline for clinical trials.

guidelines as part of quality assurance and quality control schemes (International Conference on Harmonisation, 1996, 2008).

Other disadvantages may be the result of organisational changes and downsizing that may precede or be associated with the strategic decision to outsource, such as loss of internal knowledge and understanding, role-confusion and loss of employee morale (Kakabadse & Kakabadse, 2000; Lowman, Trott, Hoecht, & Sellam, 2012; Piachaud, 2002). Many companies also struggle to realise the expected financial benefits of outsourcing, as internal cost and effort associated with managing the relationship and overseeing the outsourced projects are often neglected (Winter & Baguley, 2006).

Along with increased outsourcing, contract research has shifted to the so-called emerging markets, to middle- and low-income countries where labour cost is low and access to large populations or treatment-naïve volunteers and patients is good. Cultural differences, language barriers, political instability, corruption and legal and ethical risks may present barriers when working in these regions, calling for even greater commitment from the pharmaceutical companies to ensure integrity of the research (Submitter, Van Huijstee, & Schipper, 2011).

2.4 Outsourcing relationships

Outsourcing relationships in the pharmaceutical industry may be divided into two principal categories: tactical outsourcing (fee-for-service) and strategic partnerships, see Table 2 for an overview (Erasmus & Khera, 2012; Jones & Minor, 2010; Glass & Beaudry, 2009; Winter & Baguley, 2006).

Tactical partnerships are less mature relationships with a CRO. Strictly transactional relationships can include single or multiple area outsourcing, typically on a project basis, with limited upfront requirements placed on the vendor. Contracting is driven by an immediate client need for rapid deployment. These are typically established to maximize cost and/or time savings and often entered into through a competitive bidding process. Preferred provider agreements (PPA) reside on the border of tactical and strategic relationships. Outsourcing is to a selected set of pre-qualified CROs, sometimes for a number of studies at a time, based on competencies, therapeutic match, geographic reach or specialised services. These engagements typically have a defined lifespan and there is focus on improvements in cycle time and quality of deliverables over the term of the PPA.

The most common form of strategic partnerships is the functional service provider (FSP) agreement, where a whole service area is outsourced (such as data management, statistics and programming, clinical monitoring, site start-up services), effectively capitalising on the vendor's core competencies and gaining efficiencies through mutual development of processes and technologies, with improved operational function resulting from repeated use of the same vendor. Alliances mature the relationship even further, wherein the CRO becomes an extension of the sponsor in execution of the whole development of the NME or specified parts of the clinical development plan. The partners agree on a strategic vision and mutually design metrics to determine how well the strategy is being implemented. Alliances generally involve greater investment in the project by the CRO and risks and profits are shared between partners. Cost savings does not drive these outsourcing relationships as much as the established trust that develops between the sponsor and the vendor. Although not the initial purpose of a strategic alliance, the integration between partners can ultimately lead to merger or acquisition.

Table 2 – Types of outsourcing relationships

	Transactional	Preferred	Partnering	Alliances	Integration
					
Description	Fee for service	Reduced fee for service	Risk sharing and shared milestones	Sharing both profits and risk	One profit/loss
Attributes	Price dominants	Assured standards	Performance improvement	Business objectives	Core competencies
Features	Tenders tactical negotiation	Pre-conditions Pre-qualifications	Mutual development	Joint ventures	Mergers and acquisitions
Benefits	Capacity management Cost reduction	Reduced costs of CRO oversight, operational efficiencies	Optimal proactive resource management Knowledge transfer	Enhanced productivity Mutual converging organisational development	Competencies brought in-house Strategic advantage
Drawbacks	Effort in vendor oversight Limited opportunity to gain efficiencies	Must qualify large pool of CROs	Lock-in		Increased fixed costs

Sources: *Outsourcing Clinical Development: Strategies for Working with CROs and Other Partners* (Winter & Baguley, 2006)
New, Strategic Outsourcing Models to Meet Changing Clinical Development Needs (Jones & Minor, 2010)

CROs must possess substantial capabilities in order to be able to serve as FSPs or form alliances to support a sponsor's portfolio. Small to midsize pharma companies still report that their vendor relationships are predominantly tactical; small CROs are focussed on transactional relationships and subcontracting to larger CROs; and many midsize CROs are building more capacity through acquisitions and mergers to compete with the largest CROs for FSP agreements and alliances (Getz, 2012). Similarly, small pharmaceutical companies rely predominantly on transactional outsourcing, whereas midsize and large companies use a combination of functional and tactical outsourcing (Calaprice-Whitty, 2010).

2.5 Generics companies and outsourcing

Generics companies in broad terms have the primary role of producing and marketing generic pharmaceutical products (see Box 1) that are equivalent to the reference product, i.e. originator or brand pharmaceutical product. The same requirements and quality standards apply for the formulation and manufacture of generic drugs as brand drugs. However, generic developers are not required to submit non-clinical data for the marketing authorisation, and where clinical data are needed, these are most often derived from bioequivalence (BE) studies, typically single-site studies conducted in a small number of healthy volunteers (European Medicines Agency, 2010, 2012). In order to support each marketing authorisation, generics companies may need to conduct and submit results for only one or a small number BE studies (European Medicines Agency, 2008). A survey reveals that on average, generics companies conduct 3 BE studies during their development process (Best Practices LLC, 2012).

Overall development costs for generic drugs are only a fraction of the estimated cost of developing a new drug. It has been estimated that from the time a decision is made to produce a generic pharmaceutical product, manufacturers typically invest between three to six years (compared with 8-15 years for brand drugs) and an estimated 4 million USD to bring the product to market (compared with nearly 2 billion USD for brands) (Canadian Generic

Pharmaceutical Association, n.d.). In contrast with branded drug development, the majority of the cost lies in the formulation and development of the physical product, but not clinical testing.

Box 1 – Generic medicines

- A generic medicine is a medicine that is developed to be the same as a medicine that has already been authorised, called the 'reference medicine' (i.e. the originator or brand drug)
- A generic medicine contains the same active substances as the reference medicine, and it is used at the same doses to treat the same diseases. However, a generic medicine's inactive ingredients, name, appearance and packaging can be different from the reference medicine's
- Generic medicines are manufactured according to the same quality standards as all other medicines
- As for all medicines, generic medicines must obtain a marketing authorisation before they can be marketed
- As the reference medicine will have been authorised for several years, information is already available on the efficacy and safety of the active substance(s) it contains
- A company producing a generic medicine needs to provide information on the quality of the medicine
- In most cases, it will also need to supply data from a bioequivalence study to show that the generic medicine produces the same levels of the active substance in the body as the reference medicine
- A company can only develop a generic medicine for marketing once the period of exclusivity on the reference medicine has expired. This is usually 10 years from the date of first authorisation

Source: *Questions and answers on generic medicines* (European Medicines Agency, 2012)

Competition between generic medicine manufacturers is fierce, where price competition, even in the form of discounts to pharmacies and wholesalers, is well-known (Simoens, 2012). Under US FDA law, the first generics product granted an approval may be eligible for 180 days of exclusivity on the market during which no other generics approval will be granted, giving generics companies a large incentive to be the "first-to-file" (Center for Drug Evaluation and Research (CDER), 1998). The first generic product to market is also likely to become the best know in the minds of those who de-facto control their sales, i.e. prescribing physicians. Speed to market is therefore of even greater importance to generics than brands as small reductions in cycle times may carry significant competitive advantage.

In this sector, outsourcing clinical operational tasks has become routine, rather than exception. A recent benchmarking survey of outsourcing in the generics industry showed that all of the respondents outsource clinical activity some of the time and 65% always do (Best Practices LLC, 2012). The reasons for outsourcing fall into the same categories as other outsourcing of clinical research (see section 2.2). Generics companies' core competencies lie in pharmaceutical manufacturing and marketing, not in clinical research, so they seek resources with minimal investment. The emphasis on cost-effectiveness, speed and on-time delivery results in vendor relationships that are predominantly tactical in nature (Winter & Baguley, 2006).

BE studies are most often conducted by CROs that specialise in the conduct of these clinical studies (European Medicines Agency, 2008). These small to midsize CROs often provide full service for generic drug sponsors, including research protocol development, recruiting volunteers and full study conduct at their specialised clinics, bioanalytical laboratory analyses, data management, statistics and clinical study report generation.

2.6 Performance measurement

The purpose of performance measurement is to encourage behaviour that achieves the goals of the organisation (Lake, 2010). There must be the true understanding of "why" behind metrics; otherwise there is the risk of misinterpreting the

information. Any measures employed should be actionable. It is not enough to simply measure and track metrics, i.e. unless action (or decisively no action) is taken based on a measure it serves no purpose and represents a futile data collection effort (Lake, 2010; Tillmann & Shepherd, 2009). The use of measures may be dependent on whether they are lagging or leading, i.e. demonstrating the outcome of events already taken place or allowing an indication of where a process might be slipping, respectively (Lake, 2010; Tillmann & Shepherd, 2009).

Spitzer (2007) put forward the "four keys" to transforming performance measurement: context; focus; integration; and interactivity (see Table 3). His book echoes the message that a measurement must be relevant, practical, and understandable. This means relevant to the people involved, relevant to the company's objectives and technologically easy to execute.

Table 3 – The four keys to transforming performance measurement

Key	Elements
Context	Everything that surrounds a task or measure, including how measurement is perceived by employees The first key to progressing toward transformational measurement is to change the context in a positive direction
Focus	Select the right measures Focus on a critical few transformational measures that will make a real difference to competitive advantage and differentiate the organization from others
Integration	Develop a framework that shows how each measure is related to other important measures, and how they combine to create value for the organization Align measures with strategy, and then integrate across the entire organization Frameworks spotlight the potential of ''cross-functional measures'' that can help to integrate functions and lead to higher levels of collaboration
Interactivity	Interaction at each phase of the process leads to new insights about what to measure and how to measure it Feedback loops should and will all be highly social and interactive

Source: *Transforming Performance Measurement* (Spitzer, 2007)

Pharmaceutical companies implement clinical vendor oversight schemes (Submitter et al., 2011). Their approach is systematic and based on the "good practices" principles of the applicable regulations and guidances for drug development. However, to align measurement with the business strategy in order to achieve competitive advantage, the context and focus of measurement must first be considered (Spitzer, 2007).

3. RESEARCH PROJECT

3.1 Project description and objectives

This research was undertaken to establish the context and areas of focus for performance metrics for clinical outsourcing for a generic pharmaceutical company, under the assumption that the results may be of relevance for this industry sector as a whole. It was further of interest to consider whether or not differences exist in how the case study company handles evaluation of its external or internal vendors.

3.1 Research methodology

The research was conducted as a case study of a multinational pharmaceutical generics company and employed different data collection methods. The purpose of this research is to collect information on the context, focus and relevance of outsourcing performance measures for the case company to gain a better understanding of what is of primary interest to the outsourcing management.

A quantitative or empirical approach might be applied, e.g. through a structured questionnaire survey, however, at this early stage rich, descriptive information is sought and a questionnaire may be restrictive or limited by the researcher's own opinions of what should be measured or what already has been published in the literature or commercial solutions on the topic. Therefore, the method of conducting semi-structured interviews with key informants within the organisation with first-hand knowledge of and responsibility for outsourcing clinical activity to vendors was selected. Semi-structured interviews are a qualitative method that provides opportunity to explore the opinions, views and experiences of the interviewee. They are conversational in nature, and while they are arranged around a pre-determined set of open-ended questions, they allow both the interviewee and interviewer to delve deeper into aspects that become of interest during the discussion, gain a deeper understanding of cause and effect and clarify unclear points (DiCicco-Bloom & Crabtree, 2006; Diefenbach, 2009).

Interviews were conducted in April and May 2013 with heads of all three clinical R&D units responsible for outsourcing clinical activities and a vendor manager at the wholly-owned subsidiary CRO. Interview guides were developed for the two types of interviewees (see appendices). Interviews were scheduled with at least 3 days advance and all but one were conducted by telephone, each lasting approximately an hour. The interviews were recorded, with interviewees' permission, and subsequently transcribed for data analysis. The case company's quality system and other procedures relating to vendor qualification, oversight and contracting were also reviewed. Compliance with the audit procedures was determined through review and analysis of audit statistics and reports covering the period from 2008 to 2012, inclusive. As a last step in the research process, an interview and review of a draft of this manuscript was organised with a Clinical Quality Assurance executive at the case company to validate findings and prevent any possible misunderstanding or sensitive information being inadvertently made public.

Table 4 – Interviewees

	Position/role	Company	Relevant industry experience
1	Clinical R&D head responsible for outsourcing	Generics	6 years in generics clinical R&D, all with the case company Previously, 6 years in early drug development, i.e. drug delivery formulation through to pre-clinical testing and clinical phase I, and 2 years in pharmaceutical marketing
2	Clinical R&D head responsible for outsourcing	Generics	10 years in generics clinical R&D, thereof 7 years with the case company Previously, 8 years in brand clinical research
3	Clinical R&D head responsible for outsourcing	Generics	5 years in generics clinical R&D, thereof 4 years with the case company Previously, 20 years in brand clinical research
4	Head of CRO	CRO	17 years in the generics industry, thereof 6 years with the case company, mostly in a contract services setting for clinical research and manufacturing
5	Clinical QA head, responsible for qualification of CROs and auditing Verification review	Generics, previously CRO	17 years in the generics industry, in manufacturing, quality control and quality assurance, registrations, managing BE studies and clinical QA, thereof 6 years in generics clinical QA with the case company Served as technical director for the case company's CRO for a period of 2 years Within the last 15 years, 8 years as manager in a CRO, primarily servicing brand companies

4. RESULTS

4.1 The case company

The case company is multinational pharmaceutical generics company, one of the top 10 leading generics companies as measured by global sales. It has operations in over 50 countries and a workforce of more than 12,000 employees worldwide. It develops, manufactures and distributes generic and biosimilar products in a range of dosage forms, for diverse therapeutic indications. At the time of the study, the company had over 250 on-going R&D projects. The company's 15 R&D sites are geographically distributed and supported by three clinical R&D operations management units that support different marketing regions. All clinical activity is outsourced to contract vendors, either the wholly-owned subsidiary CRO in India or to external CROs in different regions. The company has a corporate function for Clinical Quality Assurance (CQA), independent of clinical R&D management.

4.2 Review of documented practices

Quality audits

The case company's CQA global quality policy and related standard operating procedures (SOPs) address the CQA audit program that also covers vendor oversight. The key elements are as follows:

- Any new vendors (or new CRO locations) must be qualified by CQA prior to use of services and CROs meeting the qualification criteria are subsequently listed on the company's approved vendor list
    - The first choice of method of CRO qualification is an on-site audit of the CRO's quality systems and procedures for those tasks/duties contracted out to the CRO. This includes assessment of the organisational structure, facilities, SOPs, environmental cleanliness/ hygiene, equipment, procedures for protocol development, statistical support, regulatory and ethics submission, study conduct at site, analytical laboratory, safety laboratories, monitoring, data management, clinical study report writing, third party service providers if any, etc.
    - The company policy allows an option of a simplified pre-qualification visit to be conducted, not by CQA, but e.g. by a representative of an operational unit or an auditor experienced in another field of pharmaceutical development. This may for example be the case when timing does not allow for a full audit, or when using CROs in countries where governmental policies dictate which organisations are authorised or approved by a given regulatory authority to conduct contract research
- Quality oversight is maintained throughout the relationship via
    - requalification quality system audits at least every 3 years, and
    - at least one study-specific audit per year, either conducted on-site at the CRO or by documentation review in-house at the sponsor's offices

By nature, the quality audits are primarily focused on compliance with regulatory requirements. The policy and procedures prescribe the application of risk assessment in setting the audit program priorities. Criteria that may affect the likelihood of selecting a given study for audit include among other: study complexity; number of subjects enrolled; safety considerations; changes in regulatory requirements; estimated product market size; experience with the vendor or study team; non-compliance or quality issues. For vendors, criteria that may impact required audit frequency includes: changes in ownership or management; results of regulatory inspections; increased study volume; periods of

non-activity between outsourced projects. No distinction is made within the quality system procedures between internal and external CROs.

Contracts

The case company's procedures for contract preparation with CROs are consistent with regulatory requirements in that they require an agreement between the sponsor and CRO to be in place prior to inclusion of any subjects into a study. For those vendors who repeatedly provided services to the case company, a master services agreement was executed and subsequently, work orders with attached responsibility matrices to delineate delegation of tasks and duties prepared on a per project basis. Contract templates did not specify the use of metrics or performance assessments, other than referring to direct access for on-site monitoring and audit, and stating that timelines for service delivery were to be upheld. A master services agreement was in place with the wholly-owned CRO and work orders created per project in the same manner as for other CROs.

Routine on-site monitoring

Procedures mandated the all clinical studies conducted on behalf of the case company be monitored according to a study-specific plan, approved by the sponsor. Clinical research associates or other representatives, independent of the clinical site, should visit the clinic site before, during and after study conduct to review compliance with the study protocol, check clinical site activities and verify documentation. Monitoring of bioanalytical facilities was addressed also. Risk assessment options to adjust frequency of monitoring for each study were described. No distinction was made between clinic sites in the procedures.

4.3 Clinical Quality Assurance audit data

Analysis of CQA audit data (see Table 5) revealed that the case company conducted 69 qualification or re-qualification audits of CROs for BE studies over a 5-year period, 2008-2012 inclusive. Sixty-one (61) CROs (or CRO locations) were included on the list of approved vendors. These were located in 17 different countries in 6 continents. During the same period, 535 BE studies were initiated and some 67 study-specific on-site audits were conducted at CRO locations. On average, half of the studies were conducted at the case company's subsidiary CRO locations.

Table 5 – Summary of audit data for vendors and BE studies, 2008-2012

	2008	2009	2010	2011	2012	Total	Average	Standard deviation
Number of BE studies	102	94	93	117	129	535	107	15.6
At case company's CRO	45	52	52	60	55	264	52.8	5.4
	44%	55%	56%	51%	43%		50%	6%
Number of active CRO locations	15	15	12	17	22		16.2	3.7
Case company's CRO	4	4	4	4	4		4	0.0
	27%	27%	33%	24%	18%			
Number of on-site study audits	4	12	19	12	20	67	13.4	6.5
At case company's CRO	4	7	9	7	3	30	6	2.4
	100%	58%	47%	58%	15%		56%	30%
Number of qualification audits	10	5	6	22	26	69	13.8	9.6
At case company's CRO	1	1	4	0	0	6	1.2	1.6
	10%	20%	67%	0%	0%		19%	28%
Combined number of audits	14	17	25	34	46	136	27.2	13.1
At case company's CRO	5	8	13	7	3	36	7.2	3.8
	36%	47%	52%	21%	7%		32%	19%

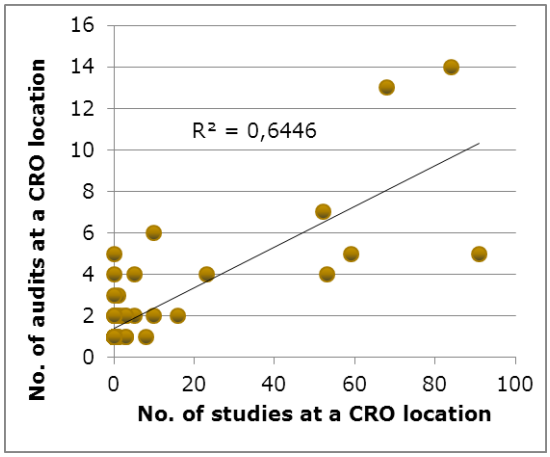

Figure 2 – Audits and study volume and CROs

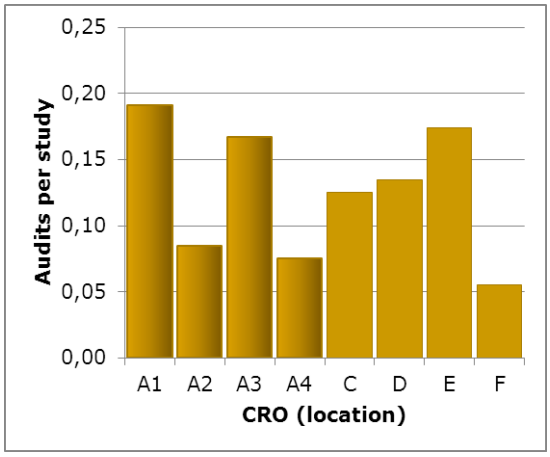

Figure 3 – Audit frequency by CRO site

Sites with ≥3 studies/year for the case company
A1-A4 represent site locations of the wholly-owned subsidiary CRO, other are external

Figure 2 demonstrates that there is a positive relationship between the number of studies conducted at a given CRO location and the number of audits conducted at the site (R^2=0.64). This confirms that even though flexibility is built into auditing procedures at the case company, the sponsor enacts the principles of the auditing program to maintain quality oversight of the activities with increasing study volume.

Figure 3 shows that for CROs that conduct 3 or more studies per year for the case company, there is little variation in their audit frequency (0.06-0.18 on-site audits/study/CRO location) and no difference observed between own CRO locations and external CROs.

4.4 Interviews

The key messages of the interviewees, who overall were consistent in their responses, are summarised below as they align with the research questions.

What are relevant measures of quality of clinical vendor performance for generic companies?

To approach this question, interviewees were asked about what areas they would evaluate at vendor selection; how on-going relationships were monitored and which metrics, if any, were collected; what they considered would make CROs stand out in terms of quality of service; in what way the sponsor could best facilitate CRO performance; and what they considered the greatest risk to the outsourcing situation.

Executives of the case company all gave responses consistent with the declared objectives of their quality management system when it came to vendor selection. All responded that expertise and quality in terms of regulatory compliance, cost and potential for expedient delivery were the areas assessed when selecting or qualifying vendors:

> *"…a CRO of good reputation…of having a good standing with regulatory agencies…someone who can meet our timelines, someone who has reasonable cost and, of course, area of expertise in that particular field. These are the four factors that in my opinion would greatly influence the selection of a vendor for any study."*

Yet, all stated that cost still remains pivotal in selecting a vendor, provided that minimum levels of quality and speed can be met:

> *"It's basically these three or four elements. It's the expert knowledge, quality, price and time. If I was forced to put them in order…I must admit that price and time are the determining factors…but then, there's quality…"*

The CRO manager mirrored this view:

> *"…generally all the generic sponsors are cost-conscious…and some start with the cost alone. But the large players, the people who are really professional, they come with the complete checklist and cover all the areas."*

In his experience, the areas most overlooked or less emphasised by smaller clients were quality and confidentiality, i.e. that cost and speed were prioritised at the expense of these:

> *"Smaller generic players are really not worried about the confidentiality part, but all the big players place a big emphasis on confidentiality…whether the CRO has an independent character or not."*

All case company executives confirmed that vendors are measured – on a per project basis – against the project timelines and budgets, however, only one of the clinical R&D units systematically collects the information on schedule times into a central repository or spreadsheet:

> *"We do have that "on-going" document…which isn't really quite well designed…and we're tracking the timelines there…we've got the start of study, et cetera […] …and then we do track the reporting time […] …and that's really it…do they manage to complete on time as originally planned or not…"*

For on-going assessment of quality of work by CROs, the case company executives declared that quality audits and routine on-site monitoring provided them with assurance that compliance and quality were upheld. When prompted for either metrics or areas that the case company executives believed to signal the quality of performance and work conducted by the CRO, the three following were specifically identified as strong indicators of the combined assessment of quality and time.

- Draft review cycles for protocol:

  > *"First of all, at the early-on stages, it is actually the protocol…the revisions. Number of revisions going back and forth is really an indicator of their quality of work."*

- Draft review cycles for clinical study report:

  > *"For example, if you have to put up with five, six, seven, eight drafts of the report…that just doesn't work. But sometimes…we get a really good report right away and we have practically no comments…that's just great. I'd say this was a true measure, you know."*

- Response time to regulatory authority deficiency on the marketing application:

  > *"…and then this…how quickly they respond to regulatory deficiency letters. That is an important measure."*

The CRO manager verified that the CRO conducts annual customer satisfaction surveys in order to obtain feedback from sponsors on their overall performance. He described a number of different metrics that the CRO management employs to monitor operational efficiency and internal quality compliance, however, declared that sponsors rarely, if ever, request this information. If they did, he would not be obliged to provide the information.

Speaking to what it is that makes a CRO outperform others, assuming that compliance, cost and timeliness were acceptable; all interviewees responded that expertise was key, i.e. therapeutic area expertise, deep understanding of the regulations and guidelines as well as a developed, strategic approach to study design and communications with authorities, specifically, in dealing with all the different comments or deficiencies that could be received from different regulatory authorities reviewing marketing applications.

> *"I think it lies in how they anticipate problems for us and try to head them off. […] That's where the CRO experience comes in…based on the study design, based on their understanding of the therapeutic area, understanding of what the FDA wants and collecting not too much or too little data and exactly how to use. […] Things like that are value-added…they foresee problems before we even get started."*

> *"We need good support… […] …the European authorities, there are so many that we apply to…and all of them…they have different opinions of the study report or results or anything else…we get so many questions. […] Then, it is enormously important that they [add: the CROs] …well, can respond…respond well and respond quickly."*

The flexibility of the CROs in rescheduling studies at relatively short notice in case of delays was identified as a major advantage by the case company executives:

> *"…it goes down to maybe five, six months up to, maybe, a year that we have to prepare. […] We, of course, do not want to commit to a slot, or even commit to the CRO, until we know that we will have product ready. And this is the constant Limbo…and the CROs, of course…well, understandably…they apply a penalty if you're changing the dates, the closer it gets, you know, to starting the study. […] …some of the CROs have been flexible and can delay by a week or half a month, last minute."*

The opinion expressed by all interviewees was that a skilled project manager on the CRO side provided clear advantage to the CRO.

> *"…and we do kind of ask for that too, that we have a project manager there, one, always the same one. Clearly, the CROs attempt this too, it proves best. […] The project manager knows us, knows the way we work… […] …knows our people, what keeps getting delayed and what our procedures are."*

> *"…key to the communication is the project manager at the CRO. The studies we have most problems with are those where we have multiple project managers, they change. […] Having one project manager helps you ensure that the person shares your vision for the study…"*

In order to facilitate good performance by the CROs, case company executives suggested that sponsors, first and foremost, emphasised communication of accurate timelines to the CROs with proper advance. Further, that scheduling

would allow adequate time to develop the study design and write the study protocol, in close collaboration and interaction between sponsor and CRO.

The primary risk factor to CROs and the outsourcing situation was identified as being of a financial nature. A recent bankruptcy of a phase I CRO, before courts in USA when this is written, was brought up by all of the interviewees in this context.

> *"Financial issues, financial crises…those are the biggest risks right now. It does seem like many of them are not steady. And this information is not easy to come by…what their financial standing is."*

> *"Are they [add: the CROs] financially stable? Not just for the time of our study, but in a five years' time? Will they be there to help us answer FDA questions? Or assist with FDA audits? That's one of the big risks."*

> *"We really have no control. We have CROs filing for bankruptcy in the midst of running studies, so we are vulnerable. And then process we have to go through in retrieving what actually belongs to the sponsor…it is something that is time consuming."*

> *"As in that last CRO that went under, I mean, we're talking millions of dollars in projects. I kid you not. And now, I have no access to the data…as is…and no access to the expert knowledge that was there. It's no joke. And we still have to go through authorisation. This will test us in the coming time, responding to the authorities… Because it's all going to come our way and, as I say, these are not straight-forward projects."*

The other major risk factor mentioned related to changes in the regulatory environment. One interviewee stressed that CROs must be forward thinking in spotting upcoming changes in regulations and guidelines, particularly with respect to bioanalytics and BE testing of more complex dosage forms:

> *"Take, for example, the new analytical guideline… […] …it came out last year, but the draft was out earlier. They [add: the subsidiary CRO] were quick to adopt some things that were there, in the draft, and that is paying off now, because we have a longer history… […] …last year, we were already doing the things that came out in the new guideline."*

Given the location of the CRO owned by the case company, in India, more emphasis was placed on the changing regulatory environments in emerging markets. In the words of the CRO manager:

> *"Guidelines and regulations in India are getting stricter and stricter. The media and political climate is not favourable for pharmacokinetic research of this kind, because they do not see any particular benefit for the local population or the local market. These products are evaluated locally and the exported, they are not benefiting patients here. The benefit the country will get is very, very small compared with the size of the country and overall economy but the risks are very high. Therefore, they are of the opinion that the multinational companies dump high-risk drugs in India, especially when it comes to clinical enrolment, but when it comes to the pharmacokinetic evaluation, they say that because the drug will not be launched in India, why test it in Indian subjects?"*

What are the benefits of owning a CRO?

All interviewees were asked about the benefits and drawbacks related to the case company's ownership of a CRO. From the sponsor's perspective, the benefits to owning a CRO were expressed in terms of gaining control, maintaining flexibility of timelines without added costs and trust in the quality of operations:

> *"…flexibility of timelines…that is the main benefit, because we do not have to pay penalties and we have priority to all slots."*

> *"…the risk is less because we know our own CRO, we know how well they are operated and we also have some control over how things are done."*

> *"I think it is essential that they work also with other sponsors. Because then you get the other experience maybe, another view, if you will, or perspective on the projects."*

However, it was highlighted by the case company executives that the current regulatory environment in India did restrict them in the types of studies that could be placed in India. Studies involving controlled drugs were not feasible as controlled drugs were subject to stringent importation laws and high-dose studies were considered high risk in the Indian population and their conduct therefore not likely to be authorised.

Discussing the benefits and drawbacks of being a subsidiary CRO, the CRO manager added:

> *"You can rest assured, when you work with your own arm, you can be very sure that people are not disclosing anything about what you are working on and what we are talking about for 2014, 2015. The third thing is, using the resources, you can employ how much resources as you wish in order to get your study done, you have a better say in the timelines and quality control."*

> *"Having an anchor client is always beneficial because it provides you good volume […] but at other times it also gives you a lot of uncertainty because […] your business model is oriented mostly towards one client and if you don't have that client's work coming you will have a big vacuum in the business. So it has contradictory effects on your business continuity."*

> *"When the third party business sees that this is owned by a generics company, a cross-section of companies is concerned with contracting with a company that is owned by a competitor. So we will not be able to make business with many people. They do not like it."*

> *"But it's a two-way street. We get to ask more questions of [the case company], rather than external customers. […] I have the freedom to ask the internal customer why the formulation is delayed; I cannot ask an external customer that."*

Are there differences in how the case study company handles evaluation of its external or internal vendors?

All interviewees for the case company were explicit in stating that the same procedures were applied for assessment of external CROs and the wholly-owned subsidiary:

> *"At [the case company] we try to follow the same rules, whether its internal or external, so we pretty much treat both the same way, and they go through the audit process and everything as well. […] So I don't see any way that we would treat one differently than the other."*

The CRO manager expressed his view that the case company aligned with other large pharmaceutical companies in their emphasis on quality oversight:

> *"[The case company] is a big player and their requirements are generally in line with other large sponsors…the top-five generics."*

5. DISCUSSION

When it comes to performance measurement, Spitzer (2007) stated: "Be ready to start small." That would certainly be appropriate in the situation of the case company, in spite of its size, as the overall opinion of the managers responsible for outsourcing appeared to be that the areas covered by quality auditing and routine on-site monitoring require supplementing with only few, but important additional metrics. Aside from the measures already being collected for time and cost, the case company representatives identified three key measures that would be of value to them in addressing quality of the work performed. A low number of protocol or report review cycles can be a simple measure of efficiency and quality of the output that is easy to collect. How quickly CROs respond to deficiency letters is rather a true cycle time measure, however, coupled with a repeat-query rate, it would also reflect the quality of the responses.

It is important to note the unused opportunities in centrally collecting and displaying or making available to those who work with the company's vendors on a daily basis, the data for performance monitoring that already is accumulating at the case company, specifically in on-site monitoring reports. Examples of these could be protocol deviation rates and types or seriousness of deviations, repeat deviations, comment resolution times and repeat comment rates (i.e. corrective action responsiveness), all of which would be strong measures of quality of service. Monitoring appears to be directed mostly at the study basis, when the nature of the studies and the services arrangement could allow for a more central overview of the CROs service as a whole.

The concept of the project triangle – quality, time and cost – was clearly represented in responses of the interviewees; however, a fourth element – skill or expertise – was brought up repeatedly. This was specifically mentioned as the area that makes CROs stand out in terms of performance and shows that even if cost-lowering aspects weight heavy in the outsourcing approach, the right fit with respect to regulatory strategy is emphasised.

Further, the project management competencies at the vendor's side were important to the case company executives. However, there seem to be considerable opportunities for improved project management on the sponsor's side. Interviewees indicated that delayed study drug was a common occurrence, not only within the case company, but in this sector of the industry as a whole. There is clearly room

for improvement in handover of this key deliverable to vendors that they need to conduct the study. Penalties imposed by vendors as a response to these scheduling issues or delays from the sponsor's side reflect the traditionally transactional relationship. Again, in this context, interviewees from both the case company and the CRO expressed views that more open communication helps. That requires building trust between parties.

The case company has developed a fairly clear preferred provider tactic for outsourcing to CROs; although the perspective of not "putting all your eggs in one basket" was mentioned – yet, work with few, good vendors. Quality system procedures reflect this clearly. It may seem contradictory to the outsourcing decision to own a subsidiary CRO, i.e. committing to a long-term investment in an operational unit where the function has already been fully outsourced. The obvious benefits for the case company were stated as control of operations, leading to more flexibility, and confidence in quality of service and protection of confidentiality. Expertise is developed at the CRO through working with different external clients, extending not only to therapeutic areas and technical development, but also in strategic regulatory aspects and quality system improvements.

It is a convoluted situation, due to the need to maintain "China walls" to protect the CRO's third party clients. The relationship between the case company and the subsidiary CRO is at present the closest to a partnership that the case company engages in with its vendors. Interviews, quality system procedure review and analysis of audit data clearly show that the case company does not manage the subsidiary vendor differently from external CROs – hence, the operation cannot be argued to be internal – however more information on timelines and product development status is shared between parties, evidence of the trust between parties and the mutual sharing in risks and successes.

6. CONCLUSIONS

The case company, possibly representative of larger players in the generics industry, has been evolving its vendor relationships from strictly transactional settings to more strategic preferred vendor relationships. The greater emphasis placed on access to expert knowhow for the longer run and project management skills is a strong signal for this.

While speed and cost still remain the first considerations in generics companies' outsourcing behaviours, established procedures for vendor qualification and on-site monitoring form the necessary foundation when advancing vendor oversight to include a consistent approach to metrics. Next steps for the case company could be to develop a pilot system of metrics for which data could be collected in a simple manner. Few, key metrics that couple cycle times and quality of output should form the basis of the system and have clear ties to the overall objectives of the company.

In light of recent industry events, ways of assessing vendors' financial standing is likely to become an area of attention for sponsors in the near future. Perhaps the most real advantages of owning a subsidiary CRO are obvious and lie in the control a company can have over operations and financial stability; in the words of an interviewee, "we are then in control of our destiny", while at the same time continue to build in knowledge at the CRO through the exposure to third-party practices.

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8. REFERENCES

Best Practices LLC. (2012, February 1). *Pharma Bioequivalence Strategies - Performance Metrics, Processes & Trends*. Business & Mgmt. Retrieved from http://www.slideshare.net/bestpracticesllc/pop-234-a-pharma-bioequivalence-strategies-performance-metrics-processes-trends-report-summary

Bureau of Labor Statistics. (n.d.). CPI Inflation Calculator. Retrieved 4 May 2013, from http://www.bls.gov/data/inflation_calculator.htm

Calaprice-Whitty, D. (2010). The State of Clinical Outsourcing. *Applied Clinical Trials*, *19*(3), 42–48.

Canadian Generic Pharmaceutical Association. (n.d.). Generic Prescription Drug Development. Retrieved 6 May 2013, from http://www.canadiangenerics.ca/en/resources/docs/GenericDrugDevelopment.pdf

Center for Drug Evaluation and Research (CDER). (1998). *Guidance for Industry: 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act* (No. Procedural Guidance 5). Rockville: Food and Drug Administration (FDA).

DiCicco-Bloom, B., & Crabtree, B. F. (2006). The qualitative research interview. *Medical Education*, *40*(4), 314–321. doi:10.1111/j.1365-2929.2006.02418.x

Diefenbach, T. (2009). Are case studies more than sophisticated storytelling?: Methodological problems of qualitative empirical research mainly based on semi-structured interviews. *Quality & Quantity*, *43*(6), 875–894. doi:10.1007/s11135-008-9164-0

Erasmus, T., & Khera, J. (2012). Navigating Beyond the Plateau. *Applied Clinical Trials*, *21*(7), 44–49.

European Commission. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Pub. L. No. 2001/20/EC (2004).

European Commission. (2012). *The 2012 EU Industrial R&D Investment Scoreboard*. Seville: Joint Research Centre, Directorate-General for Research and Innovation.

European Medicines Agency. (2008). *Reflection Paper on advice to applicants, sponsors, CROs of BE studies* (No. EMEA/INS/GCP/468975/2007). London: European Medicines Agency GCP Inspectors Working Group.

European Medicines Agency. (2010). *Guideline on the Investigation of Bioequivalence* (No. CPMP/EWP/QWP/1401/98 Rev. 1/Corr). London: European Medicines Agency Committee for Medicinal Prodcuts for Human Use (CHMP).

European Medicines Agency. (2012). *Questions and answers on generic medicines* (No. EMA/393905/2006 Rev. 2). London.

EvaluatePharma. (2012). *World Preview 2018 - Embracing the Patent Cliff*. London.

Getz, K. A. (2006). CRO contribution to drug development is substantial and growing globally. *Impact Report*, *8*, 1–4.

Getz, K. A. (2012). Outsourcing Landscape. *Applied Clinical Trials*, 22,24–26.

Getz, K. A., & Vogel, J. R. (2009). Successful Outsourcing: Tracking Global CRO Usage. *Applied Clinical Trials*, *18*(6), 42–50.

Getz, K. A., Lamberti, M. J., Mathias, A., & Stergiopoulos, S. (2012). Resizing the Global Contract R&D Services Market. *Contract Pharma*, *14*(5), 54–62.

Glass, H. E., & Beaudry, D. P. (2009). CRO Selection & Management. *Applied Clinical Trials*, *18*(4), 48–54.

International Conference on Harmonisation. (1996). *Guideline for Good Clinical Practice (E6 R1)*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

International Conference on Harmonisation. (2008). *Pharmaceutical Quality System (Q10)*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Jones, J., & Minor, M. (2010). New, Strategic Outsourcing Models to Meet Changing Clinical Development Needs. *Perspectives in Clinical Research*, *1*(2), 76–79.

Kakabadse, N., & Kakabadse, A. (2000). Critical Review--Outsourcing: A Paradigm Shift. *Journal of Management Development*, *19*(8), 668–728.

Lake, E. (2010). Improve the Business of Science. *Applied Clinical Trials*, *19*(10), 40–50.

Lee, T. Y. (1998). Contract Research Organizations. *Drug Information Journal*, *32*(1 suppl), 1259S–1263S. doi:10.1177/00928615980320S117

Lowman, M., Trott, P., Hoecht, A., & Sellam, Z. (2012). Innovation risks of outsourcing in pharmaceutical new product development. *Technovation*, *32*(2), 99–109. doi:10.1016/j.technovation.2011.11.004

Morgan, S., Grootendorst, P., Lexchin, J., Cunningham, C., & Greyson, D. (2011). The cost of drug development: A systematic review. *Health Policy*, *100*(1), 4–17. doi:10.1016/j.healthpol.2010.12.002

Mullard, A. (2012). 2011 FDA drug approvals. *Nature Reviews Drug Discovery*, *11*(2), 91–94. doi:10.1038/nrd3657

Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., & Schacht, A. L. (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews. Drug Discovery*, *9*(3), 203–14. doi:http://dx.doi.org/10.1038/nrd3078

Pharmaceutical Benchmarking Forum. (2012, August 8). Annual R&D General Metrics Study Highlights - New Success Rate & Cycle Time Data. Retrieved 4 May 2013, from http://kmrgroup.com/PressReleases/2012_08_08%20KMR%20PBF%20Success%20Rate%20&%20Cycle%20Time%20Press%20Release.pdf

Piachaud, B. S. (2002). Outsourcing in the pharmaceutical manufacturing process: an examination of the CRO experience. *Technovation*, *22*(2), 81–90. doi:10.1016/S0166-4972(01)00081-5

Simoens, S. (2012). A review of generic medicine pricing in Europe. *Generics and Biosimilars Initiative Journal*, *1*(1), 8–12. doi:10.5639/gabij.2012.0101.004

Spitzer, D. R. (2007). *Transforming Performance Measurement: Rethinking the Way We Measure And Drive Organizational Success*. New York: AMACOM American Management Association.

Submitter, S., Van Huijstee, M., & Schipper, I. (2011). *Putting Contract Research Organisations on the Radar: An Exploratory Study on Outsourcing of Clinical Trials by Pharmaceutical Companies To Contract Research Organisations in Non-Traditional Trial Regions* (SSRN Scholarly Paper No. ID 1759265). Rochester, NY: Social Science Research Network.

Tillmann, A., & Shepherd, C. (2009). How do you Measure up? A Perspective on Metrics for Quality Assurance Departments. *QUASAR*, (109), 9–11.

William Blair & Company. (2011). *CRO Industry Update - Results from Fifth Survey of Pharma and Biotech Sponsors*. Chicago: William Blair & Company.

Winter, J. E., & Baguley, J. (2006). *Outsourcing Clinical Development - Strategies for Working with CROs and Other Partners*. Aldershot: Gower Publishing, Ltd.

9. APPENDICES

9.1 Interview guide for sponsor/generics company

Introduction
Thank you for taking the time to meet with me, your input is greatly appreciated
The research project is for a program I am attending in project management, but will be useful for work purposes as well
I will be recording the interview, however, the recording will not be shared in any way, but destroyed once it has been transcribed verbatim and QC'd for analysis
Your name will not be included with the transcript or any information resulting from the project
Confidentiality also applies for any potentially sensitive information that may be disclosed about the company, vendors or clients
[An executive of the case company] will review the final report for the project to ensure that no sensitive information will be disclosed
Purpose: • Capture the opinions/perceptions of managers responsible for outsourcing clinical activities at a generics company about areas of importance in assessing quality of service and success of vendor relationships with CROs • Lead to the selection of meaningful measures of CRO performance
Vendor selection
What are some important areas that you evaluate (or have evaluated for you) when selecting new vendors?
Performance monitoring (own and external)
What do you do to monitor performance of vendors that you place work with? • At the project level? • For certain services?
Do you have examples of items that are measured or otherwise monitored (for the projects or service)?
What do you consider to be the main benefits of owning a CRO?
What drawbacks to that arrangement do you see, if any?
Is there any difference in what is monitored for subsidiary vendors than for external vendors? • If yes, in what way?
Of those service providers/CROs that you consider "the best" in terms of quality of service, what sets them apart from other CROs?
What do you consider the main current or upcoming risks that could impact performance of the CRO vendors and, thereby, its products?
What do you consider to weigh the most in the company's own performance or actions in supporting or contributing to good vendor performance?
Background questions
How long have you worked in the generics industry?
How long have you been with Actavis or its legacy organisations?
Do you have any other drug development experience outside clinical research?
Closure
If needed, would it be possible for me to send you the final report, or sections thereof, in order to obtain your verification of correct interpretation of your input?
Thank you for your participation

9.2 Interview guide for CRO

Introduction
Thank you for taking the time to meet with me, your input is greatly appreciated
The research project is for a program I am attending in project management and does not constitute a part of the case company's vendor oversight program
I will be recording the interview, however, the recording will not be shared in any way, but destroyed once it has been transcribed verbatim and QC'd for analysis
Your name will not be included with the transcript or any information resulting from the project
Confidentiality also applies for any potentially sensitive information that may be disclosed about the company, vendors or clients
[An executive of the case company] will review the final report for the project to ensure that no sensitive information will be disclosed
Purpose: • Capture the opinions/perceptions of managers responsible for providing clinical research services to a generics company about areas of importance in assessing quality of service and success of sponsor relationships • Lead to the selection of meaningful measures of CRO performance, when reflected against sponsor's expectations
Vendor selection
What are some areas that have been emphasised by the case company and other sponsors when your organisation has been evaluated for selection?
Have there been areas that you perceive as overlooked by sponsors?
Performance monitoring
What are the most common metrics or measures of performance that sponsors ask you to provide? • At the project level? • For certain services? Do you have examples of items that are you are asked to measure or otherwise monitor (for the projects or service)?
Do you employ any tools to measure performance? • Customer satisfaction surveys? • Excel timeline trackers to collect data on startup timelines?
Is there any difference in what the case company and other sponsors monitor in your services? • If yes, in what way?
What do you consider to be the main benefits of operating as a wholly-owned subsidiary of a generics and specialty pharmaceutical company?
What drawbacks to that arrangement do you see, if any?
What have you perceived as being key in retaining repeat business? Your company's strengths of performance?
What do you consider the main current or upcoming risks that could impact your performance or the CRO industry as a whole?
What do you consider to weigh the most in the case company's or other sponsor's performance or actions to support or contribute to your company's success in providing good services? How can sponsors help you deliver the best?
Background questions
How long have you been in the generics industry or servicing generics companies?
How long have you been with this or other CRO/phase I unit?
Do you have any other drug development experience outside clinical research?
Closure
If needed, would it be possible for me to send you the final report, or sections thereof, in order to obtain your verification of correct interpretation of your input?
Thank you for your participation