Awakening the Dragon's Breath: Biostatistics, Competency and Competition in the Pharmaceutical Industry

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Abstract

Innovations in chemistry and biology have generated multiple products and built significant revenue streams in the pharmaceutical industry. However, the complex and multi-disciplinary process of drug discovery and drug development makes it difficult to identify specific core competencies within a company. There is a need to better identify and manage sources of innovation that lead to new markets as ever-increasing investments in R&D have recently been accompanied by mediocre success in new product introduction. Additionally, outsourcing of clinical research and even early-stage discovery research continues to increase, creating a need to better define core competencies for strategic management decisions in pharmaceutical innovation.

In this context, we investigated the possible role that biostatistics - a key competence – could play in innovation in the drug development process. A sampling of case interviews from biostatisticians and executives in the pharma industry indicate that biostatisticians do contribute to innovation in the drug development process. Data gathered from contract research companies in the pharma industry suggests that outsourcing practices in the pharmaceutical industry increasingly include the outsourcing of biostatistics capabilities. We conclude that pharmaceutical companies should consider directing their management and outsourcing practices to retain and gain novel innovation through biostatistics.

INTRODUCTION

The process of drug discovery and drug product development is complex and multi-disciplinary. Drug companies today are investing heavily in their R&D efforts and extending their resources to include the new information and insight from the human genome project. While pharmaceutical company R&D investments over the last decade have increased dramatically, paradoxically there has been reduced innovation as seen by the low number of new product introductions. A big concern in the life science based industry is the product life cycle. The drug approval process increased from eight years in the nineteen sixties to almost sixteen years in the nineteen nineties. The clinical and regulatory review phases, which rely heavily on biostatistical related activities, are big factors in the lengthening of the approval processes time-line. Comparing small and large firm drug development time (Parexel R&D Sourcebook, 2001) not only indicates that there may be opportunities for increased efficiencies but that large firms have developed competitive capabilities in the drug approval process for increased efficiency. We infer from the above that there is an opportunity for enhanced managerial capability and resource deployment and that there is a clear need to more efficiently manage the drug discovery and development process to generate innovations that lead to new products.

The theme seen throughout the pertinent literature is that firms gain competitive advantage from resources that are difficult to trade, transfer, imitate or replicate. These characteristics are most prevalent in intangible resources and likely to be embedded in high-level managerial capabilities. Biostatistics know-how is an intangible resource when it involves decision making about when, how and what techniques to employ under innovative circumstances. Prahalad and Hamel (1990) merge the concept of 'unique' resources presented by Penrose (1959) and tacit knowledge presented by Nelson and Winter (1982), stressing that firms achieve competitive advantage by developing their core competence. A core competence is defined as "the collective learning in the organization, especially how to coordinate diverse production skills and integrate multiple streams of technologies." Regardless of whether resources are referred to as strategic resources (Barney, 1986), invisible assets (Itami, 1987), strategic assets (Dierickx & Cool, 1989), core competencies (Prahalad & Hamel, 1990) or intangible resources (Hall, 1992) the premise remains that firms must continually acquire or develop heterogeneous resources to generate economic rents (Conner, 1991; Barney, 1989; Dierickx & Cool, 1989). Given the importance of the drug approval process in life science new product development, we ask to what extent is biostatistics a core competency.

Furthermore the literature frequently distinguishes between core competencies and core capabilities (Lucarelli and Peters, 2001). In particular, competencies often result from blending technology and production skills whereas capabilities are rooted in managerial processes (Marino, 1996, Lucarelli and Peters 2000). As Teece (1998) states, "Superior technology alone is rarely enough upon which to build competitive advantage… Recognizing strategic errors and

adjusting accordingly is a critical part of becoming and remaining successful." Managerial capability encompasses successful coordination of heterogonous resources in new or existing routines according to information and knowledge requirements (Lucarelli and Peters 2000). Both concepts define strategically significant resources. The technical know-how of biostatistics is essential to the life science product approval process and therefore it can be a core competence. Understanding how firms build and deploy capabilities has been the focus of much recent theoretical and empirical analysis (Teece, Pisano and Shuen, 1997; Helfat and Raubitschek, 2000; Cockburn, Henderson and Stern, 2000; and Eisenhardt and Martin, 2000). Others have characterized capabilities as "learning systems". These characterizations of capabilities fit certain characteristics of biostatistical activities.

In the pharmaceutical industry, innovation is recognized as the cornerstone for competitive advantage and is fostered by strong investments in biological discovery, biotechnology or chemistry processes. However, recognition of a core competence is a complex issue in various industries [Walsh and Linton, 2002]. In the pharmaceutical industry, drug discovery productivity is dependent on internal organization or R&D and firm-level expertise in diseases [Henderson and Cockburn, 1994]. However, the risky and time-consuming drug discovery process, along with skewed economic returns in major firms, wherein a few blockbuster drugs dominate the portfolios, make it very difficult to assess the significance of a specific competence on any measurable firm-level outcome such as sales, profitability, market share.

Recent papers on innovation and management in the pharmaceutical industry have identified specific expertise in particular chemical families or drug pathways as core competencies for companies in that area [Coomb and Metcalfe, 2002 and Achilladelis and Nantonakis, 2001]. Pfizer is recognized as having a competency in marketing, Merck in R&D, Eli Lilly for manufacturing and recently for alliance building, etc. However, within the literature, there has been little exploration of resource-based competencies of these pharmaceutical companies for some of the reasons discussed above.

As regulatory oversight and guidelines define the drug development process, it stands to reason that successful firms have a core competency in processes that help them clear regulatory hurdles. Statistical analysis of the clinical data is a key point of regulatory scrutiny, suggesting that biostatistics would have to be developed as a core competence for pharmaceutical companies to be successful. As outsourcing of drug development functions to contract research (CRO) firms increases, we asked this question – are pharmaceutical companies giving up their core competence to the CROs? What are the key biostatistics-related core competencies and functions in drug development? What role if any can biostatistics play in developing dynamic capabilities?

Drug development process and the role of biostatistics.

The drug discovery phase has not employed heavy statistical analysis, until recently, with the advent of large amounts of bioinformatics data that requires fairly sophisticated statistical analysis to interpret and validate results. However, we reserve analysis of the use of bioinformatics and data mining in drug discovery for a later paper. The focus of this study is on the key competencies of the pharmaceutical industry in managing and conducting drug development, and clinical trials, and interacting with the FDA.

In the drug development phases, a biostatistician is typically involved in early planning of an experimental study, in the preclinical (animal studies) and clinical stages (protocol design). The bulk of a statistician's work lays in analyzing data, as shown below in table I.

Table 1: Biostatistics role in drug development

Drug Development Stage	Biostatistician Function/Role
Preclinical data	Basic analysis with pharmacological data (rarely double blinded)
Chronic toxicology, safety studies	Analysis of data from toxicology study – some study design work, especially for complex dosages or combination drug studies
Clinical studies	▪ Design of trial protocol with physicians – determine sample size, relevance of parameters, methods of data analysis defined ▪ Make sure data is entered correctly ▪ Interim analysis as per protocol ▪ End of study –reliability, quality of data ▪ Analyze – write report and check medical report to make sure analysis is accurate ▪ Combine data across safety studies (not efficacy data)
Phase IV – follow up or extension clinic studies	Analyze data, follow adverse events, analyze, interpret, and report to FDA.
Manufacturing - Quality control	Not specific to biostatistician – general statistical analysis

Trends in R&D Outsourcing:

All drug companies seek to reduce costs and reduce the time to market in a time-consuming and expensive product development process. In the high-risk process where a project could fail at many different steps, it is more attractive

to rent or outsource the resources needed at a given stage. For smaller companies involved in the clinical trials process, outsourcing is not a choice but a need, as they cannot afford to build up internal resources with required skills and efficiency. In general, the global pharmaceutical R&D outsourcing market continues to grow at about 8-10% annually, with clinical trial management (83% of all CRO revenues) dwarfing the rest of the R&D functions (7% toxicology and safety, 10% other) [Parexel R&D sourcebook, 2001, p25]. More telling, spending on outsourced clinical trials as a percent of total spending on clinical evaluation studies in pharma/biotech companies has increased from 16% in 1995 to 25% in 2002 [Parexel R&D sourcebook, 2001, p25]. This increase in outsourcing is particularly interesting, considering that the large pharmaceutical companies view management of large clinical trials as a core competence. An example where more and more R&D functions are viewed as non-core is the large pharma, Glaxo SmithKline (GSK). GSK, a few years ago, restructured its business and R&D units, launching a hub and spoke model, where the R&D units were independently organized around the core hub which contained clinical Phase III management capabilities, marketing, manufacturing and corporate functions. "In the middle stages of R&D … GSK has created six Centres of Excellence for Drug Discovery, or CEDDs. Each CEDD is dedicated to specific therapeutic categories; each is responsible for taking lead compounds forward to the point where the therapeutic rationale for those compounds is demonstrated sufficiently to justify the start of large-scale clinical trials." (From www.gsk.com).

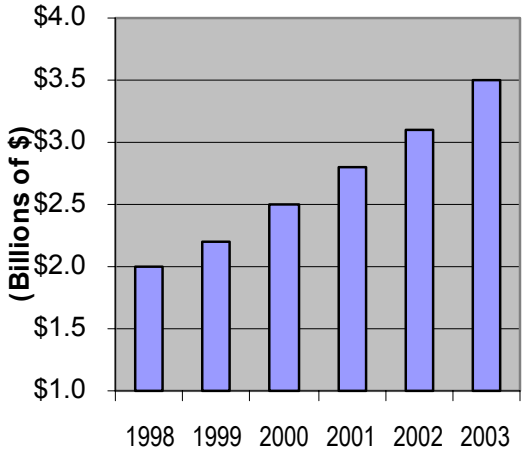

Figure 1: Outsourcing of biostatistics consulting services in US$Billions (projected and actual data from Parexel 2001 R&D Data Sourcebook)

METHODS:

In order to assess the kinds of activities in biostatistics that were being outsourced by pharmaceutical companies, a questionnaire was sent to eighty-eight contract research organizations (CROs). These organizations had clinical biostatistical functions contracted to their organizations from large and small pharma. Most of the companies were identified from three main sources, vertical industry websites listing service providers of contract services, Bioscan (a commercial database of the biotech industry) and R&D Directions magazine. Surveys were received over the course of 6 months and results were compiled. In several instances, larger CROs had to gain legal and marketing department approvals to release the data on the company's practices. We will be presenting here only one specific dataset from this survey, as described below in the results section. Additional interviews (open ended with guiding questions) were conducted with five biostatisticians from the pharmaceutical industry to qualify the survey results. The biostatisticians were identified and approached through publications from American Statistical Association.

RESULTS

In all, a total of 34 responses were received (39% response rate) and 33 were included in the analysis. One response was discarded as the identity and validity of the respondent was unclear. The responders include not only some of the largest CROs but also some smaller CROs where the biostatistics group is composed of two statisticians. The CRO respondent (typically a director of biostatistics or in a smaller firm the senior biostatistician) summarized the clinical trials outsourced to their companies by noting how frequently specific functions in biostatistics were included in all client projects with which they were familiar. The table below represents the mean and median response from all companies.

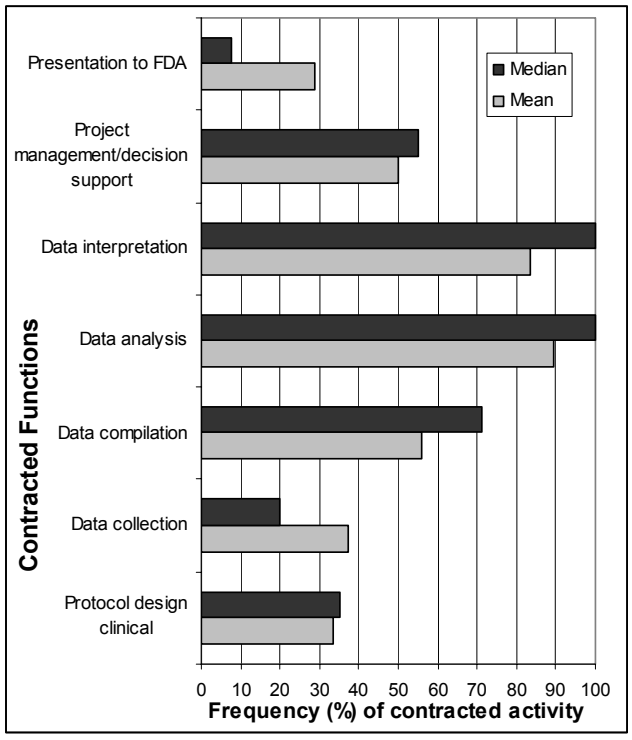

Figure 2: Mean and median of data received from CROs who were asked about the frequency of these functions/activities contracted to them by their clients, considering all projects known to the CRO survey respondents.

The data shows the frequency of activities outsourced by pharma companies in clinical trial projects contracted to the CROs. The data indicates that most respondents performed tasks that were both mundane and technically challenging out-sourced to them. Data compilation, collection and analysis are the more technically mundane chores. Notably, data analysis, which requires a higher level of engagement with the data, was also almost always included in the contracted functions. However, interviews with pharmaceutical company biostatistics directors showed that this CRO activity is usually carried out using guidelines and templates issued by the client. A biostatistics director from one of the top 5 pharma companies indicated that the "analysis methods development is never outsourced" and that selection of the CRO sometimes depended on which one "…can adopt and understand our methodologies well," showing flexibility and competence.

About 50% of the contracts involved support for project decision-making, which is expected considering the intermediary role of the CRO between the data and the client. Surprisingly, a significant number (35%) of respondents indicated that they were involved in clinical trial protocol design, which is a key function of biostatisticians and clinical teams in pharmaceutical companies (Table 1). Interviews with a few of the sampled firms indicated that while it was not common for all protocol design to be outsourced, frequently the clinical/contract research organization had skills and expertise in the area and would collaborate with the pharmaceutical counterparts to refine the study protocol design.

Other comments from the pharmaceutical companies' biostatistics directors or managers in reference to outsourcing were as follows:

"… We would never outsource vital studies – and even if we had to, we would never outsource anything in the critical path of drug development. On the other hand, we would completely outsource extension studies."

"Stability of CRO personnel (turnover) and commitments of time to the project are always an issue with large CROs. We would prefer to work with a smaller CRO that had a focus on biostatistics and much lower turnover than a big CRO." This particular concern was reflected by several of the pharmaceutical statistical group directors.

DISCUSSION

Outsourcing research and development functions is a "buy versus build" decision in most companies suggesting a transaction cost logic (Williamson, 1995) Projects will be outsourced when tasks are readily programmable as in extension trials. When projects are long term and monitoring at arms length is difficult, the cost of outsourcing may be too high. For pharmaceutical companies, where the risks are high and capital costs for product development (clinical trials) are significant, outsourcing may seem like an optimum solution. However, benefits of outsourcing and the transaction costs of managing external actors have to be constantly balanced, keeping the strategic interests of the company in mind. In the knowledge management literature, it is recognized that outsourcing practices can have the short-term effect of diluting the firm's competencies and can have the long-term effect of increasing the level of competition in the industry by diffusion of best knowledge, skills and competencies to other players in the field through service companies [Takeishi, 2002].

In this study, we looked at the outsourcing practices for biostatistics functions in drug development clinical trials as a way of understanding management of biostatistics competencies by the large pharmaceutical companies. By examining data from CROs we were able to understand the distribution and outsourcing of specific competencies as related to biostatistical functions. Interviews with pharmaceutical biostatisticians and directors of biostatistics groups enabled qualification and validation of the results. From the results, we note that although large pharma companies would outsource only extension studies or non – critical studies, there is still an exchange with the CRO in terms of best practices, standard operating principles (SOPs) and analytical methods which relate to the diffusion of competencies in the industry. The data from the CROs (Figure 1) demonstrates the surprising number of projects which involve either trial design or have CRO's write-ups presented to the FDA directly, both practices identified as "never outsource" and of "key importance to grow and retain" by the pharmaceutical statistics directors. The sharing of these big pharma best practices knowledge and experience with the CROs is an advantage to the smaller competitors, pharma or biotech companies, These smaller companies who do not have the history or resources to develop optimal processes in biostatistics, particularly as related to analysis methods and protocols that are likely to be accepted by the FDA. From this perspective CROs can be viewed as instruments for diffusion of institutional practices and thereby a route for small firms to gain legitimacy (Scott, 1995). In this view CROs through their role in institutionalization of biostatistical practices in drug development are a mechanism for bringing greater stability to drug product life cycle dynamics.

Gaining experience in areas of strategic competence for success in the industry – regulatory interactions and study protocol design – the CROs are gradually positioned to take on an increased role in the drug development process. A direct recognition of their growing competence in these areas is seen in the steadily increasing amount of outsourced R&D from pharmaceutical companies. In fact, the capabilities of some of the larger CROs combined with

their cash positions and steady income stream from long term contracts will eventually lead to their emergence as risk-takers and co-investors in the drug development process, where they will appropriate more value due to their increased competence. New business models will emerge with a sharing of jobs among players in the industry, hopefully leading to reduced risk for each of the players, and increasing pipeline productivity, which could lead to greater innovation and new products reaching the public. However, this scenario is still developing, in conjunction with significant changes in the entire pharmaceutical industry, in response to currently severe pricing, market and regulatory pressures. Biostatistics is a contested immobile competency in the drug development. Essentially, this perspective builds on the path dependency model of management of technological innovation (Dosi, 1982). This approach projects accumulation of critical resources and tacit knowledge that will allow the CRO to eventually become a new type of independent competitive player in the drug development process. This would perhaps increase turbulence in the pharmaceutical product life cycle, instead of the stabilizing influence that the CRO could exert as an interdependent player in the industry. This implies that managerial decision making coupled with complex biostatistical methodology should reevaluated by pharmaceutical companies in terms of how biostatistical competence should be developed into a core capability that contributes to a sustained competitive advantage

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REFERENCES

[1] Achilldelis, B. and Nanonakis. The dynamics of tech innovation: The case of the pharmaceutical industry. *Research Policy.* 30:535-588. 2001.

[2] Barney, J. (1991). Firm resources and sustained competitive advantage. *Journal of Management,* 17(1), 99-120.

[3] Barney, J. Strategic factor markets: Expectations, luck and business strategy. *Management Science*, 32, 1231 – 1241.1986.

[4] Chuang-Stein, Christy. Pharmaceutical statisticians in the US: Our future and direction. Biopharmaceutical Report (Biopharmaceutical section, American Statistical Association). 7(3): 1-5. 1999.

[5] Cockburn, Ian, Rebecca Henderson and Scott Stern, Untangling the Origins of Competitive Advantage. Strategic Management Journal 21:1123-1145.2000.

[6] Conner, K. A historical comparison of resource-based theory and five schools of thought within industrial organization economics: Do we have a new theory of the firm? *Journal of Management*, 17, 121-154. 1991.

[7] Coombs, R., and Metcalfe JS. Innovation in Pharmaceuticals: perspectives on the coordination, combination and creation of capabilities. *Tech Analysis and Strategic Management.* 14(3), 261-271.2002.

[8] Dierickx, I., and Cool, K. Asset Stock Accumulation and Sustainability of Competitive Advantage. *Management Science*. 35(12), 1504-1511.1989.

[9] Donahue, Rafe M. J. Some commentary on maximizing the statistician's value to the pharmaceutical industry, Drug Information Journal, 34:1261–1264, 2000.

[10] Dosi, Giovanni. Technological Paradigms and Technological Trajectories: A suggested Interpretation of the Determinants and directions of Technological Change. Research Policy 11(3): 147-163. 199

[11] Fairtlough, Gerard. A marriage of large and small: R&D for healthcare products. Business Strategy Review. 7(2): 14-22. 1996.

[12] Grobler, Anneke, Harri, Sharon L, Jooste, Hanna-Liza. The role of the statistician in the data management process. Drug Information Journal 35:665-670. 2001.

[13] Hall, R. The strategic analysis of intangible resources. *Strategic Management Journal*, 13, 135 –144.1992.

[14] Henderson, Rebecca and Ian Cockburn. Measuring competence? Exploring firm Effect in Pharmaceutical Research. Strategic Management Journal 15:63-84.1994.

[15] Itami, H. (1987). Mobilizing invisible assets. Cambridge, MA: Harvard University Press.

[16] Prahalad, C.K. and Hamel, G. The core competence of the corporation. *Harvard Business Review*. 90(3), 79-93. 1990.

[17] Jones, Oswald. Innovation Management as a post-modern phenomenon: The outsourcing of pharmaceutical R&D. British Journal of Management, 11: 341-356. 2000

[18] Lucarelli, Chris and Lois S. Peters. "Developing Competencies and Capabilities Through Knowledge Management: a Contingent Perspective" 2001. In: Technology Management

in the Knowledge Era (ed.) Dundar F. Kocaoglu and Timothy Anderson) p. 257-267. .2001.

[19] Marino, K. Developing consensus on firm competencies and capabilities. *Academy of Management Executive*. 10(3), 40-51.1996.

[20] Nelson, R., and Winter, S. *Evolutionary theory of economic change*. Harvard University Press: Cambridge. 1982.

[21] Parexel R&D sourcebook, 2001, p25

[22] Penrose, E. *The Theory of the Growth of the Firm*. John Wiley & Sons: New York. 1959.

[23] Prahalad, C.K. and Hamel, G. The core competence of the corporation. *Harvard Business Review*. 90(3), 79-93. 1990.

[24] Scott, W. Richard. . Institutions and Organizations. Sage Publications 1995.

[25] Takeishi, Akira. Knowledge Partitioning in the Interfirm Division of Labor: The Case of Automotive Product Development. *Organization Science.* 13(3), 321-353. 2002.

[26] Teece, D Capturing value from knowledge assets: the new economy, markets for know-how and intangible assets. *California Management Review*, 40(3), 55-79.1998.

[27] Teece D., G. Pisano, and A. Shuen (1997). Dynamic Capabilities and Strategic Management. *Strategic Management Journal*. 18(7), 509-533.1997.

[28] Williamson, Oliver Srategizing, Economizing and Economic Organization. Strategic Management Journal 12:75-94. 1991.

[29] Walsh and Linton, The measurement of technical competencies, Journal of High Technology Management Research, 13: 63-86, 2002

[30] www.gsk.com