5 *Outsourcing, fragmentation, and integration*

The pharmaceutical industry

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Introduction

The outsourcing of non-core standardized tasks and processes which permit relatively easy measurement of performance and quality is a well-known story. Outsourcing is presented as an opportunity resulting from technological changes that permit the springing up of thick intermediate markets (Langlois, 2003; Milberg, 2004; Narula, 2001; Williamson, 1981). This allows firms to use markets to obtain intermediate products and services, with the associated benefits from specialization, economies of scale, and competition, resulting in lower costs and better quality intermediate products (Langlois, 2003). This is treated as a dynamic transaction cost story. Advances in the standardization and codification of production processes promotes a smooth interface between vertical stages of production. This allows principal firms to concentrate on core competence activities, with few coordination costs required to maintain the vertical relationship. Coordination costs are low because the outsourced intermediate product is the result of rote labor which can be easily measured and monitored by the new technology embodied in production equipment. In addition, the principal firm benefits from conservation of capital, diminishing uncertainty, and the spreading of risk. In this story, the principal firm retains knowledge-process core competences within the firm, not only because these competences rely on tacit information and ongoing knowledge creation (and are thus difficult to transfer to an outside entity), but also because they are the sources of the firm's competitive advantages, requiring protection from appropriation (Dosi *et al.*, 2006; Kogut and Zander, 1993; Sen, 2006). Langlois (2003: 347) describes the preconditions for this organizational transformation:

> Decentralization implies an ability to cut apart the stages of production cleanly enough that they can be placed into separate hands without high costs of coordination . . . decentralization implies some degree of standardization of "interfaces" between stages.

However, the literature also provides a more complex story about outsourcing, involving long-term and collaborative inter-firm relationships (Lamoreaux, Raff, and Temin, 2003), and indeed a full "partnership continuum" of possible degrees of inter-firm engagements (Kleyn *et al.*, 2007: 334). Outsourcing with "fuzzy" (relationship-complex) rather than smooth boundaries is typically associated with investment-based rather than intermediate-product-sourcing strategies (Cantwell, 1991; Narula, 2001), such as capabilities-seeking or technology-seeking (Doshi, 2004; Grant, 1996; Kleyn *et al.*, 2007) or supplier-upgrading (Takeishi, 2002). Investment-based outsourcing usually involves the firm's need to acquire tacit inputs such as skills, technology, or other tacit knowledge. This process leads to uncertain and difficult-to-measure results and unclear property rights, requiring closer monitoring and more "face-to-face interaction"; hence the fuzzy boundaries or relatively higher coordination costs (Balconi, Pozzali, and Viale, 2007; Cantwell and Santangelo, 1999; Narula, 2001: 369).

In the pharmaceutical industry, outsourcing increasingly encompasses non-standardized activities that were previously considered to be the exercise of the principal firm's core competences, such as research and development (R&D), with outcomes that are uncertain, risky, and hard to measure whether undertaken internally or with an external partner (Bhatt, 2005; Doshi, 2004; John, 2006; Mehta and Peters, 2007). Furthermore, some of these new outsourcing arrangements, while contributing further to the formal (equity-based) vertical fragmentation of the production process, can involve substantial transaction or coordination costs, and in some instances require forms of *integration* between principal and vendor firms (Sen and Shiel, 2006). Thus the interfaces between stages of production in the pharmaceutical industry are fuzzy, requiring a substantial expenditure of resources to maintain satisfactory outcomes (Daniel *et al.*, 1997; Galambos and Sturchio, 1998).

This chapter explores the nature of outsourcing and offshoring of R&D in the modern pharmaceutical, biopharmaceutical, and medical devices ("pharma") industry, particularly with respect to the

outsourcing of the management of clinical trials and of drug discovery. Both of these functions have been considered part of the core competences of pharmaceutical firms in the past (Piachaud, 2004), and both involve complex relationships rather than smooth interfaces between principal and vendor firms.

Two questions emerge: (1) How do these pharma practices fit within the typology of intermediate-product-based and investment-based outsourcing? (2) Does outsourcing of high-skill R&D functions imply that standardization and codification of tasks and skills is making redundant scientific labor not previously thought amenable to codification?

Typically, it is assumed that codification of skilled processes replaces high-skill tasks with standardized rote tasks and creates the possibility of replacing skilled labor with less skilled labor. This allows the reallocation of codified tasks to lower-margin contract providers working with less skilled and therefore poorly remunerated labor. In addition, typically, standardization and codification of production processes are embodied in new capital equipment and measuring instruments providing control of the labor process and quality of outcomes (Lamoreaux *et al.*, 2003). This process, which redesigns human labor and its interaction with capital equipment, creates the smooth interface permitting relatively less costly outsourcing (Balconi, 2002; Balconi, Pozzali, and Viale, 2007). Coordination costs are low because new technologies give the principal firm sufficient control over the nature and quality of the outsourced intermediate products.

This chapter demonstrates that the pharmaceutical industry has been undergoing a trial-and-error transition period of restructuring in response to emerging constraints and opportunities. This has led to a variety of re-organizing responses, including mergers, alliances, outsourcing, and offshoring with respect to R&D operations.

The chapter shows that the outsourcing of parts or all of clinical trials (drug development or "DDV") with high coordination costs is being accompanied by the beginning phase of standardization of aspects of clinical trials, and by the creation of new technological tools which can embody a codification of many of the tasks traditionally embedded in the clinical trial process. However, the outcome of this standardization process is unlikely to involve a larger role for unskilled labor. Instead, new technologies are separating out codifiable from non-codifiable tasks currently mixed together in the skilled-labor conduct of clinical trials. The new technology will perform previously time-consuming

codifiable tasks much faster, enabling an intensification, or significantly increased productivity, of the skilled labor involved.

An analytical focus on the transaction costs emanating from fuzzy boundaries associated with the outsourcing of clinical trials could direct attention away from the process by which investments in standardization and codification produce a smoother interface which can permit less costly (transaction costs) outsourcing in the future. A static focus on transaction costs must give way to a dynamic focus on firms' investments to transform the economic environment, including current constraints such as transaction costs (Lazonick, 1991; Kapler, 2007).

The usually collaborative outsourcing of drug discovery ("DDS") is different. This is more likely the manifestation of the continuing development of opportunities and threats presented by the explosive emergence of new biomedical science. What might be thought of as the transaction costs involved represent, instead, investments in new assets, i.e., in new capabilities and equipment necessary to exploit the emerging science, and the reallocation of fixed costs and risks among a network of contract research organizations (CROs). Focus on static transaction costs could obscure the endogenous production, through investment, of vertical fragmentation *and* integration (Ietto-Gillies, 2002).

The chapter is organized as follows: the next section discusses the extent of outsourcing and offshoring in pharmaceutical R&D, and the pressures leading to the restructuring of the industry. This is followed by a presentation of the modes of restructuring, and the standardization and codification of some labor processes in, the drug development (clinical trials) phase of R&D. We then examine restructuring in the drug discovery portion of pharmaceutical R&D. The final section provides concluding comments.

Outsourcing, offshoring, and restructuring pressures in the pharmaceutical industry

Outsourcing

In 2006, Goldman Sachs estimated that global pharmaceutical R&D spending by the US pharmaceutical industry[1] would grow from $95 billion in 2005 to $161 billion in 2010, an average annual

growth rate of 13 percent (Parexel, 2007). Cockburn (2006) estimates that since 1990, European-based pharma firms' research expenditures have been the equivalent of about 80–90% of the US bill, while Japanese firms have spent about 30–50% as much as US-based firms. This suggests pharmaceutical R&D expenditures by global pharma at $340–390 billion by 2010.

Drug development (DDV), including preclinical testing and clinical studies, usually makes up about 70% of the R&D budget (Piachaud, 2004). Outsourcing of US pharma's DDV has been growing steadily since the late 1980s (16% annually from 2001–07 according to Getz, 2007) and represents the largest share of pharma R&D outsourcing, now estimated to include 22–25% of US clinical trials (Mehta and Peters, 2007; Parexel, 2007). Miller (2007a,b) conducted a survey of pharma firms and CROs showing that 94% reported an increase in outsourcing. CROs play a "major role" in 60% of all pharma R&D projects, up from under 30% in 1993 (Mehta and Peters, 2007: 30). US pharma's global R&D expenditures are expected to grow 13% per year to 2010, while outsourcing of clinical studies is expected to grow 13–15% per year, reaching approximately $26–36 billion by 2010 (Gassman, Reepmeyer, and von Zedtwitz, 2004; Mehta and Peters, 2007: 30; Parexel, 2007). That would amount to about 20% of the US R&D budget, and about 30% of clinical trial expenditures.

Eighty three percent of CRO revenues come from clinical trials management (Mehta and Peters, 2007: 30). In 2003, there were approximately 270 CROs in North America, and over 1,000 CROs globally (Hindin, 2004). Between 2002 and 2005, CRO annual head-count growth of 7% exceeded that of US pharma by a factor of three, reaching 50,877 in 2005 (Getz, 2007).

Since the mid-1990s, outsourcing of DDS (drug discovery) processes has also become more familiar. In 2004, the outsourced DDS market was about $2 billion (King, 2004), with the market expected to amount to $7.2 billion by 2009 (Boswell, 2005; Finkelstein and Temin, 2008: 66). That would amount to 4.5% of the 2009–10 US R&D budget and 15% of the US DDS budget, with an average annual growth rate of approximately 50%.

Thus, total US pharma outsourcing, while expected to amount to only 24% of the total 2010 R&D budget, is clearly growing at a more

rapid rate than the R&D budget. CRO employment is also growing much faster than employment in pharma.

Offshoring

Increasingly, US pharmaceutical R&D expenditures are being offshored, either through offshoring to affiliates (through foreign direct investment or "FDI") or via contracts with foreign CROs or with domestic CROs that are globalizing their resources (i.e., offshoring to unaffiliated [contract] parties or "offshore outsourcing"). According to UNCTAD (2005: 125), the pharma industry has the second largest proportion of offshored R&D at 38%. It is estimated that offshored US pharmaceutical R&D amounted to about 16% in the 1970s, growing to 21% in 2006 to $9 billion (Parexel, 2007: 5). In 2006, the top twelve US pharmaceutical firms by number of studies accounted for 41% of the clinical trials being sponsored by the industry, but they accounted for 48% (or 544 of 1,125) of the studies being conducted outside the US. Sixty-two percent of these foreign-located studies were being conducted in Germany (175 trials) and the UK (161 trials). Other favored locations included Eastern Europe and Latin America. India and Ireland each accounted for 4.7% (26 trials), China for 4.4% (24), and Russia for less than 1% (5). However, the growth rate in foreign-located clinical investigator participation in US Food and Drug Administration- (FDA-)regulated trials is highest in India, China, and Russia (see also Thiers, Sinskey, and Berndt, 2007). From 2001 to 2006, the number of participating investigators in India grew by 625%, in China 284%, and in Russia 253% (Parexel, 2007: 130). From 2002 to 2006, the number of FDA-regulated investigators globally grew by 15% annually, while the number of investigators in the US declined by 5.5% annually (Parexel, 2007: 129).

Drug discovery is also being offshored, with Indian, Chinese, and Russian firms especially making more deals currently with western pharmaceutical firms (Doshi, 2004; Finkelstein and Temin, 2008: 67). Drivers include an abundance of low-cost skilled labor, large "drug-naïve" populations, good health and information technology (IT) infrastructures, and offshore government attempts to address intellectual property issues (Bhatt, 2005; Clark, 2007; Doshi, 2004; *Pharmaceutical Executive*, 2006).

Pressures and opportunities in the industry promote restructuring

The restructuring of the pharmaceutical industry has been explained in the literature within the context of changing science and technology, pricing, cost, and regulatory pressures, concerns about a dwindling drug discovery pipeline among the large pharma corporations, and the decline of the blockbuster drug model[2] (Hall, 2000; Hindin, 2004; John, 2006; Kleyn *et al.*, 2007; Piachaud, 2004). Squeezing the pharmaceutical firms are increasing price pressures from governments, world health authorities, and insurance entities (Harris, 2008; King, 2004; Scherer, 2004: 929–31), increasing competition in a globalized industry, the fast-rising cost and length of development time to bring a new profitable drug to the market (Hall, 2000; Sen, 2006), and the declining proportion of new drug approvals (Doshi, 2004). Other pressures come from losses to generic drugs and expiring patents (Martinez and Goldstein, 2007).

Until 1980, the big US pharma firms were fully integrated operations performing tasks ranging from drug discovery through marketing in-house (Cockburn, 2004: 13–14). This model dated back to the interwar years.[3] The chemistry-based discovery process (DDS) necessitated large labs and significant human capital, financial resources, and expensive technology (Piachaud, 2004: 93, 114). There was no need for outsourcing; internal personnel and expertise were sufficient to carry out the whole process. In addition, outsourcing would have raised concerns about dissipation of intellectual property and possibly diffusion of the pharma firms' core competences. Patent applications are typically based upon data emerging from the lead optimization phase of drug discovery (Clark and Newton, 2004: 4). Lead optimization is "the process of determining whether a compound found to be effective against the target can be converted into a drug candidate for testing" (Finkelstein and Temin, 2008: 66; see also Clark and Newton, 2004).

An important driver in the restructuring of drug-discovery R&D has been the ongoing transition in the industry from the older chemistry-based science to that of molecular biology (Galambos and Sturchio, 1998). This transition has been accompanied by advances in drug-discovery technology (rapid throughput screening, combinatorial chemistry, bioinformatics, and proteomics, etc.) that have increased

possible drug targets by a factor of ten (Cockburn, 2004: 12; Doshi, 2004: 128). The new technologies are capable of boosting productivity, but they are extremely costly, as they require the acquisition of new scientific capabilities, infrastructure, and managerial reorganization by the big pharma firms (Cockburn, 2006: 14; Galambos and Sturchio, 1998; Piachaud, 2004: 73–74).

With respect to the drug development process (DDV), including preclinical testing and clinical trials, until the late 1980s, pharmaceutical firms viewed outsourcing to be too risky given a lack of trust in the practices that might be adopted by outsider vendors (Daniel *et al.*, 1997). But pressure to cap internal resources (fixed costs) and the rise of CROs led to limited outsourcing attempts, initially in response to strained internal capacity during peak activity (Hall, 2000). Another push factor was the FDA's skeptical response to results from trials monitored by the big pharma firms themselves (Hindin, 2004). Initially, some scientists relocating from pharma firms set up small, regional operations, specializing in clinical trial monitoring, project coordination, or data management (Hindin, 2004). CROs originally functioned as an offshoot of the pharmaceutical company, simply offering staff to supplement the pharma company's internal resources, with little innovation or new process development occurring (Mattingly, 2003).

A few years ago, the estimated cost of bringing a new drug to market (i.e., the cost per approved NDA – or new drug application) was $802 million (DiMasi, Hansen, and Grabowski, 2003). In constant year 2000 dollars, this amounted to an increase of 70 percent since 1991. The real cost had grown by a factor of almost six from 1979 to 1991 (Cockburn, 2006: 11–12). About half of this is out-of-pocket costs; the rest is the estimated 11 percent annual cost of financial capital invested in research and testing (Scherer, 2004: 928; Parexel, 2007). For most of the past two decades, R&D costs have been rising at a faster rate than sales of ethical pharmaceuticals (*Future Pharmaceuticals*, 2006: 40; Parexel, 2007). Gilbert, Henske, and Singh (2003) estimated a cost of $1.7 billion for shepherding an NCE/NME (new chemical entity or new molecular entity) through successful launch during 1983–2000, and indicated that more recent data suggested higher costs and declining productivity. According to the FDA (2004: 8), only 8 percent of compounds discovered and placed in preclinical trials have reached the market in recent years, down from 14 percent

in the 1990s. In 2004 it was estimated that pharma had just 800 years remaining of the "exclusivity horizon" due to expiring patents, compared to 1,146 years in 1998 (Doshi, 2004: 28).

Many of the factors contributing to the high cost of drug development are well known. The development costs of the drugs that end up as failures must be added to the costs of the "successful" drugs. Less than one-third of the drugs that enter clinical trials make it to Phase III trials (Parexel, 2007: 147). Pharma applies for patent protection on new chemical entities (NCEs/NMEs) shortly before clinical tests in humans. Only 21–23 percent of NCEs/NMEs subjected to human testing get marketing approval, which takes place after the Phase III trials (Cockburn, 2006: 15; Scherer, 2004: 927–28). The length of time to bring a new drug from discovery to market is estimated by the industry at 90 months (Parexel, 2007: 146). Cockburn (2006: 11) estimates 6.5 to 18 years from the preclinical phase to the end of regulatory review. The time-to-market has been growing in part due to the increasing concerns about safety on the part of the regulatory authorities (Martinez and Goldstein, 2007). The US FDA (2004: 8) blames safety problems and the ineffectiveness of pre-trial testing in predicting failures before testing in humans commences.

Cockburn (2006) also suggests that some of the cost and time-to-market problems could very well be the result of the ongoing vertical disintegration within the industry, causing inefficient haggling over the division of rents. Parexel (2007: 173) reports from a survey of the industry that study delays were caused most often by the pharma-CRO contract budget, negotiation, and approval process.

Although the rising cost of developing drugs is much discussed, this does not appear to have hurt the industry's profitability (Angell, 2004). Parexel (2007: 22) reports that pharma was the second most profitable industry in the US in 2006 after mining and oil. Finkelstein and Temin (2008: 59–63) point to steady, non-volatile profits for the ten largest pharmaceutical firms since 1980, but acknowledge the threats posed by the transitions in the industry with respect to science and the prevailing business model. Kermani and Langer (2007: 1) point to investors grown accustomed to "double digit growth performance."

Critics of the industry contest the accuracy of the argument that pharma has encountered a cost crisis, charging that pharma counts marketing expenses as costs of drug development. Critics also point out the heavy reliance of the industry on public funds accessed through tax

breaks and public sector science. They charge that marketing expenses are more than double the amount invested in R&D, and that prices include huge mark-ups over cost (Public Citizen, 2003; Angell, 2004). While this debate is beyond the scope of this chapter, we rely on industry and regulatory actions that appear to follow from a fear of declining industry performance.

The FDA has been very concerned about the disappointing rate of translation of scientific breakthroughs into new safe and effective drugs. This has prompted the agency to define a "Critical Path to New Medical Products," i.e., a detailed proposal for streamlining and speeding the transformation of discoveries into safe, effective remedies by updating the "toolkits" for drug discovery and clinical trials (FDA, 2004). Under the "Critical Path" rubric, the FDA is increasing pressure on pharma and biotechnology firms ("biotechs") to invest in new technologies and practices, some of which will require substantial effort and expenditures up front.

Therefore, a combination of pressures has pushed the industry to restructure, in part, in order to achieve greater efficiencies and lower costs throughout the discovery, development, and commercialization phases. In addition to increasing the productivity of existing resources, restructuring is designed to provide access to new resources that can allow pharma to compete in areas opened up by changes in science and a spreading of risk and fixed costs among a network of pharma, biotech, service provider, and technological tool firms. The reorganization of the industry has included (1) mergers and acquisitions among pharma firms to acquire new capabilities, tools, and products for development; (2) mergers between pharma and biotech firms that allow pharma to acquire new scientific capabilities and that give access to development infrastructure to small biotech firms; (3) mergers among contract research organizations to acquire a portfolio of capabilities; and (4) vertical fragmentation of the discovery, development, and production process due to outsourcing and offshoring (Hall, 2000; Higgins and Rodriguez, 2006; Hindin, 2004; Kermani and Langer, 2007). The mergers among pharma led to layoffs of redundant scientists, thus contributing to a supply of outside skilled and experienced personnel to feed a growing CRO industry. The industry is in flux with respect to which tasks to outsource, which tasks are to be considered core competences, and how to measure and control vendor performance. The variety of new forms is a manifestation of a

trial-and-error search for a new business model to allow industry participants to compete successfully in a new environment (Piachaud, 2004).

Outsourcing and offshoring clinical trials (drug development)

Initial DDV outsourcing tended to be ill-organized and labor-intensive on the part of the sponsor firms, and therefore more costly than expected (Daniel *et al.*, 1997). This led to a period during which pharma had to devote significant time and effort to standardizing and institutionalizing many aspects of the outsourcing process itself, including search, negotiation, writing contracts, pricing and evaluation, and to creating centralized firm-level outsourcing-management teams capable of learning from experience and cutting waste and duplication of effort (Daniel *et al.*, 1997). CROs also invested in creating interface-management services to try to help to smooth the interface between sponsor and provider. However, the ideal of an outsourcing relationship characterized by an arm's-length contract with a smooth interface, eliminating the need for costly coordination and monitoring expenditures, has not been achieved. The familiar problem is the asymmetric information with respect to the quality of the vendor's product, which increases risk to the pharma sponsor and sets into motion efforts to reduce the risk (Lamoreaux, Raff, and Temin, 2003).

Azoulay (2003) describes the fraught relationships between principal pharma firms and CROs. In part, outsourcing is seen by pharma as a solution to the peaks and troughs of demand for skilled clinical personnel, as trials go through stop-and-start adjustments, without adding fixed costs in-house. However, these outsourcing arrangements are often unsatisfactory to pharmaceutical firms, which complain about a high labor turnover rate at CROs (Azoulay, 2003; Mehta and Peters, 2007: 32). One problem is that CROs are unwilling to commit a dedicated team to a long-term trial, or from trial to trial with the same product, due to the stop-and-start nature of clinical trials and to varying peaks of activity for each of the CRO's projects. Therefore, the pharma sponsors are continually "starting over" with new CRO staff with varying qualifications who are unfamiliar with the product and trial history. In addition, continuity of procedures is not assured. Furthermore, when contracts with CROs are focused on cost and speed, the incentives are not aligned to elicit learning, discovery, or creativity

from CRO skilled personnel in response to problems that emerge, which adds to pharma's coordinating costs (Azoulay, 2003; Mehta and Peters, 2007: 33)

Therefore, outsourcing of clinical trials has tended to create new risks due to pharma's incomplete control over CRO processes and personnel (Miller, 2007a). The new risks must be addressed with extra layers of monitoring, i.e., much higher transaction costs than would normally be anticipated from an arm's-length arrangement. In other words, pharma has attempted to reallocate the risk of peaks and troughs in the demand for skilled personnel (and the risk of adding in-house fixed costs) to the CROs, but in the process, has created a new risk, i.e., the inability to control the processes and personnel assigned to specific tasks. This leads to a fear of a measure of unreliability with the results (Miller, 2007a), creating the potential for costly or even disastrous consequences in pharma's relationships with the regulatory authorities.

Why, then, engage in outsourcing of clinical trials? There is some evidence that savings due to CRO specialization have been achieved. Getz (2006) shows that CROs can shorten time to market significantly while preserving data quality; in some cases CROs can conduct clinical trials up to 30 percent faster than pharma firms (Thakur, forthcoming: 58). They also bring experience from working in multiple therapeutic areas yielding skilled problem-solving abilities, and they have contacts and their own relationships with regulatory personnel (Getz, 2006).

In an industry context of rapid change and innovation, pharma has apparently accepted, for now, the benefits from outsourcing as well as the cost of new risks. The risk is managed with more devotion of internal resources to monitoring activities than initially expected by the sponsor firm, and this is apparently preferable as an interim solution. However, Mehta and Peters (2007: 33) warn that "[t]he benefits and transaction costs of managing alliances have to be constantly balanced." That is, the transaction costs associated with outsourcing across fuzzy boundaries can erode the benefits from CRO specialization.

This situation of high-transaction-cost outsourcing is most likely a temporary solution as outsourcing practices evolve along two tracks. What is needed to reduce risk to the pharma buyer are methods to increase the buyer's information about and/or control over labor processes within the supplier firm, i.e., institutions/technologies permitting

more measurement, monitoring, or actual control (Lamoreaux, Raff, and Temin, 2003). Along one evolving track, principal and provider firms have moved closer to relational contracting, or preferred provider outsourcing in the 1990s (Azoulay, 2003; Mattingly, 2003; Getz, 2006). This represents a conscious move toward a collaborative, not arm's-length, approach to cost, risk, innovation, and complementary research streams (McCoy and Tremblay, 2003: 22). In this situation, the cost of monitoring a supposed arm's-length relationship is to be replaced by collaboration with respect to best practices to increase the trustworthiness of future joint projects. The CRO becomes a partner in innovation and problem solving (Levina and Vaast, 2008). Sen and Shiel (2006) emphasize that the process of working out the management of outsourced projects creates learning by both firms that leads to a standardization or regularization of knowledge tasks which further integrates the two parties. It has been shown in other industries as well that a sponsor firm's initial experience with intended arm's-length contractors leads to the sponsor's learning about the broader capabilities of the contractor and growing trust between the two. This often results in a more balanced collaborative relationship, with significant creative contributions from the service provider (Maskell *et al.*, 2007; Levina and Vaast, 2008; Ulset, 2008).

The second track along which pharma outsourcing is evolving is due to the fact that both pharma and CROs are investing in new technologies and processes that are intended not only to reduce costs and speed innovation, but more specifically to standardize data and procedures and to codify and automate some skilled tasks. This will have the likely effect of smoothing the fuzzy pharma–CRO interface that exists currently (Balconi, 2002). In other words, the industry is investing in the creation of interfaces that will facilitate less costly outsourcing in the future.

Standardization and codification in drug development

The traditional conduct of clinical trials has been suffused with inefficient skilled-labor processes. Now that price, cost, productivity, and regulatory pressures have been felt across the industry, applied information technology presents the opportunity to speed up and automate parts of the drug-development process (Balconi, Pozzali, and Viale, 2007). One source of inefficiency has been that clinical trial

data collected, analyzed, and submitted to the regulatory authorities have not been standardized with respect to content, presentation, or software.

> Unfortunately, the pharma industry is not standardized at all; there is often inconsistent information that eludes the review processes and quality checks . . . We believe standards will revolutionize clinical development. (*Future Pharmaceuticals*, 2006: 41)

> Hospitals and clinics have no standard database for even weight, blood pressure, cholesterol. A global standard would help enormously. (Hindin, 2004)

> The importance of a standard for the exchange of clinical trial data cannot be overstated . . . FDA reviewers spend far too much valuable time simply reorganizing large amounts of data submitted in varying formats . . . [A] standard structure will . . . speed new discoveries to the public. (FDA, 2004)

In order to speed up drug development, the FDA has been pushing the industry toward standardizing data collection and presentation, and announced in 2004 a preferred standard electronic format for submitting data in support of NDAs (New Drug Applications). The Study Data Tabulation Model (SDTM) format was developed by the Clinical Data Interchange Standards Consortium (CDISC), a global nonprofit multidisciplinary organization "committed to the development of industry standards to support the electronic acquisition, exchange, submission, and archiving of clinical trials data" (FDA, 2004).

CDISC has developed standards for each stage of the drug-development process, including data transmission, data analysis, laboratory data, and non-clinical data, and standards cover both content of data files and processes such as data file formats, definitions and terminology, and submission procedures (Souza, Kush, and Evans, 2007). The goal is to create a single accepted format for data collection and exchange in order to create efficiencies in data collection and analysis of clinical trial data and in the review process by the FDA. In addition, long-term goals include the ability to share information more readily among agencies, the ability to analyze data across trials for similar products, and to create a central repository for all clinical trial data (Wood and Guinter, 2008). In 2004, approximately half of North American pharma reported using CDISC standards (Souza, Kush, and Evans, 2007). In November 2007, the FDA and Duke University

Medical Center entered into an agreement in which Duke would lead the effort to modernize clinical trial processes (FDA, 2007).[4]

CDISC is a part of a larger global endeavor to standardize drug-discovery and development tools and processes which began in the late 1980s as Europeans were standardizing pharmaceutical regulatory procedures across borders. Europe, Japan, and the US initiated a joint effort to adopt pharma standards with the International Conference on Harmonization in 1990 (ICH "History," n.d.).[5]

As acknowledged by the FDA, standardization will promote "enhanced communication among sponsors and clinicians" (US Department of Health and Human Services [HHS], 2006). Furthermore, since CDISC is a global standards organization, it has ties with the European Medicines Agency (EMEA) and Japan's Ministry of Health Labor and Welfare (MHLW) (CDISC, 2008a). It has been meeting with regulatory and academic bodies around the globe, including recently in China, Singapore, India, and Brazil (Kush *et al.*, 2008). Standardization of data, in short, will help significantly to smooth the sponsor interface with outsourced and offshore vendors.

Codification refers to the transformation of tacit knowledge or competences into information, i.e., knowledge that is easily transmitted in written or spoken form (Balconi, Pozzali, and Viale, 2007).[6] Dosi *et al.* (2006) define information as knowledge that is easily accessed, reproduced, and diffused. Tacit knowledge refers to know-how which requires direct personal interaction and experience in order to be acquired by another person. Tacit knowledge that is necessary to exercise judgment, interpret, solve problems, and create novelties is most difficult to codify. Codifiable tacit knowledge includes that which can be separated into bits of measureable logic once measurement technology has reached the necessary level of sophistication. Codified tacit knowledge may be "inscripted in artifacts (machines) that apply the rules followed by knowledgeable individuals" (Balconi, Pozzali, and Viale, 2007: 833). Subsequently, automated processes can substitute for older tacit knowledge. Applied IT has significantly increased codification possibilities in pharma as it has done previously in manufacturing and in technology services (Balconi, 2002; Ernst, 2006; Nolan, Sutherland, and Zhang, 2002).

But codification requires costly investment, so whether it occurs is dependent upon the evolving context of economic costs and benefits. Tacit knowledge enabling judgment and creativity is less likely to be

codified because it is constantly devoted to different situations, limiting the repetitions of use which would be necessary to make codification efficient as sunk costs rise (Lamoreaux, Raff, and Temin, 2003).

Codification enables vertical disintegration for three reasons. First, it significantly improves the buyer's knowledge of the content and quality of the purchased object or service because the required specifications are more securely built into the automated process (Balconi, 2002; Nolan, Sutherland, and Zhang, 2002). Thus codification reduces transaction costs associated with outsourcing and offshoring (Balconi, 2002: 375), indeed, enabling a relationship closer to the ideal of an arm's-length contract.

Second, while the above discussion implies a sharp distinction between types of knowledge, i.e., codifiable and non-codifiable, these types are often mixed in any particular process. As Balconi, Pozzali, and Viale (2007) put it,

> In general, all types of knowledge are somewhat mixed. For example, the scientists' specific methodological knowledge about experimental procedures and techniques or their expertise about physical instrumentation and laboratory equipment are usually partly tacit and partly articulated but not externalized (843).

Similarly, in the conduct of clinical trials, skilled labor is applied to a process that includes codifiable tasks in the mix. In a somewhat different approach, Pedersen (2008) points out that not all tasks classified under R&D are high-skill tasks.

But, as Balconi also observes, this mixture comes under pressure in the face of cost and competitive challenges (2007: 841). In the context of pressures in the pharmaceutical industry, pharma, CROs, regulatory bodies, and standards organizations are developing technologies to separate out some of the routinizable components in the prevailing skilled-labor process in order to standardize and speed them up, thus intensifying skilled labor by expanding the outcomes associated with any "unit" of skilled labor. Here, codification is understood as a restructuring of the production process involving a finer division of labor, the replacement of some tasks previously performed by humans with artifacts embodying new technology, and the emergence of new tasks and new nodes for task completion, e.g., the "operator" role interacting with the new artifact (e.g., machine or computer), sending and responding to signals.

Third, codification and automation raise sunk costs and the risk of under-utilization of new capital equipment. This creates pressure on the principal firm to outsource to specialized providers, turn fixed costs into variable costs, and distribute the risk of investment (Balconi, 2002: 373).

The target for applied IT in pharma is the structure and sequence of skilled-labor tasks in the development process. One example is electronic data capture (EDC), a tool to reduce errors in data collection, speed the delivery of data to the sponsor, and thereby speed up the data analysis process. These systems replace a paper-based data reporting system which calls for the CRO trials monitor, when visiting study sites at hospitals, physicians' offices, and universities, to gather, verify, and correct paper CRFs (clinical report forms), and duplicate and deliver them to the sponsor firm where the data are entered into an electronic database and subsequently analyzed by the statistical team. With electronic CRFs (eCRFs), the patient data are entered electronically at the study site, and immediately evaluated for errors with built-in logic checks, leading to an immediate prompt for clinical site staff to make corrections where necessary. This eliminates the delay in delivery of data to the sponsor and the need to enter data at the sponsor site before analysis can begin. It also economizes on skilled-labor tasks and reduces the number of monitoring visits necessary to achieve a reliable result. It has been estimated that use of EDC can reduce clinical development costs by up to 20 percent (Mitchel *et al.*, 2006). By 2006, 29 percent of clinical trials were using electronic software, and usage on new studies had increased to 32 percent (Cline, 2007).

Another efficiency-improving tool is ePRO (electronic patient reported outcomes), which allows patients to electronically enter their own outcome data, economizing on the tasks performed by clinical staff and trial monitors. Looking forward, it is expected that the market for EDC and for ePRO will grow more than 23 percent annually (Getz, 2006). Thus, electronic tools are being created that will codify and replace some of the data gathering and monitoring tasks currently performed by clinical staff and monitors. The result will be an intensification of skilled labor, as more uncodifiable tasks will now be able to be performed by the same skilled-labor workforce.

In addition, the EDC tool makes possible further electronic streamlining of the clinical trial process through the possibility of the adoption of "adaptive" trial design. The more rapid analysis of data permitted

by EDC introduces the possibility to change the trial design mid-study in response to adverse events or the need to correct erroneous assumptions, without starting over with new trials. This conserves on skilled labor and could further speed the development process, possibly by as much as 30 percent (Tufts Center for the Study of Drug Development [TCSDD], 2006; Cline, 2007).

However, the change in industry practices takes time. For example, the SDTM model was recommended by the FDA in 2004, but the agency only recently began preparing a regulation to require it (CDISC, 2008b), which will most likely be followed by a two-year transition period (HHS, 2006). According to Getz (2006), most investigative sites have staff trained on eCRF and ePRO systems, but they complain that most sponsors have not yet standardized data collection, leading each site on average to have three disparate systems requiring incompatible computer terminals cluttering the site space and disparate reporting procedures for clinical staff and monitors.

Another tool developed to streamline clinical trials is an eProtocol system. The protocol is the design blueprint for the conduct of clinical trials. Because these are complex descriptive documents, and because of the lack of standardization in pharmaceuticals and the ambiguity in language, protocols are subject to varying interpretation and to amendment during operationalization. An eProtocol tool creates a modular approach to creating protocols that relies on a library or warehouse of electronically accessible modules of accepted processes and known chemical and biological properties and reactions. While these systems are familiar in the US, exporting the systems can help to increase offshored participation in trial design if the new libraries contain data and procedures acceptable to sponsor pharma firms.

Summing up the likely effects of widespread applied IT tools,

> The most profound impact of the shift to an integrated [electronic] clinical development environment will be that of standards on outsourcing activities . . . The adoption of standards will greatly facilitate the exchange of information across technology platforms and *will foster new partnering and outsourcing relationships. Many of the activities that are so important today will ultimately be replaced by technology and entirely new ways of working will emerge*. (*Future Pharmaceuticals*, 2006: 42) [emphasis supplied]

In other words, the pharma industry's evolving applied IT tools are eliminating some of the tasks currently performed by skilled personnel.

Automation embodied in new capital equipment and software can conserve skilled labor and increase its productivity by reducing the amount of time committed to codifiable tasks. Suggesting a parallel to the experience with skilled jobs in the IT field, an executive with a western CRO says "[N]ot all the jobs have gone away in information technology . . . They have evolved to *different things*. *And the same may happen for [pharma]*" (McCoy and Tremblay, 2003: 23) (emphasis supplied).

Offshoring

Given the pressures and opportunities for outsourcing, the location issue arises. Offshoring clinical trials offers an additional opportunity to reduce costs in countries with low-wage skilled labor and low-cost high-quality infrastructure, including IT infrastructure. For example, India's health infrastructure and pharma/biotech industry offer 50–60 percent cost savings in the conduct of clinical trials (Doshi, 2004). But the advantages go beyond labor costs. Patient recruitment in the US and other industrialized countries is slow and costly, in part due to more highly medicated and healthy populations than in the rest of the world. This creates the need for trials to be geographically fragmented across the US, often with only a few patients at each site. Large "drug naive" populations in some developing countries offer "an abundance of disease" and therefore much faster identification and recruitment of patients, as well as geographic concentration of trials (Doshi, 2004: 133; *Pharmaceutical Executive*, 2006). Unitary public health systems also speed up the identification of patients and the conduct of trials. Countries trying to attract this business are revamping intellectual property laws, adopting good clinical practice (GCP) norms, and otherwise upgrading health infrastructure to FDA standards (Doshi, 2004; Bhatt, 2005). The ongoing standardization and codification in the industry will only make the offshoring relationship less costly to manage.

Transaction costs and investments

Current transaction costs associated with outsourcing are not determinative of inter-firm alliances in pharma. The problem of transaction costs is a dynamic one (Balconi, 2002), which evolves along with

technology and which is transformed by firms' investments to modify the constraints facing them (Kapler, 2007; Lazonick, 1991; Milberg, 2004; Nolan, Sutherland, and Zhang, 2002). With respect to clinical trials, it is clear that high transaction costs resulting from inter-firm alliances are gradually being reduced by investments in learning, standardization, and codification, and an IT infrastructure that will foster a global convergence of skilled labor practices in clinical trials. The sponsor–provider interface will become smoother, and outsourcing and offshoring will likely become more common.

Outsourcing and offshoring drug-discovery research

Drug-discovery outsourcing began only in the mid-1990s in the US (Boswell, 2005); however, large European firms operating in small markets with few R&D resources started outsourcing in the 1980s (Gassman, Reepmeyer, and von Zedtwitz, 2004: 97). Now the crucial lead optimization phase is outsourced by most major pharmaceutical companies (Clark and Newton, 2004; Finkelstein and Temin, 2008). Early discovery research is often licensed in by big pharma from small biotechs and universities; in some pharma firms, more than 50 percent of drugs in development come from outside the firm (Mehta and Peters, 2007: 30; Rogers, Maranas, and Ding, 2004).

The changes were catalyzed by the growing cost-, competition-, and science-based pressures on the industry discussed above. The science involved in drug discovery changed fundamentally from the mature chemistry-based model with declining productivity to a model founded on the life sciences. The life sciences expanded the possibilities for drug discovery, including a significant increase in the number of potential drug targets, but they also require many new scientific and technological capabilities, making it impossible for any one firm to acquire all of them (Galambos and Sturchio, 1998; Gopalan, 2007; Gradwell, 2003; Kermani and Langer, 2007). In addition, the capital investment requirements to take advantage of the new technological possibilities are steep (Piachaud, 2004: 73–74; Rogers, Maranas, and Ding, 2004). Small biotechs, often formed by academics taking advantage of new patenting possibilities, were created to develop new product leads made possible by the changing science and new technological tools (Cockburn, 2004; Cockburn, 2006: 14–16). Thus big pharma, biotech firms, and academic researchers created a new vertical structure in DDS

research, involving both contractual and collaborative arrangements. Piachaud (2004: 75) argues that this was an appropriate response to changing science, since the sources of innovation are to be found in scientific communities or networks made up of firms, universities, and research labs, where expertise is dispersed, and not within individual firms.

The choice of technology and network location for this DDS innovatory activity is strategic, based upon the principal's specific expertise and the availability of external complementary capabilities. For example, Abbott teamed with Cambridge Antibody Technology to combine the latter's new technology with Abbott's targets and animal and human models to develop a successful rheumatoid arthritis drug. Separately, Abbott used its developing internal DDS technologies to speedily develop an important HIV drug. "We had developed a high-through-put, highly robotized, crystallography lab that could determine the structure of proteins very quickly" (King, 2004). Abbott's combination of partnering and internally developed innovations led to a tripling of the annual number of compounds available for clinical development compared to the rate it experienced in the 1990s (King, 2004).

The outsourcing of drug discovery, at least within the western countries, is not about contracting out rote tasks; drug-discovery partnerships are meant to be collaborative in order to facilitate the transfer of tacit knowledge. As such, they are recognized as coordination-cost heavy, involving a fuzzy interface between the collaborating firms. Nevertheless, outsourcing is seen as a necessity within the environment of rapid technological progress and heightened uncertainty. It would be considered risky to tie up capital with large new infrastructure and associated personnel because these would limit the firm's ability to respond flexibly to scientific and industry changes in the future (King, 2004). "If it doesn't work out after two or three years, they switch to some other options. They don't have the infrastructure costs and large investment scenarios for drugs that did not work for them" (King, 2004: 7). Because of the innumerable possibilities and continuing changes in science, DDS partnering probably is not temporary (Galambos and Sturchio, 1998; Piachaud, 2004).

However, the managing costs associated with these collaborations should be seen not as transaction costs, but as investments that are required to obtain access to new technological assets and capabilities

which offer a promising route to new drug discovery and to processes which shorten time to development (Lazonick, 1991; Cantwell, 1991). In other words, DDS outsourcing fits the investment-based type of outsourcing.

At the same time, increasing competition among vendors (Clark and Newton, 2004: 8) has caused some restructuring in that sector as well. According to Clark (2007), three different models have been adopted in the CRO sector. Due to declining margins in this sector, some providers are making the transition out of services and into proprietary drug discovery. Others are adopting a hybrid model, combining services provision with proprietary drug discovery. Clark calls the third model a "hybrid onshore-offshore model" (2007: 10). Western-based vendors have built or acquired or made collaborative arrangements with offshore facilities in order to access skilled scientific labor at much lower costs and in some cases in response to their own clients' offshore arrangements. Western CROs face some of the same pressures afflicting pharma: speed and cost (McCoy and Tremblay, 2003: 15–16).

The first publicly announced DDS CRO offshore operation took place in 2003, with the displacement of chemistry R&D from the US to India (McCoy and Tremblay, 2003: 15). In the onshore-offshore model, the western providers offer their clients either direct access to foreign scientists and facilities, or offer a western-based management of the interface between western and eastern labor. This yields cost advantages from geographic fragmentation along with the CRO's management of fuzzy boundaries by experienced personnel. For example, SAFC Pharma offers clients the opportunity to work directly with scientists in India or through its UK team that offers to manage the relationship between the client and the offshore scientists (Clark, 2007).

According to Clark (2007), one of the drivers of the offshoring activity is the blossoming of vendor firms in Asia and Russia, and the efforts by these firms and their governments to move swiftly to address infrastructure quality and protection of intellectual property. These are attractive opportunities due to the availability of skilled labor at low cost. In 2001 it was estimated that Indian R&D cost 75 percent less than R&D by multinational pharma firms (Doshi, 2004: 132). In 2003, an executive of a German CRO estimated that the FTE (full-time equivalent) pay of a PhD chemist in India was 27 percent of that in the US; an FTE in China would earn 23 percent

of the US pay. Nevertheless, in 2003 it was estimated that India and China together had only 2–5 percent of the market, but their shares are expected to grow rapidly. Offshoring is also pursued by small biotech firms in areas where they lack capability (McCoy and Tremblay, 2003: 16, 23).

The nature of offshored tasks is more difficult to determine: Are they pedestrian and thus more amenable to arm's-length contracting? Many pharma firms have expressed the opinion that offshored work is more routine, unsophisticated, less complex, more appropriate for scientists with less experience, and complementary to the advanced work of in-house scientists. An executive of one western offshore-outsourcing firm draws the distinction between information and tacit knowledge:

> If you can write it down and give it to somebody to make it, that's probably going to be made offshore . . . But if you are looking for input on planning or computational modeling . . . that's probably still going to be done in the US and Europe. (McCoy and Tremblay, 2003: 18)

Another executive says

> [F]ast-moving projects or collaborative drug discovery agreements involving biotech firms must be conducted locally [in the US]. (McCoy and Tremblay, 2003: 23)

However, some offshore CROs are working in sophisticated areas such as lead optimization (Bhatt, 2005; Clark, 2007; Finkelstein and Temin, 2008). Furthermore, non-western CROs aspire to provide more complex services, and are taking steps to acquire more capabilities. One example is an Eastern European CRO that has established a lab in California to access the capabilities to offer more customized work (McCoy and Tremblay, 2003: 23). The possibility of moving advanced work to offshore CROs has grown as the CROs and their governments push changes in their pharma industries, and as trust and collaborative relationships between western pharma and offshore CROs have grown (Bhatt, 2005). An example is GlaxoSmithKline's contract with an Indian firm for lead optimization. Another offshore CRO finds that some of its western clients

> enthusiastically do away with their arm's-length relationship with the contractor's scientists . . . The customers do trust us, and there is a very high value addition in their teaching our people their way of doing things. (McCoy and Tremblay, 2003: 22)

In other words, part of managing the sponsor-vendor boundaries includes transfer of western pharma procedures and practices to CROs. CROs are also offering "near-shore" offshored operations by acquiring facilities in or nearer the industrialized countries, such as Pfizer's manufacturing plant in the UK and a marketing-and-distribution firm in Denmark (Bhatt, 2005).

As in the case of offshored DDV, big pharma has been learning about CROs' talent and capabilities, and entrusting them with more advanced projects (Bhatt, 2005; Maskell *et al.*, 2007; Ulset, 2008). Where this leads to more equal partnerships, even offshored DDS resembles investment-based outsourcing more than arm's-length intermediate-product-based arrangements.

Conclusion

According to the New Institutional Economics, associated especially with Oliver Williamson (e.g., 1981), vertical fragmentation of industry (including outsourcing and offshoring) and the emergence of intermediate markets is likely a response to a reduction in transaction costs between the stages of production. Yet, outsourcing and offshoring in the US pharma industry is growing rapidly while coordination costs are acknowledged to be high.

This chapter has described outsourcing and offshoring trends in the industry and the pressures and opportunities driving these trends, including the emergence of biomedical science requiring new capabilities and capital investments, and the increasing cost and falling productivity of new drug production. The huge capital investments that would be required to keep all R&D in-house given the new scientific possibilities would expose the firm to unacceptable levels of risk, especially given the still rapidly evolving science and technological toolkit. Outsourcing and offshoring have become the vehicles for investing in new scientific capabilities, and reallocating fixed costs and risk among a network of biotech and technology-tool firms, academia, and CROs. In addition, fragmentation of research elicits cost savings due to CRO specialization and wage and overhead arbitrage. Nevertheless, equity-based fragmentation of the industry, especially with respect to drug-discovery research, is associated with increasing *integration* as pharma clients and vendors move toward more equal partnership roles

involving frequent and complex interaction. What might be thought of as the transaction costs involved actually represents investments in the quality, reliability, and productivity of the collaborative effort.

With respect to the outsourcing and offshoring of clinical trials, pharma clients and vendors are investing in technologies, tools, and management initiatives that will have the effect of reducing coordination costs between the parties, creating a smoother interface and allowing these relationships to approach a more arm's-length character. Part of this investment effort involves the use of IT to standardize and codify many of the skilled-labor tasks involved in clinical trials, just as has happened in manufacturing and the IT industry itself in the past. This will reduce the fuzzy boundaries between clients and vendors because it will increase pharma's control over CRO procedures and personnel and reduce the problem of measuring the quality of the CRO's product. That is, the asymmetric-knowledge problem will be reduced. It will also increase the productivity (and thus lower the cost) of skilled labor. Attention to static transaction costs tends to obscure the dynamic process of investing and learning as firms seek more control over their environments (including transaction costs). In this view, the conditions yielding new intermediate markets are, in part, endogenous. Investing and learning transform static transaction costs.

Notes

1 Data apply to the members of the Pharmaceutical Research and Manufacturers of America (PhRMA).
2 Blockbuster drugs are those that achieve sales of more than $1 billion (Gilbert, Henske, and Singh, 2003).
3 Prior to the interwar years, outsourcing to universities or independent scientists was common (Piachaud, 2004: 114).
4 Among the goals of the collaboration were (1) creating standards for monitoring, auditing, case report form design, and data quality; (2) creating standards for clinical trial sites, establishing accreditation programs for investigators and sites, and developing tools to measure performance; (3) identifying best practices and providing training; (4) utilizing electronic data management systems (Clinical Trials Transformation Initiative [CTTI], 2007).
5 Harmonizing efforts are directed toward development of tools, procedures, and practices to improve safety and quality, electronic data transfer,

and standardization of medical terminology and coding dictionaries (ICH "Guidelines," n.d.).

6 Much of this discussion of codification relies upon Balconi, 2002 and Balconi, Pozzali, and Viale, 2007.

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