Original Article

Exploring technology agglomeration patterns for multinational pharmaceutical and biotechnology firms

Received (in revised form): 18th February 2009

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ABSTRACT **This paper provides an empirical analysis of leading global multinational pharmaceutical and biotechnology firms with respect to technology agglomeration patterns, proximity to alliance partners and firm performance for the period 1996–2006. Our findings suggest that multinational pharmaceutical and biotechnology leaders are converging in terms of their technology agglomeration strategies; and increasingly competing over innovation from small biotechnology companies. Further, our analysis suggests that the absolute number of alliances is more than twice as important compared to proximity to partners in terms of firm performance defined as revenue, profitability and market valuation growth. Thus, for market leaders this study indicates a strategy of relentless pipeline building, with less regard to geographic proximity of alliance partners, appears to enhance relative and absolute performance of biopharmaceutical industry leaders.**

Journal of Commercial Biotechnology (2010) **16,** 17–32. doi:10.1057/jcb.2009.8;
published online 7 April 2009

Keywords: biotechnology; agglomeration; clusters; alliances

INTRODUCTION

Leading multinational pharmaceutical and biotechnology firms need to dynamically optimise pipeline portfolios of internally and externally generated product candidates to ensure sustainable growth. Simultaneously, broad advances and commercial success in biotechnology have captured the attention and aspirations of economic development officials, multinational executives, life science

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entrepreneurs and investors worldwide. These stakeholders are keen to identify ways of strengthening industry cluster competitiveness and productivity by enhancing those conditions that enable biopharmaceutical leaders to thrive, as well as to compel start-up firms to locate, grow and remain in a particular geographic area.

This paper provides an empirical analysis of leading global multinational pharmaceutical and biotechnology firms with respect to technology agglomeration patterns, proximity to alliance partners and firm performance for the period 1996–2006. Within the context of pharmaceutical industry and biotechnology industry trends, as well as industry cluster and technology agglomeration literature, we analyzed the impact of agglomeration patterns on performance by identifying market leaders who disproportionately dominate the pharmaceutical and biotechnology industry. Next, we constructed a database of all alliance activity (for example, technology agreements, licenses, mergers and acquisitions) by type and locality, as well as financial performance defined as revenue, net income and market valuation growth for the study period. We then measured the patterns of proximity from industry leaders to alliance partners in terms of concentration and dispersion. Finally, we analyzed the patterns of technology agglomeration to determine the correlation between the volume of alliance activity and spatial proximity to key measures of firm performance. Conclusions and implications for researchers, practitioners and policy makers, as well as extensions and limitations, are considered.

Industry background

A pharmaceutical company is defined as an entity that commercially researches, develops and distributes drugs.[1] While the use of medicine has its roots in antiquity, forms of drug companies date back to 754 AD in the Islamic world.[2] The enduring nature of pharmaceutical companies is illustrated by the fact that eight of the current top 20 pharmaceutical companies were founded before 1900 (the oldest, Merck, dating back to 1668).[3] The birth of the modern pharmaceutical industry, however, corresponded with the discovery and mass manufacturing of drugs such as penicillin, aspirin and insulin in the early twentieth century. This early drug development was founded in natural sciences or the observation, use and synthesis of naturally occurring phenomena (for example, antibiotic compounds found within flora and fauna).[4]

Drug development has steadily moved away from random drug screening and synthesising of natural compounds that require large libraries to establish chemical-biologic activity (for example, rational drug design, high throughput screening) whereby new biologic insights and tools are used to identify and develop new drug targets.[4] Further, biotechnology-based tools such as genomics and proteomics have increased the numbers of drug targets from about 500 to, at least, many thousands found in the tissues and genetic material of previously un-addressable and complex human diseases. In addition, emerging biologic insights and tools (for example, RNAi, theranostics) are increasingly shifting the role of diagnostics from active disease confirmation to treatment decision-making, prevention, and, wellness.[5]

For the purposes of exposition, the pharmaceutical industry has been largely reliant on traditional and advanced chemistry techniques to discover and develop drugs for the treatment of human diseases. In contrast, biotechnology is defined as the process of applying '*biological* knowledge and techniques to develop products and services … [with] any technique that uses living organisms to make [or] modify products, improve plants or animals, or develop microorganisms for a specific use'.[5,6]

Both the pharmaceutical and biotechnology industries address large global markets, increasingly led by biotechnology-based

growth. In 2007, the global pharmaceuticals market generated US$577.1 billion in revenues, with a compound annual growth rate of 5.6 per cent over the 2003–2007 period. The industry employs nearly 80 000 scientists globally and is one of the most research and development (R&D) intensive industries, spending $58.8 billion on R&D in 2007. Further, the industry is heavily regulated by agencies such as the Food and Drug Administration (FDA) in the United States and European Medicines Agency in the European Union (EU); and is characterised by R&D costs per individual drug of over $1 billion and high failure rates. The incessant increases in R&D costs have led to industry consolidation with the top 10 companies comprising over 50 per cent of global market shares.[7–9]

The USA FDA approved the first biotechnology drug (recombinant insulin, developed by Genentech and licensed to the large pharmaceutical Eli Lilly & Company) in 1982. Since then the biopharmaceutical industry has had 254 drugs approved for 385 indications, with over $70 billion in sales in 2006. Currently, an additional 300 drugs (targeting over 200 diseases) are in clinical development. The development of these drugs represents $20 billion in annual R&D. Moreover, the biotechnology industry is an important source of new venture creation with over 700 publicly listed firms posting double-digit growth in North America, Europe and Asia-Pacific.[5,10,11] Nonetheless, the biotechnology industry remains comparatively small with approximately 85 000 employees in the top 10 biotechnology firms and approximately 815 000 employees in the top 10 pharmaceutical companies.[3,12]

As a result of these dramatic strides made by biotechnology companies, the relationship between pharmaceutical and biotechnology firms has changed significantly over time. At first, biotechnology firms were seen as pursuing high risk, esoteric science projects that would not address large patient populations. If biotechnology companies did succeed, they were perceived as lacking drug development and commercialisation capacity and required alliances with larger pharmaceutical companies who could provide regulatory and late stage clinical development, as well as global marketing and distribution.[8] However, as fully integrated biotechnology giants such as Genentech, Amgen and Biogen-Idec have emerged, the landscape and power relationships between industry players has significantly changed. One important indicator is that the market valuation of the biotechnology industry recently surpassed pharmaceutical firms despite comprising a minority of current sales.[10] Consequently, pharmaceutical and biotechnology leaders are increasingly competing for alliance partners and technology.

Both the pharmaceutical and biotechnology industries are dominated by a small number of firms, who pursue strategies of complimenting internal R&D with an increasing number of external alliances of different forms. Owing to their importance to both the industries, comparing the alliance strategies of biotechnology and pharmaceutical firms is of interest for those connected to these industries through investment, policy and academic research. This study examines the agglomeration patterns and performance of leading biotechnology companies compared to traditional multinational pharmaceutical companies to test the degree of business model convergence and performance. The context for this analysis is key strategic trends in the pharmaceutical and biotechnology innovation systems.

PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRY TRENDS

The biotechnology and pharmaceutical industries are fundamentally about creating innovative medicines and exploiting the finite period of intellectual property (IP) exclusivity. Key industry pressures include the rate of

patent expirations on current product portfolios, generic substitution and decreasing effective exclusivity periods. In addition, R&D productivity has declined as a result of higher costs of drug development and longer clinical development timelines.[9,13] Owing to these trends, large pharmaceutical and biotechnology leaders are increasingly agglomerating technology and product pipelines externally through a range of alliances and acquisitions.

Pressure from patent expiries, generic substitution and decreasing effective exclusivity periods are important factors behind forecasts for continued declines in pharmaceutical industry growth and market valuations.[14] Over 40 per cent or $90 billion of pharmaceutical sales from 70 major drugs will lose patent exclusivity before 2012.[15] As an example of how patent expiry impacts individual firms, industry leader Pfizer will lose 74 per cent of its 2005 revenue to patent expiry by 2014.[16]

The pace of generic substitution has also increased dramatically which, in turn, has also shortened effective exclusivity periods. For example, 90 per cent of Bristol-Myers Squibb's sales of multi-billion dollar diabetes drug Glucophage® (metformin) were converted to generics within 90 days after patent expiry. Paradoxically, reliance on blockbuster drugs with sales exceeding $1 billion makes the pharmaceutical industry far more vulnerable. The top 20 pharmaceutical drugs generated approximately 50 per cent of revenues of the top 500 selling drugs meaning that the large pharmaceutical companies are dependent on these few blockbusters for the majority of their profits. Further, blockbuster drugs are the focus of patent challenges by generic companies, increasing competition in the form of substitutes, improvements such as dosage forms and reduced administration frequency, and cost containment legislation.[8] Such pressures mean that there is a trend towards decreasing exclusivity for drugs generally, and blockbusters specifically.

In comparison, the biotechnology industry has experienced minimal impact from generics because no regulatory pathway yet exists in the United States for bringing them to the market, although the EU recently announced approval standards.[17] However, biotechnology leaders such as Amgen, Genentech and Biogen-Idec will increasingly face the emerging threat of biogenerics.[18] Of course, the competitive pressure from patent expiries, generic substitution and decreasing effective exclusivity periods would be inconsequential if R&D productivity kept pace with the loss of IP protection.

R&D productivity has declined as a result of higher costs of drug development and longer clinical development timelines. Between 2002–2006, the pharmaceutical industry commercialised 43 per cent fewer novel drugs than in the previous 5 years, despite more than doubling R&D expenditure.[8,14] The average drug now costs over $1.0 billion and takes over 12 years to go from laboratory to approval.[19] One reason for rising development costs is the high failure rate of product candidates in clinical trials – the overall success rate for drug candidates that progress from animal testing into human trials is 11 per cent. Other reasons include increasingly specific molecular targets for unmet diseases, complexity of biologic systems with compensating mechanisms, overlapping IP claims and shifting regulatory requirements. Furthermore, getting approval is no guarantee of commercial success with only 4 out of 10 products that reach the market achieving profitability.[5,9,13,19,20]

This falling R&D productivity has major implications because even the largest companies with strong current portfolios of blockbuster drugs are at risk, as without strong pipelines they are unable to guarantee investors expectations of future earnings growth. Namely, pipelines are linked to earnings per share and share prices within the market.[8] As such, the lack of development productivity (either increasing the value

Table 1: Forces impacting pharmaceutical multinational, biotech leaders and small biotech companies

	Large pharma	*Large biotech*	*Small biotech*
Pressure from patent expiries, generic substitution and declining exclusivity	High	Low – Medium	Low
Innovation gap because of declining R&D productivity	High	Medium	Low
Need to build pipelines via alliances	High	Medium – High	Low

created or decreasing the time required to create value) has taken its toll on industry financial performance and sustainable profitability.[5,9,13,19,20]

For example, pharmaceutical industry leader Pfizer's R&D productivity (defined as new product launches versus revenue losses because of patent expiry) is expected to produce a steady net loss of sales. As a result of these trends, Pfizer has serially acquired both pharmaceutical and biotechnology companies such as Warner-Lambert, Pharmacia, Agouron, Idun, Encysive, PowderMed and Vicuron to strengthen its pipeline. As Jeff Kindler, Pfizer's CEO, remarked: 'We're not looking for some short-term financial benefit from an acquisition. We want to strategically grow our business. We think there are opportunities in biotechnology, in vaccines, in specialty areas like oncology'.[21]

The incessant need of large pharmaceutical and biopharmaceutical companies for additional pipeline products means technology agglomeration is an important industry strategy. The need to strengthen R&D capabilities and fill late stage pipelines has driven high levels of merger and acquisition activity across both the pharmaceutical and biotechnology sectors.[8] Although there has always been a strong flow of IP from academic labs and small biotechnology firms to large pharmaceutical firms, pipeline concerns have forced pharmaceutical leaders to increasingly depend on biotechnology firms to provide late stage (and consequently more costly) products.[8] For example, an estimated 30–50 per cent of new molecular entities in the last 5 years came from in-licensing versus internal development, driving dramatic increases in alliance activity. Specifically, 33 per cent of all Phase II (intermediate stage) and 55 per cent of all Phase III (statistically significant, late stage approval seeking) clinical trials in large pharmaceutical companies are in-licensed.[16,22]

Thus, distinctions between traditional multinational pharmaceutical and biotechnology companies are increasingly blurred because of alliances and converging research interests. Large biotechnology firms now compete directly with pharmaceutical companies for both therapeutic markets and access to the best deals with smaller companies.[8] Further, increasing competitiveness for the same molecular targets is resulting in shorter periods of effective IP exclusivity and further profit margin pressure.[23,24]

Slowing growth in the pharmaceutical industry, the rise of fully integrated global biotechnology firms, and an increasing reliance on external alliances with small biotechnology firms for pipeline development is substantively changing industry structure and negotiating power.[25] These industry forces and how they affect large pharmaceuticals, large biotechnology firms and small biotechnology ventures are outlined in Table 1.

Thus, alliances with research institutes and small biotechnology companies represent another way of flexibly organising a larger firm's value chain and may be preferred to vertical integration. Moreover, globalisation and the ability to operate virtually makes access to the biotechnology ecosystem – contract manufacturers for process development, research organisations with unique testing capabilities, patent lawyers,

venture capitalists and others who enable start-up formation and development – increasingly accessible. The next section provides an overview of the industry cluster and technology agglomeration literature, which establishes the basis for our empirical analysis of intra-industry alliance patterns.

INDUSTRY CLUSTERS AND TECHNOLOGY AGGLOMERATION

Porter[26–28] popularised the term 'industry cluster', which he defined as geographic concentrations of interrelated individuals, firms and institutions which compete and collaborate by accumulating knowledge and intellectual capital. However, this concept has a long history starting with economist Alfred Marshall[29] describing how early industrialised clusters enable advantages in marginal costs through resource and production concentration, as well as spillover effects from firm-to-firm interactions. Entrepreneurship was linked to cluster theory when Schumpeter[30] observed that through a process of creative destruction entrepreneurs in close proximity represent a driving force for economic progress. Such thinking was further developed by Solow[31,32] and Romer[33,34] focusing on technology-based change as a fundamental source of growth and cluster development. As a result of post-industrialisation, knowledge (rather than capital and labour) became the focus of cluster research, the ultimate example being the exploitation of synergistic relationships between industry and academia in Silicon Valley.[35,36]

Agglomeration theory builds on the cluster framework by suggesting that a firm's performance is influenced by other firms with which it is co-located. These advantages are attributed to knowledge, skilled labour, innovation (as a result of accumulated human capital and face-to-face communication), input spillovers and infrastructure scale advantages,[37,38] which have been studied in several industries including the biotechnology sector.[39] In this context, geographic proximity facilitates the exchange of skills and ideas, which consequently improves productivity in a virtuous cycle. In knowledge intensive industries, such as pharmaceuticals and biotechnology, tacit knowledge antecedents to competitive advantage are said to require proximity or regular face-to-face interactions and trust in order to be effectively transferred,[40–43] as well as to reduce the time and costs of transacting.[44] Further, firms located within clusters often compete for the same employees, technologies and infrastructure; routinely sell outside their local or regional markets; represent influential forces for economic development and government policy in their home markets[27,45] and share a common cultural and social background.[46] If these assertions hold, biotechnology and pharmaceutical firms that are located in agglomerated knowledge clusters should accrue sustainable competitive advantages and superior performance.

Thus, a paradox exists with regards to firm location in that proximity is apparently increasingly important within high-tech industries (such as pharmaceuticals and biotechnology), despite the affects of globalisation.[26,27] In this case, globalisation refers to the infrastructure of the drug development ecosystem, which is increasingly available to any individual company worldwide. Interestingly, the success of the companies within biotechnology relies on interdependent relationships rather natural resources or physical distribution – and this has increased the importance of proximity and social capital. Consequently, specialised factor conditions tend to be both more vulnerable and more important with increased globalisation.

Development of pharmaceutical biotechnology clusters and technology agglomeration

In terms of revenues, large pharmaceutical firms are clustered around three sites in

developed countries, with 8 out of the largest 20 firms headquartered in Western Europe ($164.8. billion), eight in the United States ($158.9 billion) and four in Japan ($30 billion). These pharmaceutical industry leaders routinely partner globally, and one study found they were more likely to form alliances outside, rather than within, their own geographic cluster.[47] Valuable and highly specified knowledge was also shown to be sourced from any location, with both upstream and downstream alliance activity being positively correlated with alliance formation. The study consequently classified large pharmaceutical clusters as global hubs that search for complementary knowledge through 'international' alliances.

In comparison, biotechnology leaders, as measured by revenue, net income and market capitalisation, have largely been a United States' phenomenon to date. However, nearly every developed country has biotechnology companies operating within its borders and forming global alliances. The biotechnology clusters in Cambridge, La Jolla, Research Triangle Park and the San Francisco Bay Area are often cited as exemplars by communities worldwide trying to emulate their success.[48] Such successful biotechnology clusters take advantage of unique local strengths to create economies of scale and capture synergies across functional areas such as biology, information systems and engineering to drive economic activity and growth.[49] These initiatives, and the corresponding sector development, are supported by government incentives (such as research grants, subsidised office and lab space at research parks, education and tax credits) in the majority of US states, as well as other developed and many developing countries.[50,51]

Consequently, identifying and enhancing decision-making factors for locating and growing biotechnology companies is a critical success factor for bioentrepreneurs, policy makers and investors. Decisions around location can enable success in a highly competitive industry because collaboration with high-status academic institutions increases the probability of success for technology transfer. Proximity may also enhance alliance formation due to firm and institutional affiliations which heightens the likelihood of firm survival, organisational learning, innovation and credibility among investors.[52] In the biotechnology industry, the most emphasised production factors include proximity to world-class research science centres, access to skilled staff and talent pools, and access to funding from diverse sources.[53–60] Interestingly, studies have found that the critical factors influencing location decisions were the same for new and established companies alike.[61] However, within this context, large biopharmaceutical companies are increasingly geographically agnostic, in that the number of alliances was shown to be more important to performance than geographic proximity to partners.[25,62,63]

In the next section, we will empirically analyze technology agglomeration and alliance patterns for leading global pharmaceutical and biotechnology firms with respect to geographic concentration and density, as well as firm performance.

METHODOLOGY AND RESULTS

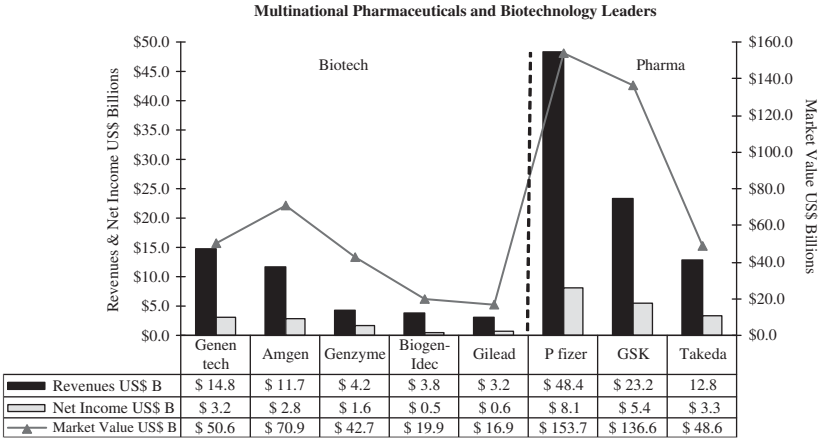
To analyze the impact of agglomeration patterns, we first identified market leaders who disproportionately dominated the pharmaceutical and biotechnology industries for the study period 1996–2006. Next, we identified and coded all alliance activity (for example, technology agreements, licenses, mergers and acquisitions) by type and locality, and we collected financial performance information including revenue, net income and market valuation growth. We then measured the patterns of proximity from industry leaders to alliance partners in terms of concentration and dispersion. Finally, we analyzed the patterns of technology agglomeration to determine the correlation between the volume of alliance activity and

spatial proximity, respectively, to each key measure of firm performance.

First, we identified market leaders who disproportionately dominated the pharmaceutical and biotechnology industries (Figure 1). Although there are thousands of pharmaceutical companies globally, there are only about 200 major firms in the sector, and the top 10 comprise approximately 50 per cent of total market share. In particular, Pfizer (North America), GlaxoSmithKline (EU) and Takeda (Asia) are dominant in their regions and fully integrated multinational pharmaceutical companies that conduct basic research, drug development and marketing operations globally. As an illustration of the enormous financial strength and strategic options available to pharmaceutical industry leaders, Pfizer's revenues were $48.4 billion and net income was $8.1 billion in 2007, with a year end market valuation of $153.7 billion.

In contrast, although there are approximately 350 publicly traded biotechnology companies in the United States and 700 worldwide, market leadership is dominated by the largest five companies: Amgen, Genentech, Genzyme, Biogen-Idec and Gilead. Market leadership for this analysis was defined as the largest in sales, profitability and market valuations at the end of 2006.[64] In this case, although the top five biotechnology companies account for less than 2 per cent of publicly listed firms in absolute terms, they account for 52 per cent of the revenues, 43 per cent of R&D and 74 per cent of the market capitalisation for the entire sector, respectively. In addition, the top five leaders had $4.1 billion of net income in 2006 whereas the industry as a whole posted a loss of $2.1 billion, meaning that the remainder of the industry experienced a net loss of $6.2 billion.

It would be expected then that if geographical proximity was key to competitive advantage, a correlation between alliance activity and performance would be observed for these firms. Intra-firm performance for industry leaders, however, reflects a variety of strategic approaches to building pipelines. It should be noted that while the selected companies are global leaders across key geographies (that is, North America, Europe and Asia which comprises 85 per cent of the world biopharmaceutical market), the number of selected companies may limit generalisations about the entire industry. Thus, this analysis may be viewed as a multiple-case approach because it permits a 'replication' logic in which cases are treated as a series of independent experiments that confirm or refute emerging conceptual insights.[65,66] Performance has varied widely among firms in terms



	Genentech	Amgen	Genzyme	Biogen-Idec	Gilead	P fizer	GSK	Takeda
Revenues US$ B	$ 14.8	$ 11.7	$ 4.2	$ 3.8	$ 3.2	$ 48.4	$ 23.2	12.8
Net Income US$ B	$ 3.2	$ 2.8	$ 1.6	$ 0.5	$ 0.6	$ 8.1	$ 5.4	$ 3.3
Market Value US$ B	$ 50.6	$ 70.9	$ 42.7	$ 19.9	$ 16.9	$ 153.7	$ 136.6	$ 48.6

Figure 1: MNC pharmaceutical and biotechnology industry leader financials.

of share price performance, but every biotechnology leader has outpaced multinational pharmaceutical leaders in terms of shareholder returns during the study period (Figure 2).

Second, to capture the evolution of value in the pharmaceutical and biotechnology industries, as well as allow for heterogeneity in deal structures over time, we developed a database of alliances and financial performance for the period 1996–2006. Industry leaders have used both strong and weak tie alliances to pursue highly heterogeneous approaches to building, resourcing and managing the development of product pipelines. Included in our data set are: licensing, basic research agreements with academia, co-development agreements, co-promotion alliances, co-marketing arrangements, and mergers and acquisitions.[67,68]

This broader definition of alliances allows us to capture changing business development trends over the study period. For example, owing to the risks inherent in drug development some pharmaceutical and biotechnology partners have increasingly sought to create alliances with companies that are further along their evolution to achieve marketable products. In the early 1990s, the highest market valuations went to companies with technology platforms which could potentially lead to biologic targets (for example Human Genome Sciences, a biotechnology start-up, granted GlaxoSmithKline access to its gene-based drug technology in a partnership valued at $125 million). Gradually, over the course of the last decade, the industry value chain has evolved from valuing novel drug targets (for example, Bayer paid 5-year-old Millennium Pharmaceuticals over $1.0 billion to deliver 225 drug targets over 5 years); to focusing on product leads (for example, Hoffman-La Roche acquired a 60 per cent stake in Genentech in exchange for right of first refusal to all Genentech products outside the United States); to acquiring development candidates in clinical trials (for example, Amgen entered into an alliance with Abgenix to co-develop monoclonal antibodies over 5 years and

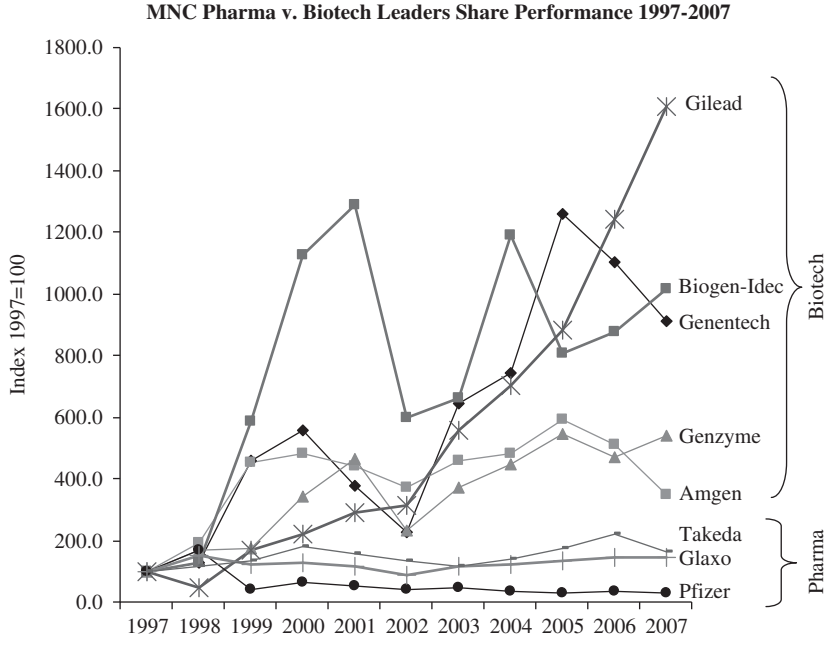


Figure 2: Selected multinational (MNC) pharmaceutical versus biotechnology leaders: Share price performance.

subsequently acquired the company for $2.2 billion after positive Phase III clinical trial results for Vectibix®(panitumumab); to paying for revenues from approved products that led to increased merger and acquisition activity (for example, Pfizer acquiring Agouron, Johnson & Johnson acquiring Centocor).[25] Following Big Pharma's lead, over the course of three decades, biopharmaceutical industry investors went from ascribing value solely to platform technologies, to requiring clinical-stage product candidates, to expecting revenues and finally to demanding sustainable profitability. That is, as in all other industries based on technological breakthroughs, investors in biopharmaceutical companies increasingly demand commercially realisable opportunities to justify additional capital.[69]

To identify alliance agreements, we used the MedTRACK (www.medtrack.com) database which contains information on licensing and technology agreements, as well as alliances to include co-promotions, co-marketing, and mergers and acquisition activities on more than 11 000 public and private biomedical companies covering 48 000 products classified and tracked in 17 therapeutic areas and 765 sub-categories, and 35 000 deals.

We determined the relative location, dispersion and concentration of product and technology alliances, by obtaining location information from publicly available company profiles. The addresses used to measure location were the corporate headquarters of each company, respectively. Using these addresses, longitude and latitude coordinates for each company were obtained in order to accurately measure relative distances among alliance partners globally using the GPS Visualizer geocorder utility (www.gpsvisualizer.com/geocoder). After the coordinates of both the primary company and its partners were compiled, metric distances between them were calculated using the GPS Visualizer calculator utility (www.gpsvisualizer.com/calculators).

As pipeline development is dynamically shifting from independent research centres to coordinated networks of complex internal and external alliances, we selected corporate headquarters as the appropriate unit of analysis.[70] As researchers have pointed out, there are methodological challenges associated with analyzing the R&D activities of multinational biopharmaceutical companies related to 'scale, and levels of importance of research cooperation, and the ways in which the objectives of research cooperation and networks can change overtime'.[71] However, we believe corporate headquarters as the unit of analysis was appropriate because biopharmaceutical development is a managed open innovation system which includes a broad range of interdependent and fractionated actors.[68,72] As outlined in the exploration of industry trends above, the use of outsourcing (for example, contract research organisations, research contracts with academia) and alliances (for example, licenses, mergers and acquisitions, co-development, co-promotion) have a prominent role in pipeline development (for example, four of the last five products launched by Genentech were licensed from academia) and IP protection. As such, the fragmented nature of the biopharmaceutical innovation system may also overstate the importance of internal R&D centres.[68,73] Thus, we chose to focus on headquarters as the unit of analysis because of its central role in bundling and deploying resources which is critical to achieving and sustaining competitive advantage.[74]

For example, Amgen researchers coordinated the development of Thrombopoietin (TPO) with a broad range of alliances and patents, which included Novo Nordisk (Denmark), Kirin (Japan) and Enzon (protein manufacturing technology). In addition, Amgen collaborated with universities in Canada and Australia in basic research, and outsourced clinical trials to a contract

research organisation. All of the associated activities and patents for TPO, however, are coordinated and managed by Amgen headquarters. While untangling which research component was the 'most' responsible for TPO is not possible, the fact that Amgen's headquarters coordinated, resourced and managed the entire effort is objective and measurable.

In this case, the cumulative inter-firm proximity from leaders to alliance partners has remained remarkably stable over the study period, despite a substantial increase in the number of alliances for both pharmaceutical and biotechnology leaders. Overall, pharmaceutical firms averaged 4540 km between partners; and biotechnology leaders averaged 3832 km between partners. Amgen, for example, has completed 171 alliances and increased revenues from $2.1 to 14.3 billion (or 494 per cent) over the 10 year study period, but the average proximity to all partners only increased from 2187 to 3400 km. On the other hand, intra-firm variability of cumulative average proximity from leaders to alliance partners is wide and stable, ranging from a low of 2928 km for Amgen to a high of 5371 km for Gilead. This nearly two-fold (1.8) intra-firm distance from the lowest to the highest proximity ranges, reflects an ever-widening set of approaches to alliance activity (for example, licensing different geographies to partners, co-promotion agreements, mergers and acquisitions).

Third, we further analyzed physical proximity from pharmaceutical and biotechnology leaders to alliance partners with respect to two important parameters: concentration and dispersion. The spatial clustering or proximity of industry leaders to alliance partners was measured by the standard distance deviation (SDD). The SDD reflects the standard deviation of the distance of each point from the mean centre and represents the two-dimensional equivalent of standard deviation. Thus, the average of distances between the mean centres of a region may be represented as a single vector.[75,76] The SDD is defined as

$$\mathrm{SDD} = S_{xy} = \sum_{i=1}^{N} \frac{(d_{iMC})^2}{N-2} \qquad (1)$$

where d_{iMC} is the distance between company i and the mean centre MC of a region and N is the total number of alliance partners.

Although the SDD is a useful single measure of dispersion around the mean centre, it does not show the potential skewed nature of the data (anisotropy). From a firm's perspective, the relative dispersion or skewness of distances between alliance partners may impact communication and coordination effectiveness, as well as operational costs and efficiency. Thus, the standard deviation ellipse (SDE) measures the relative shape and orientation of proximity to dispersion between alliance partners as follows:

$$\mathrm{SDE} = \sqrt{\frac{(\sigma^2{}_x + \sigma^2{}_y)}{2}} \qquad (2)$$

where σ_x and σ_y are standard deviations along the x and y directions with x and y being orthogonal to one another. The results allow us to analyze the degree of dispersion relative to the degree of skewness in alliance partner relationships. The SDD is 1605 km and the SDE is 391 km for multinational pharmaceutical industry leaders; and the SDD is 1389 km and the SDE is 396 km for biotechnology industry leaders. This analysis suggests that multinational pharmaceutical and biotechnology leaders are converging in terms of global technology agglomeration patterns, with both sectors increasingly reaching out further and more frequently for external alliances.

Further, although no clear pattern emerges between the value of concentration and dispersion in this analysis, it is interesting to note that Gilead has the highest average distance, widest distribution and the best

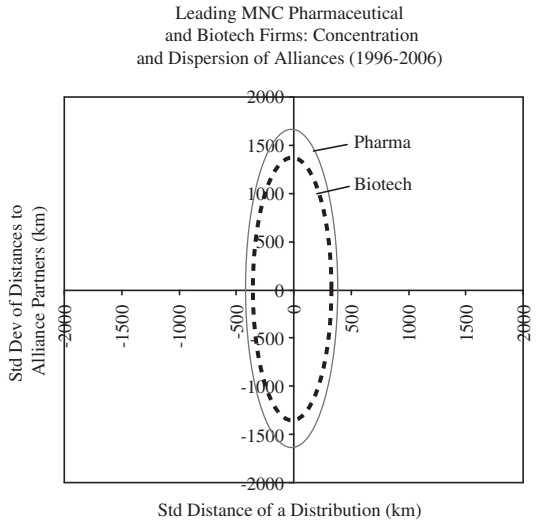


Figure 3: Multinational (MNC) pharmaceutical and biotechnology leader alliance dispersion and concentration.

performance in terms of annual market value growth (32 per cent versus 23 per cent for all other biopharmaceutical leaders) and revenue growth (38 per cent versus 32 per cent for all other biopharmaceutical leaders) over the entire 1996–2006 study period (Figure 3).

Fourth, we analyzed these patterns of technology acquisition over time to determine the correlation between the volume of alliance activity and spatial proximity patterns relative to revenues, profitability and market value. Financial data sources for sales, profits and market value of industry leaders were obtained from SEC reports (www.sec.gov), company annual reports and Reuters (www.reuters.com).

We assessed the impact of external alliances on firm performance by analyzing the correlation coefficients (r) between the independent variable represented by the number of partnerships, licenses and acquisition activity with respect to dependent performance variables represented by market capitalisation, revenues and net income, respectively. In this case, the data suggests that the independent variable of industry leaders' alliance activity is positively – to highly positively correlated with dependent variables – market capitalisation (pharmaceuticals $r=0.39$; biotechnology $r=0.77$), revenues (pharmaceuticals $r=0.96$; biotechnology $r=0.91$) and net income (pharmaceuticals $r=0.86$; biotechnology $r=0.30$) – over the 1996–2006 study period.

Another key question was the impact of proximity on firm performance, which we assessed by analyzing the independent variable represented by the cumulative average proximity with respect to dependent performance variables represented by market capitalisation, revenues and net income. In this case, the data suggests that the independent variable of proximity is moderately positively correlated with dependent variables – market capitalisation (pharmaceuticals $r=0.16$; biotechnology $r=0.39$), revenues (pharmaceuticals $r=0.57$; biotechnology $r=0.42$) and net income (pharmaceuticals $r=0.62$; biotechnology $r=0.12$) – over the 1996–2006 study period.

In sum, our results indicate that total deal quantity over time may be approximately twice (2.02 times) as important relative to proximity in terms of firm performance as measured by revenues, net income and market capitalisation growth for both multinational pharmaceutical and biotechnology leaders for the period 1996–2006. These results are necessarily limited by the small sample size of leading pharmaceutical firms, but we believe choosing leaders from each region (that is, North America, Europe and Asia) constituted a representative sample in terms of global companies, as well as formal (that is, legal, regulatory) and informal (that is, cultural) institutional diversity.[77,78]

CONCLUSIONS

This analysis suggests that multinational pharmaceutical and biotechnology leaders are converging in terms of their technology agglomeration strategies; and increasingly competing directly for innovation from small biotechnology companies and academia. The increasingly popular use of the term

'biopharmaceutical' industry is therefore descriptive of the current industry context.

Broad advances and commercial success in the biopharmaceutical industry have captured the attention and aspirations of economic development officials, business people and investors alike. These stakeholders are keen to identify means to strengthen industry cluster competitiveness and productivity by enhancing those conditions necessary to enable biopharmaceutical leaders to thrive and compel start-up firms to locate, grow and remain in a particular geographic area.

Our analysis suggests that: (1) Market leadership among multinational pharmaceutical and biotechnology firms is highly concentrated, although there are striking intra-firm differences in strategy and results; (2) A broad definition of alliance activity is desirable in conducting a proximity analysis as business development terms and deal structures have become increasingly heterogeneous over time; (3) Geographic proximity of multinational pharmaceutical and biotechnology leaders to alliance partners has remained remarkably stable over time, despite a substantial increase in the number of alliances for all leaders; (4) No clear pattern emerges between the degree of cluster concentration, dispersion of alliances and firm performance; and (5) Perhaps, owing to the high attrition rates of pipeline candidates and patent expiry pressure, our analysis suggests that the absolute number of alliances is approximately twice (2.02 times) as important in comparison with proximity to partners in terms of firm performance defined as revenue, profitability and market valuation growth. Thus, for both pharmaceutical and biotechnology market leaders we propose that a strategy of pipeline building, with less regards to geographic proximity of alliance partners, appears to enhance relative and absolute performance of biopharmaceutical industry leaders.

This study has several implications for practitioners, policy makers and researchers. First, from a practitioner's perspective this analysis indicates that large biopharmaceutical firms may benefit from pursuing pipeline building regardless of the proximity to potential alliance partners. This is an important finding, as firms need to set strategic priorities and assess the impact of alliance proximity on resource utilisation, efficiency and firm performance. Second, from a policy-maker's perspective this analysis suggests that prioritising resources (for example, technology parks, tax incentives education) can spur economic development and competitiveness because all firms can compete for alliances with industry leaders regardless of location. Third, this study has contributed to agglomeration theory by expanding the normative construct through the empirical analysis of proximity and IP-driven industries generally, and the biopharmaceutical industry specifically. In addition, our analysis indicates that measuring performance as outputs (for example, revenues, profits and market value) is preferable to the conventional measures of inputs (for example, employment levels, assets).

Limitations and extensions for future research

Although the results of our study indicate the growing importance of alliance activity, there are several limitations and extensions, which may be further explored. First, a limitation of this study is that we do not determine the relative value of different types of alliances. Thus, we suggest a comparison and contrast of agglomeration patterns and performance of biopharmaceutical leaders with respect to specific types of agglomeration (that is, licensing versus mergers and acquisitions) to determine patterns of preference, measure risk adjusted returns on capital relative to stage of product development and internal versus external core competency development (that is, the extent to which the pattern of technology agglomeration impacts a firm's business model).

Second, another extension is to assess networks effects in terms of the relative value and effectiveness of strong ties (for example,

jointly coordinated research, establishing a network of research centres to enhance proximity) versus weak ties (for example, non-directed research where the small company or academic lab works independently) in alliances strategies.

Third, another limitation that also represents an opportunity for extension is to capture the experience of small biotechnology companies within alliances. It is expected that small biotechnology companies outside of established clusters can be more confident that the value of innovative science holds primacy over geographic proximity in terms of downstream access to alliance partners. However, a symmetrical relationship for all those in alliances (that is, both the large multinationals and their smaller alliance partners) cannot be assumed and requires further investigation.

Finally, another possibility is to explore the impact of globalisation (for example, regulatory harmonisation) on reducing or enhancing the competitive advantages of existing biopharmaceutical industry clusters. In addition, we suggest extending our analysis of output performance measures to include cash flow and economic value added to analyze the wide heterogeneity in firm maturity and growth rates. In addition, another area of needed study is the role of culture and risk taking within innovation systems by comparing and contrasting key stakeholders across geographies (for example, venture capitalists, scientists, university technology transfer offices, management from large and small companies) to determine factors of competitiveness such as preferences for localisation in collaboration, exit strategies and time horizons, and degree of focus versus diversification in pursuing technology strategies.

ACKNOWLEDGEMENTS

We would like to thank the editor and reviewers for their excellent guidance and encouragement, as well as the participants who provided their insights. All views and errors are ours.

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