BIOTECHNOLOGY IN AGRICULTURE, INDUSTRY AND MEDICINE

STRATEGIC ALLIANCES IN BIOTECHNOLOGY AND PHARMACEUTICALS

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FOREWORD

The book explores several aspects of the biotechnology industry. Why the U.S. biotechnology industry is now dominating the market and why European pharmaceuticals firms, once top leaders in their markets, now lag well behind in innovation capabilities? Why bio-pharmaceutical companies in Asia remained lagging in the last decades, relatively to their Western counterparts? The book focuses on the alliances between between small biotechnology start-up and established firms from the downstream sectors as a crucial element of the success of the U.S. industry. Other aspects explored in the book are: What factors affect the incidence of collaborative innovation relative to alternative modes? What are the common structural characteristics of these collaborations? What role do network economies play in such collaborations? How the evolution of technological progress in the biotech industry affected the structure the pharmaceutical industry.

Chapter 1 analyses the effect of strategic alliances from the point of view of antitrust concerns.The chapter stress that traditional antitrust policies have focused more on the anticompetitive effects of joint ventures on market power of the firms than on anticompetitive strategic behaviour of such alliances. In high tech and network industries such anticompetitive strategic behaviour could be caused by exclusionary practices, as exclusive dealing, tying, cross-licensing, etc. The chapter analyses for each anticompetitive practice the current antitrust literature and then focus on strategic alliances.

Chapter 2 covers the recent literature on the determinants of firms' boundaries and on strategic issues to understand essential factors of alliance formation. The chapter reviews transaction cost theory and shows, as already investigated in the literature, that transaction costs alone are not a prime rational for strategic alliances. One important topic discussed in this chapter is a definition of strategic alliances that could be used to understand when network arrangements allow competitive advantages relative to other forms of organization. The chapter provides the motivation for forming alliances. It considers three categories that explain why firms become involved in network relations (network economics, innovation/competencies, market structure).

Chapter 3 analyses the evolution of the biotechnology industry from a scientific and institutional point of view and the institutional factors (science technology entrepreneurship, biotechnology industry. university industrial relationship, venture capital etc.) that allowed the success of the U.S. biotechnology industry. The chapter analyses why in the U.S., differently from Europe, biotech is dominated by small and medium sized firms.

Chapter 4 reviews several aspects of collaborative innovation and alliances in biotechnology. It applies network economics to the formation of alliances in the biotechnology industry.

Chapter 5 analyses the relationship between alliance activity of pharmaceutical firms and economic performance.

Chapter 6 examines biotech-Pharma industries in Europe. Europe has a very strong tradition in the pharmaceutical industry with a large number of firms in the top twenty but none of these firms played much part in the first decade of the new biotechnology. In Europe, on the other hand biotech firms have not grown in the same way as in the U.S., partly because favourable institutional frameworks (high funding/leading edge research in the life science, active venture capital market) did not exist. Strategies of large pharmaceutical firms in Europe till the late 1980s were more concentrated on vertical integration and were concerned with building up in-house competence. In the same period in the U.S. an effective division of labour was developed between new, small companies, large corporations and other research institutions, which have different comparative advantages in the "exploration" and "exploitation" of new innovation opportunities. It was only in the last few years that in Europe "vertical collaboration" between large companies and biotech companies have become more common.

Chapters 7 and 8 analyse the biotech-pharmaceutical industry in Asia. Though the biotech sector in the more advanced countries of Asia started decades ago it has remained lagging relative to their Western counterparts. Most R&D in biotech is still done in public laboratories and national universities. Also science/technology entrepreneurship is not at all developed. The collaboration between small biotech firms and large pharmaceuticals firms is quite weak. The small biotech firms in Japan have to work on their own with their limited capital since, unlike in the U.S. and Europe, pharmaceutical companies would rather do in house R&D than form alliances. So, Asian governments are involved to develop the biotech sector. Large funds go to universities and public laboratories, and some small biotech companies spin off from these public and university laboratories.

In recent years, also, in Asia bio-pharmaceutical companies have built strategic alliances to reduce R&D cost and increase the number of new products. But bio-pharmaceutical Japanese firms are consolidating and rationalizing their operations through mergers to compete with well-established foreign firms. Vertical integration strategy is still the dominant organization mode in pharmaceutical companies. Therefore the biotech-pharmaceutical industry in Asia seems characterized by 1) Strong government support 2) High vertical integration of biotech-pharmaceutical firms and 3) limited number of small biotech firms.

We believe that the issue is an impressive informative contribution to understand biotech industry.A key feature of the authors' research approach is the application of network economics to study alternative forms of organization in the biotechnology industry. Its hypothesis is that alliances are best organizational form in the bio-pharmaceutical industry.

The study of motivations of collaboration in biotechnology has been analysed in the literature several times. One the first works on this subject was that of Pisano, Shan, Teece (1988). They showed that motivations of collaboration in biotechnology are linked to the distinctive competencies of the three types of organizations involved in biotechnology innovation:

1) universities and other non profit institutions, 2) new biotechnology firms 3) established firms in the pharmaceutical industry interested in the application of the new technologies.

The Pisano, Shan, Teece work concludes that "pressure seems to be the driving the R&D commercialization linkages away from collaborative arrangements and toward vertical integration". This forecast has not been realized as it is shown in Chapters 3 and 4. Alliances between biotechnology firms and large pharmaceutical firms are still the predominant organization of biotechnology industry. This phenomenon reflects the pattern of distinctive competencies of the different organizations involved in the production process. Gottinger recognizes this aspect: "The preponderance of biotech alliances pertain most directly to the competencies category, where firms ally to leverage complementary competencies, such as small firm's new drug discovery platform and an established pharmaceutical company's trial competency." But, he goes on to suggest that technological progress in biotech, with the introduction of genomics and proteomics by the end of the 1990s, has added a new dimension in the explanation of alliances in biotech, demand side economies of scale or *network economics*. This hypothesis creates some conceptual problems .The sharing of information between partners in the alliances reduces drastically the number of experiments that are required in a given target domain, and therefore reduce costs and time to take a product to the market .As new firms are added to a network the pool of information available to the partners of alliance increases and therefore increases the utility of each firm to belong to the alliance. But as Arrow (1975) argued in a seminal article vertical integration might also be motivated by a desire to acquire information. Therefore network economics motivates not only alliances but also vertical integration. Why cooperation between firms for a common benefit (alliances) is a more efficient form of organization than vertical integration? Both reduce the conflict between proprietary ownership of knowledge and the benefit of the sharing of information. Therefore, it is the diversity of research and technology platform, inducing *network economies*, that encourages the use of alliances as a preferred organization over vertical integration. On the other hand appropriability and transactions cost problems suggest that arms-length markets are not an alternative efficient organizational solution in the biotechnology industry. The book concentrates on the alternative of vertical integration versus alliances.

Some conceptual problems arise in the empirical investigation of Chapter 4. This chapter analyses the relationship between alliance activity of pharmaceutical firms and economic performance. If alliance is the most efficient organizational form in the pharmaceutical industry, one must find a positive correlation between the intensity of collaborative arrangements by pharmaceutical firms and an index of their economic performance. Two are indices of economic performance: total return and price-to-earnings ratio. The collaboration rate of each pharmaceutical firm is defined as the number of collaborative agreements into which a firm entered during a given period. The first test examines whether a correlation exists between collaborative activity and total return over the period from 2000 to 2005. The nine largest US pharmaceutical firms by revenues were considered. In this case the statistical analysis is run on nine observations.

The second test examines the relationship between the collaboration rate of each firm and their Price-to-Earnings ratio during the five-year period 2001 to 2005. In this case the statistical analysis is run on 45 observations. The conclusion of the author is that a strong, statistically significant, positive correlation exists between the collaboration rate of large firms and their performance in term of market valuation and total return over the long term.

The book is interesting and stimulating. The audience that will benefit most from the book include policy makers, journalists and students beginning the study of the biotechnology

industry. Probably an effort to eliminate duplications and to give a methodological unity to all chapters will make the reading of the book more easy for such audience.

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PREFACE

'In biotechnology the one '-omics' that really counts is economics'
Sydney Brenner, Nobel Prize in Medicine (2002) – From The Economist Survey, March 27, 2003, A Voyage of Discovery

Late in 2007, even before the onset of the global financial crisis, the Wall Street Journal (Dec.6, 2007) alerted industry analysts and investors with the message 'Big Pharma Faces Grim Prognosis' pointing out industry fundamentals of slowing revenues, lower profitability, employment cuts, higher cost of innovation, slashing research and development (R&D) spending leading to drier drug pipelines across the board of major drug companies. This was after many years of growth and high profitability in the industry. What is going wrong? Could it be government overregulation since healthcare systems in major developed economies are spiralling out of cost control, is it public scrutiny of safety issues (as recently witnessed on Merck, Pfizer,…) linked to the approval and sale of prescription drugs or do we experience a mysterious slowing of R&D productivity in the form of less drug discovery combined with a marked increase in generic drug competition in particular through emerging economies as India and China? There are no quick and easy answers to a complex development. But we argue in this review (and limited preview), from an industrial economics perspective, that the way out of this slump strategically and structurally is a radical paradigmatic shift in drug discovery toward biotech based compounds, biopharmaceuticals or biologics facilitated through strategic alliances between the conventional pharma industry and the medical biotech industry. What we also observe is that despite the bigness of 'big pharma'. Without a paradigmatic shift, there do not appear distinctive intrinsic increasing returns to scale in R&D, so in order for companies to grow strategic alliances with complementary partners offer a better chance with a more diversified product portfolio and broader R&D platforms.

Our analysis proceeds by applying network economics to the formation of alliances in the biotech-pharma industry. In brief, network economics deals with economic activities that through interconnectedness and complementarity provide more value combined than the sum of their separate activities. They are able to give rise to increasing returns that contribute to the growth of industries and economies. Further, we provide insights into the conditions under which firms develop hybrid governance forms, integrate strategy and economics creating a holistic perspective on network strategy. Firm network types are categorized into network economies, competencies and market structure, with integration between participants and change as additional dimensions. 'Change' introduces a dynamic, evolutionary aspect.

The conclusion reviews the network dimension as a 'mechanism design' for investigating the evolution and life cycles of firm networks.

A framework is developed through the analysis of alliances within the pharmaceutical and biotechnology industries, and an empirical examination of the relationship between the degree of collaboration and market performance of major globally operating pharmaceutical firms. Case examples, supported quantitatively and qualitatively, provide evidence for the efficacy and implications of the network dimension.

A study of the industry's history identifies 'critical events' in terms of the network dimension that has transformed industry relationships. An empirical analysis also reveals that within the last decade equities of large pharmaceutical firms with a higher degree of alliance formation also performed better in terms of market valuation and total return. A strong, statistically significant linear relationship exists between the collaboration rate and both total return and price/earnings (P/E) ratios. The strength of the correlation increased dramatically within the last decade.

We also demonstrate the value of 'network specificity' in alliance formation, as a sub part of increasing returns, developed from asset and firm specificity in the economics and strategy literature. Network specificity applies where resources or capabilities have greater value as part of a particular network of firms, than as 'stand alone' in the general marketplace.

Both biotechnology and large pharmaceutical firms compete in a network industry characterized by rapid technological change which leads to industry change and market structure. In particular, these firms depend on the creation of new knowledge. New knowledge presents particular issues regarding transferability. Innovation potentials and alliance competencies should be prevalent in any market characterized by fast changing intangible assets, given the difficulties in trading intangibles; moreover, in industries with very high rates of technology change, technologies can be introduced that create new market segments, obsolesce existing product lines, and create substantial competitors from previously little- known firms.

Under such conditions, few firms can afford to conduct research in enough directions to build sufficient R&D options. Alliances offer opportunities for firms, in essence, to outsource R&D efforts, creating options on knowledge development, without requiring more restraining mergers or acquisitions. Biotechnology provides a critical example of such intangible assets that can be difficult to trade, and are, in addition, not necessarily appropriate candidates for acquisition. Also, under conditions of rapid change and high uncertainty, network forms of governance provide preferential access to information, decreasing information asymmetries and allowing firms involved in a network to scan a broader environment.

Thus, the biotech and pharmaceuticals industries offer an ideal subject for examining the network dimension, based on multiple complexities such as

- knowledge, intangible and asset intensive
- fast evolving technology environment, in multiple direction
- knowledge creation as the primary value creation mechanism
- very long term research, development and approval horizons for products
- high uncertainty over the long term
- alliance intensive

One major source for alliance formation could be traced to declining research productivity in the pharmaceutical industries. This productivity ---as reflected by the overall industry exclusivity and patent horizon --- has been declining since the mid nineties (The Economist, 2005). More drugs are coming off patents than are being replaced, for example, by new US Food and Drug Administration (FDA)-approved products. Some industry observers believe this trend suggests that the 'easy' drugs have already been developed and that the products currently in development are targeted to much more complex and difficult ailments requiring a paradigmatic shift in research and development. There is some support for this argument. Close to 30 percent of the drugs currently identified in the New Drug Approval (NDA) pipeline of the (US) Food and Drug Administration (FDA) are targeted at curing some form of cancer. Regardless of the cause, the pharmaceutical industry is facing many challenges. For example, the industry portfolio of patented drugs is aging rapidly. The average patented product's exclusivity has been halved within five years, and this trend cannot be easily reversed. New 'blockbuster' drugs take an average of 10 to 15 years from initial recovery to regulatory approval, and over a time period of about 20 years, from 1987 to 2007, the cost of developing a novel drug has increased from US $ 230 million (m) to roughly US $ 1 billion (b), US domestic research and development expenditures have followed the same trend. In 1990, R&D expenditures for US pharmaceutical companies totalled US $ 6.8 b and have grown to over US $21.3 b in 2000, and have roughly doubled since then. In sum, the time and cost of research and development, added to the quest for products targeted to cure more complex ailments, has left the industry weakened.

The drive toward alliance formation was also promoted by the paradigmatic shift in drug discovery, away from identifying new chemical entities (NCEs) toward molecular biological, genetically engineered (targeted) therapeutical compounds. While the number of new drugs based on NCEs increased in the 1950s and 1960s, it has been declining since the 1970s and has been a source of declining research productivities giving rise to drier 'drug pipelines'. Moreover, patent protection of leading drugs in the given period were running out resulting in explosive imitation through generics, thus largely increasing price competition on research based prescription drugs. This has significantly increased in scope and scale, for example, through new players in emerging pharmaco-economies (India, China).

In response to these challenges, pharmaceutical firms have pursued several options: (1) enhance their internal R&D efforts through the acquisition of smaller pharmaceutical and/or biotech companies; (2) engage in large horizontal mergers to achieve greater economies of scale and scope in their research programs; (3) acquire existing mature products through licensing agreements; (4) increase organic internal R&D efforts independently; (5) increase alliance activity ; or (6) change their fundamental business model. These options are by no means mutually exclusive; in reality, companies engage in a number of these activities at varying levels. Among these, alliance formation plays a spearheading role as we explore the underlying economic rationales.

On the other hand, the newly emerging biotech industry – though holding significant promise for drug discovery – was slow in coming up with a battery of proven, efficacious and superior drugs exacerbating the shrinkage of drug pipelines at least for a transient period. It also appears that technically the drug discovery process was in critical need of overhauling. While conventional chemically based drug-making relied exclusively on a huge number of explorations through experimental set-ups ---'to find the needle in a haystack', proving to be extremely costly with a low probability or high cost of breakthrough success --- mathematical

tools available in bioinformatics, computational molecular biology, systems biology or combinatorial chemistry would cut through the maze of computational links and with given probability would shortlist the items most likely to yield optimal experimental results.

Section 1 – Essentials for Alliance Formation- draws the line between corporate strategy, competition, uncertainty management and technological innovation as crucial constitutional elements of alliance formation across those industries.

Section 2 – The Science and Technology Base of the Biotech Industry - looks at the science technology background of the biotech industry evolution foremost as a leading path in the institutional setting of the American industry-educational complex.

Section 3 – Alliances in the Biotech Industry: An Industry Study of Network Economies - pursues an application of network economics to the formation of alliances in the biotech-pharma industry.The framework analysis provides insights under which firms create hybrid governance forms, integrate strategy and economics into a more holistic perspective on network strategy. Firm network types link network economies, competencies and market structure, creating integration between market participants and change as additional dimensions. The resulting constructs involve the network dimension as a mechanism design for investigating the evolution and life cycles of firm networks. An analysis of alliances within the pharmaceutical and biotechnology industries develops the framework, supported by an event-based tracing.

In Section 4 –Alliance Propensity of Biotech-Pharma Companies: An Empirical Perspective - this is followed by an empirical examination of the relationship between collaboration rate and market performance of major globally operating pharmaceutical firms. Case examples, supported quantitatively and qualitatively, provide evidence for the efficacy and implications of the network dimension.

Section 5 – European Biotech-Pharma Industry Development - shifts the focus to EU Europe in benchmarking industry development both in pharmaceuticals and biotechs to the US, and overall tracing a slower, delayed and catchup growth and a more diversified path in biotech (joint) ventures.

Section 6 – Emerging Asian Biotech-Pharma Industry, Analysis and Trends - emphasizes the current strong emergence of the bio-pharmaceutical industry in both economically mature and some emerging Asian regions amid industrial policy induced pressure to innovate and improve competitive positioning beyond domestic markets. It shows how the emerging, small and underfunded bio-pharma companies in Asia form cross-border alliances as part of a catchup industrial strategy.

Section 7 – Emerging Asian Biotech-Pharma Industry, Comparative Perspectives – details scope and scale of intrinsic pharma developments in major emerging Asian economies,also in view of foreign sources, and benchmarks country-wise developments in a comparative perspective.

Section 8 - Strategic Alliances: Post-Analysis and Projection – summarizes, reviews and previews the major observations, trends and fundamentals of pharma-biotech alliance formation.

A supplement – Strategic Alliances. Mergers and Acquisitions - reviews the various industry-specific, structural and regulatory conditions that promote or inhibit strategic alliance/joint venture formation across industries with special regard to network industries, in particular those that have beneficial effects on innovation incentives.

Hans Gottinger
Munich, Oct. 2009

Chapter 1

ESSENTIALS FOR ALLIANCE FORMATION

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If you don't know where you are going any path will lead you there- Roman Proverb

ABSTRACT

This paper reviews the critical cornerstones of alliance formation and draws the line between corporate strategy, competition, uncertainty management and technological innovation as crucial constitutional elements across the pharma –biotech industries. It shows that those industries reveal structural features that qualify them as network industries with favourite characteristics of industry specific increasing returns mechanisms.

1.1. INTRODUCTION

Alfred Chandler's work, Strategy and Structure [1], illuminated the impact of the rise of the railroad and related network industries during the nineteenth century on the development of the modem capitalist corporation as the engine of free market growth. [2] During the Industrial Revolution, fixed assets produced value through the creation and distribution of hard goods, often across long distances. The wide geographic, temporal and financial requirements of managing and operating a railroad compelled the invention and evolution of substantially more sophisticated and structured corporate organizations. Earlier organizational forms and business practices were incapable of effectively managing in this new environment. As such, the railroads compelled the evolution of the modern global corporation. Later, the breadth and depth of modern corporations encouraged the evolution of ever more complex

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functional hierarchies to coordinate disparate resources within expansive, multi-divisional firms. [3]

We witness a similar phenomenon as we enter the 21st century. In contrast to the Industrial Age, the emerging new economy primarily generates value through the creation, dissemination and application of knowledge. Since the 1980's, networking technologies have created a dynamic similar to that of the railroad in the nineteenth century, influencing options for corporate structures, relationships and competition. The most important and far-reaching impacts occur as a result of how people and firms use these tools to create value. The conflict between proprietary ownership as a necessary means for profit and the social nature of knowledge comprises the fundamental dynamic compelling the transformation of organizational forms during the present period.

In partial response to this challenge, building and maintaining corporate alliances has become an increasingly important capability for the pursuit of both operational efficiencies and competitive advantage. In fact, it could be seen as part of organizational design.[4] Alliances have been transforming competition and, as such, corporate strategy. The primary objective of this paper is to develop and apply a new framework providing insight into the impact of alliances on strategy. A broader, but ultimately more important objective, is to begin to consider the impact of our transition to a knowledge focussed economy and the relationship of this transition to the emergence of new organizational forms.

1.2. THE DILEMMA OF STRATEGY

Constructing and executing strategy, proactively or passively, requires predictions, yet the future always presents uncertainty. Herein lies the dilemma of the strategist---committing resources to an uncertain future. As market and technology change accelerates, uncertainty becomes of increasing concern. In a most basic challenge to strategic venturing, in the view of Porter [5,6] how can firms effectively position themselves and their offerings if marketplace positions keep changing? Alternatively, executing on strategy in the real world requires firms to commit to directions they believe will provide sustainable profits. Commitment theory, as advanced by P.Ghemawat [7], argues that strategy requires resource investments that might be difficult or even impossible to recover from in the future if too many strategic decisions turn out to have been wrong. Strategically phrased, you can't arrive anywhere in particular if you don't commit to a direction- and you cannot know in advance if you have chosen a good destination. Developing advantageous competency and resource combinations requires substantial time and effort, so re-direction can be costly.

There exists a dilemma. How can firms balance commitments to resource and competency investments against the need to remain strategically flexible? Firms require resources and competencies that enable advantages over competitors, but resource and competency investments require long-term commitments. Moreover, the primacy of cash flow in growing and operating business complicates the matter. For small, emerging firms, cash flow presents the obvious concern that, if a firm makes financial commitments in a direction that does not prove appropriate (which is most often the case with early stage firms!), it could encounter cash flow issues threatening its viability. The ca sh flow of established firms relies on existing product and services lines. Commitments to new strategic directions in response

to marketplace change can threaten or “cannibalize” cash flow from existing offerings. Particularly true of disruptive technologies, which will reenter our discussion in a number of guises, established firms face the uncertainty not only of technology change, but also the consequent uncertainty over the market viability of their existing products.[8]

With this dilemma, we arrive at a broader statement of a number of strategic issues addressed by technology strategy over the past few years. Christensen's notion of disruptive technologies focuses on the challenge of firms successful in established technologies which are caught unprepared to deal with upstarts whose technologies undermine and in some cases obsolesce the dominant firms' core offerings. Hamel and Prahalad's work advises business leaders to map a course to continual transformation and renewal of competencies, recognizing the condition that while marketplace change requires varied competencies over time, competencies require time to develop.[9] Ultimately, the dilemma of strategy arises from uncertainty--- the fact that no one can perfectly predict the future.

Uncertainty represents a crucial, but often neglected aspect of both academic and applied approaches to strategy. Porter's Five Forces paradigm seems to recommend that a careful analysis of the marketplace enables a firm to most effectively position itself and its offerings, requiring a periodic re-evaluation of market conditions. Hamel and Prahalad's ‘Competing for the Future’ take a more dynamic approach, prescribing that firms proactively define the future and create it. A bold approach, but one that seems to de-emphasize the risks, if assumptions about the future turn out to have been wrong. Comparative analyses of the cost implications of organizational alternatives dominate the transaction cost-based strategy literature. If one cannot define alternatives prospectively, how can managers determine cost minimizing decisions in the present? Uncertainty regarding the future presents a fundamental rationale for the need for robust corporate strategy, but much of the literature seems to avoid its implications.Uncertainty of a different sort played an important role in the early development of transaction cost theories of the firm. In this context, vertical integration often arises due to uncertainty of supply or capabilities, or as a result of ‘opportunism’ that might compromise a firm's ability to meet market demand at a reasonable cost.[10,11] R. Coase's [12] original insight regarding transaction costs as the rationale for the existence of firms, as well as their boundary determinant, arose as a result of his observations of the Ford Motor Company in the 1930s. Generally, Ford vertically integrated as a result of the lack of a sufficient supply of acceptable quality inputs.

Uncertainty of this kind encourages vertical integration. The ‘holdup problem’[13] provides an example. It is uncertainty regarding access to and control of the resources necessary to execute. The increasing specialization, depth and breadth of the economy over the past two centuries have substantially decreased uncertainty regarding the marketplace availability of inputs or capabilities to accomplish economic objectives. If one needs something made or accomplished, one can probably (out)source it.

Certainly, the control over resources provided by vertical integration still provides a compelling rational for the formation and boundaries of firms; however, uncertainty of another sort increasingly dominates as we move to the future. Rapid technology and marketplace change threatens firms by challenging the relevance of every product, service and business model. This represents uncertainty regarding what to execute or, by extension, what, exactly, to integrate. Which competencies and other resources will provide a competitive advantage over the long term, most effectively integrated into the firm?

While this issue presents the most significant challenge in dynamic markets, even mature industries can transform as a result of many factors, such as changing regulatory regimes, new entrants, technologies or business models, or a significant re-direction by an established player. Moreover, smaller firms typically do not have the capability or resources necessary to achieve a broadly integrated firm, even if they have the philosophical wherewithal. The greater the uncertainty regarding the future, the more firms must construct a portfolio of strategic options, without compromising the focus necessary to successfully compete. So, effective strategy requires commitments toward an uncertain future, while marketplace change threatens to undermine or even destroy a firm's value creating capabilities.

Markets characterized by rapid technology change exhibit high levels of alliance formation compared to mature industries, which tend to exhibit consolidation and even decline [14] The high frequency of alliance formation in emerging industries will become evident when we look at the biotechnology and pharmaceutical industries, which evidenced a nine-fold increase in operative alliances between 1993 and 2000.[15] More mature industries encountering re-organization or transformation also experience increases in alliances, as occurred when the global chemical industry experienced severe over-capacity in the 1980s.[16] Alliances and mergers allowed the industry to rationalize production in a manner that competing firms could not have accomplished individually. These alliances represented an industry wide alternative to consolidation through mergers and acquisitions (M&As), which occurred as well during this period.

So, marketplace actors apply network strategies in periods of significant change and uncertainty. This seems to contradict the notion that uncertainty engenders vertical integration. We are dealing with differing types of uncertainty, but the responses are more similar than might appear. Vertical integration and alliances both integrate activities more closely than in the open market. To an extent, alliances represent integration by other means. Nonetheless, alliances present significant strategic and managerial contrasts to integrated firms, not the least of which is the opportunity for firms to interact with a broader, more diverse- and potentially more productive- universe of knowledge creating opportunities than is possible within a single firm. Let us first examine its precedents in the established organizational economics and strategy literature.

1.3. Strategy and Transaction Cost Economics

Understanding firm behaviour and performance requires understanding the nature of firms. As such, most academic approaches to understanding firm strategy have been grounded in the theory of the firm (TOF) literature. The classic to which we will continuously refer is the transaction cost theory of the firm, or transaction cost economics (TCE).[12] Firms exist to decrease transaction costs for the exchange and employment of resources relative to transaction costs for similar resources in the marketplace. Over the past decade information and communication technologies (ICTs) have begun to transform the costs to manage and execute transactions between marketplace participants. Given the notion of transaction costs as a fundamental explanation for the existence and boundaries of the firm, significant changes in transaction cost dynamics in the marketplace should eventually be reflected in changes in the structure and relationships between firms. The proliferation of emerging inter-firm

organizational forms over the past decade - from strategic joint ventures to deep outsourcing arrangements and virtual firms-- has coincided with the expansion and increasing sophistication of ICTs. This has not been merely a correlation. Many organizing opportunities exist today for firms that were impossible or impractical prior to the past decade. Given that the Internet offers opportunities to dramatically decrease transaction costs for a wide range of transactions, a transaction cost based theory of the firm must conceptually predict changes in the size, boundaries and structure of firms. [17]

Transaction costs in the marketplace include factors such as search, selection, negotiation, fulfillment and enforcement. Within firm boundaries, costs generally include agency and control costs. The hybrid condition of any sort of inter-firm governance of resources, whether through formal contractual or informal relationships, expresses transaction costs in the form of coordination costs; that is, the costs of coordinating endeavours between autonomous firms. The evolution of ICT technologies, as well as increasingly sophisticated inter-firm management capabilities, have decreased these coordination costs, thus encouraging governance regimes between the hierarchical control of the firm, and the contractual governance of the market. The trend toward outsourcing of a broad range of activities illustrates an early and rapidly diffusing form of deep inter-firm relationships.

The TCE perspective biases the discussion of this example toward costs of achieving business results. Other motivations for outsourcing should include higher quality and improved corporate focus on the part of all firms in outsourcing relationships. Effective outsourcing should provide equal or higher quality service than would be possible in-house, or at least a satisfactory level of service, at a similar or lower cost. Thus, outsourcing should represent net value creation between the contracting entities, allowing each to focus on its core competencies. While the TCE perspective approaches a successful outsourcing arrangement as a more efficient governance configuration, focusing on costs can neglect or de-emphasize potential benefits of greater value creation.

The transaction cost theory of the firm presents transaction costs reduction as the organizing principle of firms; as such, TCE should prescribe any organizational form that provides the lowest transaction costs for the economic value created. It is partly a result of the efficiency and effectiveness of the modem corporate form that a transaction cost approach has provided theoretical justification for the existence of firms. It is also partly historical. Firms, in the traditional definition, exist, so they therefore must provide transaction cost advantages over market governance, given TCE's foundation in bounded rationality[18,11] and the path dependent nature of organizational and institutional development.[19,20] Moreover, the original context within which Coase developed his transaction cost insights to understanding firm existence and boundaries likely biased the foundation of the approach. Coase extrapolated from his experience working at the Ford Motor Company in the 1930s, recognizing the company's vertical integration strategy.

He postulated that vertical integration was justified in order to decrease the transaction costs that the firm would have otherwise incurred purchasing inputs in the open market. In the 1930s the industrial production model defined by Ford strove almost exclusively for operational efficiency. TCE is fundamentally an efficiency based approach to understanding firms. Industries and strategies defined by operational efficiencies seem best suited to TCE. A number of researchers have asserted over the past two decades that inter-organizational relationships are often not well explained by TCE, particularly when efficiency issues do not

represent the primary decision factors. [21,9] Decisions to pursue new firm competencies, or to form long-term R&D alliances are unlikely to be atomizable into discrete transactions.

1.4. Corporate Governance

Alliances can be a critical strategic mechanism for the long-term success of ventures; however, alliances include a broad range of types, characterized by a number of factors such as integration, co-ownership, trust and longevity. Varied forms of alliance constellations also create varied constraints for participants, from the long term commitments into which they enter, to other potential partner opportunities which participants forego in order to build and maintain membership. For instance, membership in certain strategic blocks can preclude involvement with competing blocks, the clearest example being the automotive supplier marketplace. [22] In order to examine alliances effectively as strategic mechanisms, we must first identify a dimension that insightfully differentiates organizational forms.

Alliances and partnerships subsume a very broad range of potential relationships. The objective in creating a governance dimension is to consistently relate organizational forms from monolithic hierarchy (firm) to pure market relationships (purely contractual). While numerous factors present the opportunity to differentiate alliances, more recent exploration is focused on the strategic impact of hybrid organizational forms. As much of the strategic literature is rooted in the theory of the firm, we will develop a governance dimension grounded in this literature. The governance and contractual theories of the firm [23] prove particularly useful. Alliances represent a variation of the governance perspective's focus on the firm or market governance decision characterized by some form of contractual relationship, whether explicit, implicit or both.

The contractual tradition, a derivative of TCE most notably understands the firm as an agglomeration of contracts, both explicit and implicit. [24] This perspective unifies the nature of the relationship of the firm with its employees, managers and owners, with the firm's relationship with other firms in the marketplace by characterizing them all as varied forms of contracts!

Likewise, Demsetz's [23] contractual approach to the firm provides useful insights for developing a dimension of organization from monolithic hierarchy to pure market governance. He characterizes firms as, “a bundle of commitments to technology, personnel, and methods, all contained and constrained by an insulating layer of information that is specific to the firm, and this bundle cannot be altered or imitated easily or quickly”. Demsetz's approach provides a strong foundation for a hierarchy/market dimension, given his interest in questioning what a firm is, in addition to the traditional TCE questions such as why firms exist, and what constitutes boundary conditions. He sees firms as a nexus of contracts, implicit and explicit. But this could just as easily describe a constellation of corporate alliances. In order to differentiate a firm from marketplace contracts, he identifies three factors that are characteristic of firm-like coordination: specialization, continuity of association, and reliance on direction.

The notion of networks of firms can be very broadly defined. It presents integration as a dimension of corporate relationships from a monolithic hierarchy to a theoretically pure market relationship.[25]. Gulati [26] defines strategic alliances broadly as, “any voluntarily

initiated cooperative agreement between firms that involves exchange, sharing, or co-development, and it can include contributions by partners of capital, technology, or firm-specific assets" --- a dichotomy clearly evidenced in biotech- pharma alliances.The present discussion will focus on the more integrated network forms: Strategic Alliances and Dominated Networks.

So, when do network arrangements foster a competitive advantage, relative to firm or market organization? When are assets or resources worth more as part of an alliance than within an individual firm or the open market? How do networks assist in the creation, appropriation and sustainability of value? Some of these questions have been recently taken up for network alliances in the management literature. [27]

1.5. THE DRIVING FORCES BEHIND ALLIANCE FORMATION

The implications of network strategies vary substantially depending on the purposes for which a particular network of firms forms, as well as the purposes for which the network actually operates (which are not always identical). The creation and management of alliance constellations must be understood in light of motivations for their creation.

While transaction cost economics presents a compelling approach to understanding firm boundaries [13] managers clearly engage in mergers and acquisitions(M&A), firm growth and divestiture, re-organization and other boundary shifting initiatives for motivations quite distinct from transaction cost minimization. An extensive survey of decision makers involved in alliances in the early 1980s found that none of them cited decreasing transaction costs as a primary rationale for their decisions.[21] Marketplace competition encourages firms to minimize costs, but it also compels firms in other directions: to acquire firms to pre-empt or respond to competitors, to adjust strategic vision in the face of disruptive technologies, to innovate to create value over the long term, to name a few. Innovation by its nature requires investment in the creation of new knowledge and capabilities, whether these are capabilities new to a particular firm, or new to the marketplace. In the case of knowledge capital creation, such as in R&D partnerships, "transaction costs" in the form of inter-firm coordination can in many cases be higher than an internally controlled effort; however, the overall value created by the combination of capabilities between firms can outweigh the increased costs of coordination. The common notion of "transactional value" attempts to reflect the importance of value calculations in understanding inter-organizational arrangements.

While value creation and cost reduction reflect complementary notions for the factors that encourage firms to change their boundaries through M&A or inter-organizational arrangements, these approaches do not assist much in elucidating the complexity of motivations influencing organizational decisions. In broad terms of the field of industrial organization, cost and value creation provide appropriate generalizations. For the purposes of applied corporate strategy, cost and value paradigms are by themselves woefully limiting, particularly given an ever-uncertain future.

Economists attempt to reflect the behaviour of market actors based on preferences, available data and other decision factors, as well as provide prescriptions for the most effective economic actions as a result of the insights. The study of corporate strategy attempts

to decipher why firms organize and act the way they do, how perhaps they should act regarding the development and execution of effective strategies (but often do not), and the outcomes associated with various scenarios. The fact that much of the strategy literature seeks grounding in economics reflects their complementary nature.[28] Implicit in both of these disciplines is the notion of motivation.[13] Economic behaviour while observable in the marketplace, can only be modeled in the classical sense of optimizing functions (even given bounded rationality) by making assumptions about the motivations of market actors, known as self-interested behaviour. Strategy can only be understood by examining the motivations and purposes for which firms act. The primary motivation of any for-profit firm should be some combination of increasing shareholder value and maximizing profits. This observation is too general to provide helpful insights into network strategy; nonetheless, understanding why firms form alliances to achieve higher profits or shareholder value can help elucidate under what general conditions firms might benefit from an alliance as opposed to governing a resource internally or sourcing it from the market.

Examining 'economic motivations' for alliances differs to some extent from understanding the broadest possible set of conditions under which alliances exist. While motivations present a form of conditions, they do not include all conditions impacting alliances. Examples of conditions not subsumed by economic motivations include the personal relationships between firm actors, chance events (that might, however, impact the economic motivations for alliances), and the alliance history of a particular firm. [26] In some cases, personal relationships and social networks could be economically analyzed, by modeling factors such as trust and decreased risk, but the point remains that a number of factors exist which are not primarily economic in nature. Since corporate strategy aims to maximize the economic effectiveness of a for-profit firm, then the most pertinent factors impacting alliances should pertain to the economic and market conditions under which alliances add value.

We can examine these conditions by understanding the motivations for alliance formation. Rather, why do firms form alliances, and how must firms build and execute network strategies under-these-varied-conditions?

1.6. Dimensions of Network Formation

What are the key building essentials firms might need for network formation? There are potentially limitless reasons, but all rational, optimizing motivations for forming alliances from a firm's perspective' can be categorized into three types, aside from purely financial motivations

1. *Network Economics*: A firm is attempting to compete in some manner under conditions influenced by network economies.
2. *Innovation/Competencies*: A firm is attempting to augment, transform or further leverage its set of internal competencies in some manner.
3. *Market Structure*: A firm is attempting to compete or become involved in some manner in markets where the market structure compels a firm to form alliances.

Most prominently, this category includes industry structure, positioning [5,6], and institutional issues that impact competition, such as government regulation and political risk.[29]

The point is that these three categories- Network Economics, Competencies and Market Structure- provide the dimensions that most powerfully present implications for the creation and prosecution of network strategy. Competencies refer to the internal decisions a firm makes regarding the competencies it develops in-house, which competencies it chooses to source through partners, and which competencies it might leave for the market to provide. Market Structure refers to the environmental, institutional and competitive factors of a particular industry, market and/or economy. Network Economics refers to whether network economic phenomena significantly influence the dynamics of a particular industry or market under consideration. Network economics includes all of the issues traditionally associated with this field of economics, such as demand-side economies of scale, network effects, and positive and negative feedback loops.[30,17] Network economics could be collapsed into the Market Structure dimension, but only at the expense of crucial explanatory power. The presence or absence of strong network economic effects on a market exerts such a strong influence on the formation of firm networks that it requires its own categorization.

Network Economics

Industries heavily impacted by network economics are characterized by demand-side economies of scale, where the relative number of users can significantly impact the success or failure of a venture. Network economics most directly pertains to industries characterized by technologies which benefit from broad based standards and interoperability, and/or are information intensive. Shapiro and Varian's summary of the implications of network economics on information-intensive industries, Information Rules, underscores how strategy in markets influenced by network economics can differ substantially from those without such dynamics. [30]

For instance, in some cases an open, give-it-away strategy can provide superior long-term prospects over a proprietary approach. This distinction presents interesting challenges to the definition and application of “firm-specific” assets, from the resource-based view of firm strategy. Sun Microsystem's JAVA programming environment provides a prototype. Sun has thus far invested hundreds of millions of dollars developing and promulgating JAVA with developers, succeeding in creating wide popularity and a broad installed user base. Can JAVA accurately be considered a firm-specific asset, given that Sun has pursued an open source strategy to encourage proliferation of the language? Despite the fact that the firm still maintains various intellectual property rights to the language, Sun has found some difficulty capitalizing on JAVA's success. The wide-spread success of JAVA within the developer community arose in large part from the open source strategy pursued by Sun, which allowed easy access to the development environment. Sun has pursued a network flexible strategy that has succeeded in driving diffusion of the technology. While widespread adoption has presented Sun with many opportunities, it has also encountered significant challenges in monetizing its success. Sun's variable success with JAVA has been significantly challenged by Microsoft's attempts to usurp the programming environment by amending its application

within the Microsoft environment. Much later, in mid 2001, Microsoft announced that JAVA would no longer be supported on Microsoft's newly introduced XP operating system, a critical challenge to JAVA, given Microsoft's dominating position.

Market Structure

In many industries, market structure issues encourage firms to create alliance constellations. The monopoly position of Microsoft in the last section provides an example. Significant aggregation of market power, as in monopolies and monopsonies, can create situations in which firms that desire to enter these markets have very little choice but to ally with an existing player as in the diamond trade through DeBeers.[31] If a firm decides to participate in the diamond trade, it must ally in some way with the DeBeers cartel. While DeBeers' grasp on the diamond trade has weakened somewhat of late, the firm traditionally has been the absolute dominant player, worldwide, and continues to be. There are no inherent network economics involved in the diamond industry, and in many cases, members of the DeBeers network might not require alliances for the sake of complementary competencies, were it not for the firm's effective monopoly. Any government mandated monopoly falls into this category as well, but can also overlap with other categories, as in the case of national telecommunications monopolies (network economics), or national control of raw materials mining and export. In the case of an oligopoly, existing players might, officially or unofficially, ally to maintain the status quo, as in the case of a cartel.. The opposite can also be true. In highly disaggregated markets, firms might decide to ally in order to create economies of scale, lowering costs and developing bargaining power against suppliers. Economists use metrics such as the Herfindahl Index or a top four-firm concentration ratio to represent market concentration.

An extensive literature exists on the implications of the level of market concentration in the industrial organization literature. [32]. The purpose here is not to develop and test many possible hypotheses related to market concentration and alliance formation, but rather to underscore that market structure plays a role in motivating the creation of networks of firms, which holds implications for network strategy.

Market structure dimensions are not limited to monopolistic or oligopolistic conditions. As evident from examples presented earlier, the “market structure” category includes institutional influences such as government regulation and anti-trust issues that might motivate inter-organizational arrangements over acquisition or market relationships. Here we define “institutional” in the terms developed by North in the economic field of institutional analysis [29] (North, 1990). These institutional issues relate to the market structure category of the Taxonomy given the fact that they influence the organizational decisions between firms (i.e. to integrate or ally) by impacting competitive market conditions, providing rules of the game. In this sense, it is not necessary to separate market structure and institutional issues into separate categories. The insights turn out on close inspection to be similar.

Competencies

The Competencies dimension addresses firms allying in order to leverage competencies and knowledge between firms, create and/or learn new competencies and knowledge, or a combination of both motivations. It should be noted that alliances formed for specific knowledge creation purposes, such as to license or share intellectual property fit into this mould. Knowledge or intellectual property does not necessarily refer to a “competency” per se; nonetheless, competencies represent the broader application of knowledge sets and capabilities to accomplish objectives through operational, managerial and learning processes. As such, the Competencies dimension includes any objectives for alliances characterized by knowledge creation, learning and/or transfer.

Competency-motivated firm networks take many forms. The simplest outsourcing arrangements can resemble market relationships, while some complex, long-term cooperative arrangements can resemble single firms. In fact, equity joint ventures are often structured as single firms, where the parent, cooperative firm owns equity interests and contribute capital, competencies and even people. The proliferation of outsourcing over the past few decades has occurred largely as a result of firms' interests in shedding internal resources dedicated to secondary or periphery competencies, such as data storage or call-center management. EDS, a pioneer in information technology outsourcing, and EMC, an early leader in enterprise data storage, illustrate firms competing based on these types of relationships. In other cases, competency-based alliances reflect more than the -hands-off- character of basic outsourcing relationships. The U.S. automobile industry evolved over the final decades of the twentieth century to include fewer suppliers, longer term relationships and significant supplier involvement in the design process. All of these developments greatly improved the industry's global competitiveness[33,34] But the industry's re-organization has not been limited to increased integration between firms.

1.7. Various Levels of Biotech-Pharma Alliances

Though most of the above mentioned examples relate to other sectors than the pharma-biotech industry, similar structural principles of alliance formation apply to the latter.

A historical examination of the global pharmaceutical industry reveals that most of the leading firms were founded in the late 19th century and have remained relatively stable in terms of their market positions. For instance, three of America’s major pharmaceutical companies, Eli Lilly, Abbott Laboratories and Merck, were founded around that time, as were the European pharma firms such as Glaxo, Hoechst and Rhone-Poulenc. Since the late 1980s, the world pharmaceutical industry has undergone a series of dramatic mergers and acquisitions: Bristol-Meyers Co and Squibb merged to form Bristol-Meyers -Squibb in 1989, SmithKline Beckman and Beecham Group formed SmithKline Beecham in 1989. In the 1990s we saw Rhone-Poulenc and Rorer merge to form Rhone Poulenc Rorer, Pharmacia and Upjohn became Pharmacia, Sandoz and Ciba-Geigy to form Novartis, Glaxo and Wellcome to Glaxo Wellcome, and further on Rhone Poulenc and Hoechst tobecome Aventis, being acquired by Sanofi as Sanofi Aventis, as Glaxo Wellcome and Smith Kline Beecham are now GlaxoSmithKline (GSK). Merger activity in the new millennium extended to the US though

on a slower pace, embracing pharma-pharma mergers with a significant stake in biotechnology (Pfizer-Wyeth, 2009) and most recently to Japan (Astellas-CV Therapeutics, 2009).

On a smaller and more diverse scale and at a later stage we observe strategic alliance formation of big pharma firms with dedicated biotechnology firms (DBFs). Along the classification scheme of Barley et al. [35] a taxonomy of strategic alliance formations would result in diverse types such as (1) Unilateral technology licensing, (2) Cross technology licensing, (3) R&D contracts, (4)R&D collaborations, (5) Minority-equity-based R&D alliances, (6) Joint ventures, (7) Manufacturing and marketing agreements, (6) Other agreements (as long-term supply agreements).

From these 8 types of collaborative forms only four of them would qualify to contribute to the innovation dynamics of R&D alliances.

Unilateral licensing and cross-licensing of technologies involve transfer of existing technologies between firms, no new knowledge is created or intended to be created I these alliances. There is also no new knowledge involved in manufacturing and marketing agreements and others. All of those can be subsumed under non-R&D alliances. There is a substantial variance across these R&D alliances in terms of the relative roles of pharma and DBFs, whether these are cross-border alliances [36] and the use of equity investment in these alliances. In a typical R&D contract, a DBF is required to conduct a specific biotechnology project in a certain therapeutic or diagnostic area but the sponsoring pharma company will not participate in this project. In return, the participating DBF will typically be given an up-front payment or milestone payment (or a combination of both) to cover R&D expenses. In an R&D collaboration, in addition to making cash payments to sponsor a biotechnology project, pharma also is actively involved in the R&D activities by providing relevant knowledge and personnel.

In a minority-equity based R&D alliance, a pharma company makes a minority equity investment in a DBF, while it may or may not directly participate in the R&D project. It often appears that the dominating motive for such an R&D alliance is to obtain technologies, as opposed to gaining financial returns from the investment. In a joint venture, both pharma and the DBF contribute equity and form a legally independent company specializing in biotechnology R&D.

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Chapter 2

SCIENCE-TECHNOLOGY ENTREPRENEURSHIP AND THE NEW BIOTECHNOLOGY FIRMS

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"Investors are slowly realizing that pharmaceutical companies should stay as small as they can, avoid distracting megamergers, invest large amounts in R&D, partner aggressively across the biotech spectrum and strive for novel, breakthrough medicines that add value."

The Wall Street Journal, Oct. 13, 2004

ABSTRACT

We look at the science technology background of the biotech industry evolution foremost as a leading path within the institutional setting of the American industry-educational complex. The variety of science-technology sources bundled to a powerful science entrepreneurship serves as a Schumpeterian example of creating a sustainable industry.

2.1. INTRODUCTION

New biotechnology firms are a product of science and research, the availability of financial resources, and the characteristics of scientists and entrepreneurs founding and managing these new companies. Biotechnology is the outgrowth of a series of eventsspanning the period from the middle of the 19th century to the mid1970s when the first new biotechnology firm was founded. The building blocks consist of a series of scientific

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discoveries that became linked together to produce the new scientific discipline of molecular biology that in turn contributed significantly to changes in related disciplines of biochemistry, microbiology, and genetics. The evolution of science sets the stage for new discoveries and eventually for the formation of Genentech in San Francisco in 1976 as the first of what became many new biotechnology companies. The availability of grants from private foundations and the US government, not only supported the research, but significantly influenced its priorities. The National Institutes of Health (NIH) emerged as the dominant source of financial support for basic biotechnology research and it remains today as an impressive agent of priorities to find cures to medical problems and to understand the building blocks of life hidden in each individual's genome. The scientists receiving federal and foundation grants were on the faculty of major US universities, and these same universities were producing an increasing number of highly capable graduates that supplied the laboratories with skilled labour. Eventually, these leading scientists and their proteges became associated with existing corporate enterprises, largely pharmaceutical companies. The evolutionary process continued when new companies were formed through the support of private venture capital, setting off what would become the increasingly rapid formation of new businesses that today number in the thousands world-wide.

As a typical evolution on the growth of this industry, new private firms follow general patterns of behaviour in a large domestic market that exhibit relative ease of entry, provided substantial capital exists, they remain relatively small for many years, with employment gradually growing to several hundred at most before they go for an Initial Public Offering (IPO), that is becoming public companies. Research and development (R&D) is the primary activity for the foreseeable life of the company until market approvals are granted by the FDA, revenue from product or service sales is very limited for many years, with operating capital coming from venture capital, private investment, collaborative partners and public stock offerings. Mergers and acquisitions (M&As) by small-to-medium firms are used to increase marketable products, improve research capabilities, diversify technical specialization and improve efficiencies, whereas M&As or strategic alliances with large pharma companies or biopharmaceuticals gain expertise in manufacturing, commercialization, capture patents, improve competitive positioning and market share.

These new firms had, and continue to have, particular characteristics that are apt to profoundly influence the pattern of new business formation and their industrial behaviour as they attempt to develop, license and market new drugs and diagnostics or treatment products. The historical source of research funding remains important in the evolution of the industry and it is this national commitment that has brought the U S biotechnology industry to world prominence. This entrepreneurial, research driven culture led to the vision of an increasing returns bioeconomy [1] with all its imitations worldwide and fast expansion into complementary sectors. The importance of agglomeration (network) economies in developing concentrations of high technology firms (see Sections 3 to 6 in this issue)are offered as specific conditions necessary to the start-up and successful growth of biotechnology firms. In biotechnology, the dominant behaviour patterns of the industry is directly linked to the presence of knowledge-based factors that influence the location of firms and the way they develop alliances among themselves.[2]

2.2. DEFINING BIOTECHNOLOGY

Biotechnology is a combination of science and technology that has evolved dramatically in the last half of the twentieth century. It is marked by paradigms in science, the creation of new academic disciplines, and dramatic discoveries that have caused astounding changes in the application of medicine. The new-biotechnology holds the promise for new products and services that could cause a revolution in the treatment of disease and conditions. As this evolution unfolded through the 1970s and early 1980s there were numerous attempts to define biotechnology. Back then, the Organization for Economic Co-operation and Development's (OECD) Committee for Scientific and Technology Policy commissioned a report, Biotechnology: International Trends and Perspectives that considered numerous definitions from many of its member nations in arriving at a common definition. At this early stage they arrived at a conclusion that biotechnology is not an industry but a scientific activity; therefore, it seemed reasonable to settle on this definition:

> '…the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services'. [3]

Back then this unspectacular definition served to characterize biotechnology for the purpose of a broad classification, but the OECD conclusion that biotechnology is a scientific activity and not an industry is hardly consistent with the spread and practice of biotech activities that followed from then. It is standard practice to refer to the biotechnology industry in describing the growth and evolution of biotechnology research, manufacturing and service businesses. [4-7] Following this practice the collection of businesses that produce biotechnology goods and services are considered to constitute an industry. [8]

The OECD report follows the definition with clarifications of the critical words and phrases to further explain the meaning this definition intends to convey. The range of disciplines implied by "scientific and engineering principles" includes principally microbiology, biochemistry, genetics, biochemical engineering and chemical engineering. It omits molecular biology, genomics and systems biology but these new disciplines are surely to be included today as leading contributors to the field, as discussed further below. The term "biological agents" refers to wide collections of biological catalysts, particularly microorganisms, enzymes and animal and plant cells. In a similar all-encompassing way, the concept of "materials" includes all organic and inorganic materials. Therefore, the definition is intended to include the actual process in which the biological agent is used, those processes concerned with its preparation, and the processing of biological materials resulting from these actions.

The scope and complexity of biotechnology makes it difficult in identifying the range of goods and services that constitute as having come from the biotechnology industry and it has been changing from the onset of the "new" biotechnology industry. The provision of "goods and services" includes the products of industries concerned with food, beverages, pharmaceuticals, biochemicals and the extraction of metals occurring through water purification, and the treatment of industrial and domestic wastewater. Biotechnology is restricted in the health field to the production of useful medicines, including antibiotics, vaccines and antibodies. Excluded by the definition are those areas of medical engineering

and technology called biomedical engineering or bioengineering. Aspects of agriculture must be considered as included in the definition if plants provide raw materials for biotechnological processes or in the case of microbial pesticides the use of modem genetic manipulation techniques for plants and animals. All in all, this seems to be consistent with the US Office of Technology Policy (OTP) definition where biotech refers to a set of enabling technologies rather than a set of well-defined products [9], and more recently updated and enhanced in a European study. [10]

The historical development of biotechnology is characterized by three major growth phases. The first generation spans the period from ancient times to the beginning of the second World War and shows the product concentrations were limited to drinks, food and fuel. The second generation begins to show the first organization of science and engineering inputs into industrial-scale processes with fermentation, brewing and wastewater-treatment industries that became established after the end of the war. In the third generation, biotechnology began in the second half of the 1970s with the formalization of genetic engineering techniques and the founding of the first new biotechnology companies. [11]

2.3. Science Evolution

The changes in the sciences connected with medicine over the course of the twentieth century represent a series of linked paradigms that have propelled the evolution of biotechnology. These shifts in scientific knowledge are some of the driving forces propelling research and development of new products; and they help to explain the relationship between science, scientists, and the eventual emergence of new biotechnology companies.

Arthur Kornberg, founder and director of the Biochemistry Department at Stanford University and Winner of the 1959 Nobel Prize in Medicine or Physiology used a river metaphor, as an ever increasing knowledge stream to describe the progress in history of life sciences. He explains that anatomy, the most descriptive of the life sciences at one time, is now understandable through the assembly of macromolecules that form the cellular structure and tissues of the organism. Genetics has also transitioned from being the most abstract discipline only a few decades ago to now being reduced to the study of simple genetic chemistry. Anatomy and genetics have intersected after previously representing extremes. The missions of embryology and genetics have become indistinguishable in their mission to express the traits of each individual of a species. Gaining an understanding of the molecular basis of growth and aging, and of health and disease, is the objective of all of these fields. Through this understanding it is possible to determine how to intervene “to forestall and correct the aberrations caused by genetic deficiencies and environmental stresses”. [12]

2.4. Emphasis on Molecular Biology

Molecular biology stimulated a unique worldview that in the late 1970s would adapt easily to the profit motive, concludes Martin Kenney. [11] Entrepreneurs opened a new era for biology when they seized on the commercial potential of the discoveries at the University of California, San Francisco (UCSF) and Stanford University that DNA (deoxyribonucleic

acid) could be cut, recombined and inserted into foreign bacteria that would express the new gene. It was the rise of NIH as a funding agent that is crucial to the emergence and triumph of molecular biology.

Research universities throughout the world first explored and developed the techniques and practices represented by the primary fields of biotechnology. The core discipline for the industry is molecular biology, but microbiology, biochemistry, immunology, virology and cell biology are all important. As early as in mid 19th century German physiological chemists were actively applying chemical techniques to biological research. Biochemistry grew in research importance at Cambridge University and in the United States to become a service discipline within medical schools. Therefore, the scientific study of the chemistry of living organisms was not original or novel to the discipline of molecular biology. Biochemistry imported the techniques used in chemistry to give a more scientific aura to the medical profession.[11] A restructuring of medicine was forced during the period from 1900 to 1930 to move toward the scientific approach epitomized by the "modem" physician.

A remarkable expansion in biochemists' interests occurred in the late 1930s. Assisted by new laboratory technologies, biochemists mapped metabolic pathways and began to think of large molecules in terms of their functions in the cell. The first revelations began in the 1950s in molecular genetics, gene replication, and the genetic control of enzyme syntheses. However, most of these stunning discoveries in "molecular biology" were not made by biochemists: George Beadle and Edward Tatum's one-gene-one-enzyme concept; Jacques Monod and Francois Jacob's opus and central dogma of gene expression; Linus Pauling's alpha helix; and Watson and Crick's double helix were all the work of biologists, chemists, and physicists, who made it clear that they regarded biochemists as "plodders".[13] These patterns were not due to chance, but to the limits of vision set by biochemists' institutions. The unexpected discoveries of the molecular biologists dramatized the impact of these institutionalized habits, roles and values on the pace of change of biochemistry.

The unique concentration of molecular biology was the expression of life as an assemblage of molecules. Alternative visions of biology including those concentrating on taxonomy, non-molecular developmental biology and population biology were weak by comparison. The molecules examined went beyond simple water and carbon dioxide to the study of larger macromolecules with hundreds or thousands of atoms. Molecular biology was pursuing an agenda for discovering the "secret of life," defined as the ability of a group of molecules making up a cell to self-replicate. In contrast, biochemistry focused most of their experiments on the more numerous and immediately useful proteins. [11]

2.5. SCIENCE-TECHNOLOGY ENTREPRENEURSHIP

The freedom to pursue independent university scientific research was derived from the availability of financial support from public or non-profit institutions. This independence was not without limitations derived from the institutional priorities of the funding source. The research topics were expected to possess "practical and economic value for medicine, agriculture, and industry," according to Kohler.[13] Potentially the best early example was the research funding in "support for the application of new physical and chemical techniques to biology in the 1930s" [13] traced to Warren Weaver, Director of the Rockefeller

Foundation's biology program. A mathematical physicist and pioneer in information theory at the University of Wisconsin, Weaver had a vision of a research agenda of "exact, analytic, vigorously formulated, reductive experimentation based on the methods of physics and chemistry" [14], a view that was later reiterated for molecular biologists surrounded by powerful instruments like experimental physicists.[15] Research funds were generally distributed as project-grants of medium size, usually for three years and selectively bestowed on recipients who were top scientists. The primary objective of the Rockefeller Foundation was the creation of "centers of excellence," with grants to institutions limited in number as an example for others to emulate.

Weaver's agenda helped create molecular biology, which became increasingly clear in the post Second World War period. He had continued to support scientists using new techniques upon which the "new" biology was built. This foundation stimulated other scientists to follow suit and it provided seed money to finance the establishment of molecular biology as a field of study. The project-grant program soon expanded, finding a niche in many elite universities such as Harvard, MIT, Stanford and Caltech. The new biology's remarkable research successes encouraged biochemists to either respond to the new agenda or be left without funding support. By the 1970s, the shift in research priorities showed as increasing numbers of biochemists sought answers to basic questions of production and reproduction of life.[11]

The "management of science" approach spawned by the Rockefeller Foundation not only shaped university research priorities, it provided chemists and physicists with the resource capacity to undertake biological research. Project grant funds were used to purchase equipment to support the research team and to expand laboratory staff that in turn led to increased specialization. Evolving through this process, the top researchers became scientist-entrepreneurs whose primary task was to secure continued funds for the research effort. The scientist-entrepreneur had to be prepared to shift his or her research into areas favoured for funding, frequently capitalizing on the ideas of new graduate and postdoctoral students.

The resulting emphasis on discovering the secrets of life through ideological pursuit of success in molecular biology produced the forefathers of the discipline, including: J. D. Bernal, Linus Pauling, Salvador Luria, Herman Muller, and Jacques Monod. Many were political radicals expecting their radical scientific conceptions to transform traditional science. The ultimate outcome of their research in the 1970s provided economic growth supported by new technologies. What appeared as radical new biology and pure basic research in the period from 1930 through 1960 was transformed into basic commerce after the 1970s.

2.6. University-Industrial Relationship

There is an extensive history of university relationships with corporate institutions, federal agencies, and non-profit organizations that themselves have legitimate pursuits being achieved, in part, through university research. Martin Kenny's book [11] and Daniel J. Kevles and Leroy Hood's [16] show the formation of those relations as a powerful driver for the initiation and growth of a biotechnology industry. As biotechnology research proliferated in university laboratories new companies were being formed in the San Francisco and San Diego area, near Boston, in Minnesota, Seattle, and St. Louis by faculty from the University

of California at San Francisco, San Diego, Stanford, MIT, University of Minnesota, University of Washington, and George Washington University. Many of these early companies (Amgen, Chiron, Genetic Systems, Genex, Hybritech, Immunex, Integrated Genetics and Molecular Genetics) had one or more corporate executives who simultaneously held professorships.[11] This process surely continues today as is demonstrated by new strings of second-generation biotechnology entrants.[2]

The strong motivation to become biotech-entrepreneurs was coming from the potential of high financial reward, in a time when 'animal spirits' in finance and hightech were rampant, measured in millions of dollars in contrast to university salaries, but also from other personal aspirations. Choosing not to participate in the commercialization of their scientific discoveries meant that others would benefit from their research. Intense pressures can come from family members and friends who do not perceive the traditional separation of university from business as important, and it was quickly becoming less practical. The potential to create products that could have significant benefit in patients' treatment was, and continues to be, a big motivator. The translation of basic research into the development of new health care products is important to many scientists. Conversely, the boredom that can set in during mid-career years can certainly be offset by the excitement of a biotechnology company, particularly when success seems assured. Two scientific breakthroughs in the early 1970s lead to the commercialization of biotechnology. In 1973, Herbert Boyer and Stanley Cohen, researchers at the University of California, San Francisco Medical Center and Stanford University, respectively, discovered that DNA could be cut, recombined and inserted into foreign bacterium that would then express a new gene. Cesar Milstein and Georges Kohler of the British Laboratory of Molecular Biology in Cambridge reported the discovery of monoclonal antibodies two years later. They fused cells with specific properties as a method of producing large quantities of specific antibodies. Their work was recognized for its significance with the award of the Nobel Prize for Medicine or Physiology in 1984.[12] (Venture capitalist Robert Swanson, himself an undergraduate in chemistry at MIT, was the U. S. pioneer who recognized the commercial potential of biotechnology). Genentech was founded in 1976 as the first venture capital funded bitechnology company through negotiations between Swanson and Boyer. Genentech set the example that led to the birth of the US and indeed global biotechnology industry, producing an explosion of small firms led by academic entrepreneurs who kept close ties to their universities. Venture capitalists and 'business angels', an American phenomenon, provided the funds for early start-up companies. This supply of capital was forthcoming based on the scientific research foundation of the new company[17], and certainly based on the participation with recognized scientists. The American lead in biotechnology was created and maintained by small firms through this marriage of venture capital and university scientists. There evolved a culture that supported entrepreneurship and encouraged a close relationship between university science and industry. Biotechnology entrants as a sort of 'productive entrepreneurship'[18] often serve as key facilitator in economic development. As a result to date (2005), in terms of market capitalization and most likely medical significance, nine out of the top ten public medical biotech firms worldwide are American (Amgen, Genentech, Biogen IDEC, UCB-Celltech, Genzyme, Gilead Sciences, MedImmune, Chiron and Millenium), only one European (Swiss Serono).

Rapid growth of biotechnology firms in the US did not run parallel with a similar phenomenon occurring in Europe, where there was a distinct lack of small firms to play their key role of linking recent discoveries with the pursuit of patents and products. There were numerous other conditions that help explain Europe's inability to exploit the new biotechnology in time (with the partial exception of the United Kingdom): lack of venture capital; an underdeveloped focused science base, in particular, in molecular biology, lack of public trust in biotechnology in general, lack of knowledge of the new technology and its commercial potential by existing firms; and, a more negative attitude toward industry by European academics than that held at American universities.[19] There were policy changes in Europe from the 1980s aimed at correcting these impediments to small firm commercialization of biotechnology. Also, policies were frequently directed toward large companies in chemicals, pharmaceuticals and the agriculture-food industry to encourage the industries to assimilate biotechnology knowledge. All in all, the US biotechnology industry started to expand its lead over Europe, and more so, over the most advanced industrial economies in East Asia, such as South Korea and Japan.[20] (see Sections 5 and 6).

2.7. The Formation of New Biotechnology Firms

There is ample empirical evidence of the dominance of small-and medium-size biotechnology firms in the development and expansion of the US industry, as further outlined in Sections 3 and 4. There are particular conditions of entry that influence the formation of new firms in this industry. Saviotti [21] describes the principal barriers to entry summarized below as economic factors, knowledge barriers, risk barriers, local knowledge factors, and the effect of a technology heritage. These conditions are examined here in view of the network economic factors that will be explored in subsequent chapters.

Traditional Economic Factors

The expectation that accompanies firms (in alliance) entering the market is the presence of above-normal profits, or potentially super-normal profits as discussed in Section 1 above (see also Supplement). While profitability expectations may be necessary for new firm entry, it is not sufficient to explain entry into completely new industries chasing new technologies. Entrepreneurs founding new firms based on radical new innovations, according to Schumpeter [22], are motivated by expectations of a temporary monopoly during the initial period of diffusion of the innovation before imitations exist. Completely new technological fields like biotechnology are expected to be different than more mature industrial sectors.

Knowledge Barriers to Entry

Access to new forms of knowledge and the speed to which the knowledge can be mastered will tend to favour small-and medium-size biotechnology firms over large incumbent diversified firms. However, new forms of scientific knowledge cannot be used

alone, and must be combined with knowledge of regulatory approval procedures, marketing and sales knowledge, or manufacturing capabilities to produce large quantities of drugs through processes that themselves require regulatory approval. Typically in the past, large diversified businesses have dominated the biotechnology based industry because they possess this knowledge in the pharmaceutical and medical products sectors. These complementary assets are barriers to entry, or a deficiency that must be accommodated through collaboration agreement (Section 3).

Risk Barriers to Entry

Biotechnology is an inherently risky business because much of its knowledge base is untested and derived from chemical and engineering processes that could introduce genetically modified organisms into the environment. Regulatory responses to these risks could have an important effect on the development and diffusion of biotechnology businesses. Differences in regulatory enforcement or in the strictness of national regulations can alter inter-country barriers and entice or impede economic development of new biotechnology firms. Knowledge of regulations and the ability to accommodate regulatory change is easily acquired by larger diversified companies than by new start-up firms.Regulations are generally an important barrier to entry, but they are particularly important in biotechnology due to the potential impact on health and safety of consumers and the general public.

The evolution of technologically based industries is influenced by the character and changes in relevant knowledge and the capacity of firms to adapt to new knowledge. The speed with which changes in technologies occur, the capabilities of certain size firms to adapt to changing knowledge, the proximity to the source of knowledge changes, and the duration of changes affect the entry of new firm and the success of different sized firms in the knowledge adaptation process.

Network Externalities

Biotechnology firms thrive on what economists call `agglomeration externalities,' benefits that accrue from the concentration of resources in circumscribed geographic settings. According to many analysts, industrial ecologies composed of clustering biotech start-ups generate their own momentum by cultivating or drawing capital venturers to take advantage of opportunities for innovation and profit thrown up by biological research. This synergistic development continues to attract and develop new biotechnology entrepreneurs, who act as the seed bed of the local economic environment.

Technology Competence Affecting Entry Conditions

The value of prior knowledge investments and a track record of using existing know-how will influence a firm's adaptation to new technology.[23] Firms with a strong commitment to existing technology will be unlikely or unable to adapt when a radically new technology with

important application potential is discovered. If the new technology is a partial, or complete, substitution for the old then the existing competence and knowledge base of the prior technology suddenly lose their economic value which could be referred to as 'competence destroying technologies'.

Firms with a heritage as biotechnology and pharmaceutical companies built on organic chemistry and biochemistry derived products experienced a discontinuity in their abilities with the emergence of molecular biology and the set of techniques called genetic engineering. Even though some biotechnology processes are very old (fermentation of beer and culturing of yogurt), the greatest potential for business growth and product development is linked to the new technologies applying molecular biology and genetic engineering. The pharmaceutical industry has illustrated its adaptability by allocating the largest proportion of its investment where there could be a substitute for pharmaceutical products previously produced by different (older or more conventional) processes. Examples of this substitution reaction include the synthetic production of human insulin and human growth hormone (Section 3).

Large parts of the knowledge base and competencies required to bring a completely new pharmaceutical product to market are common to all products and are in place for all products produced by old technologies. The typical array of knowledge and competencies include research and development, securing patents, regulatory affairs, management of clinical trails, process manufacturing, quality control, marketing, sales, and protection of intellectual property. The total components of the knowledge base required in the pharmaceutical industry are separated into two categories. First, core competencies are biotechnology and the related scientific capabilities critical to the function of firms in the industry because (1) they are difficult to acquire and (2) there are no other ways to produce the results.[24] The other complementary assets are the components of knowledge base required to take pharmaceutical products from research to market. Therefore, new knowledge replaces only one part of the core competencies, however important, of the overall knowledge base of large diversified pharmaceutical firms. The other complementary assets in old production processes are required for new technology based processes. The extent to which these relationships continue relatively unchanged implies that these large diversified firms will have a good chance for survival

New biotechnologies and their associated scientific disciplines have revolutionized research and development, but have had a more limited impact on other activities associated with production and commercialization of new products.

2.8. Collaborative Agreements

In the period leading up to the 1980s, collaboration agreements were primarily set up to transfer technology and knowledge from firms in developed countries to firms in developing countries. These agreements were regarded as inefficient and unstable industrial organizations, and not a replacement for either markets or hierarchical organizations. Changes took place in the early 1980s that increased the number of collaboration agreements, improved the quality of the relationships by concentrating on the creation of new knowledge for the benefit of both parties, and frequently revised the relationship with agreements between competitors. These new forms of collaborations are more frequently in high

technology sectors, especially information technology, biotechnology and new materials industries facilitating 'increasing returns' in those industries.[25]

The most general causes for changes in collaboration agreements point to the increased uncertainty of the environment in which firms operate, in part due to globalization, increased competitiveness and the rapid-pace changes in technology. The continuing advances in biotechnology at the technological frontier give a crucial role for entrepreneurial SMEs (small and medium enterprises) as intermediaries between public research centers and large diversified companies in the transfer of knowledge generation and utilization methods. In hindsight, this factor uniquely contributed to rapid innovation and diffusion of biotech competence throughout the healthcare industry. [8]

One of the leading reasons for inter-firm collaboration is that small and medium firms and large corporations, both individually and as two classes, possess complementary assets of benefit to each other. Senker and Sharp [26], in studying cooperative alliances in biotechnology companies have identified five principal reasons for collaborations: (1) the presence of complementary assets in small-medium firms and large diversified firms; (2) the close interaction and learning required for the exchange of complementary assets; (3) the rapid scientific/technological advance that puts a premium on speed of learning; (4) the importance of preserving flexibility or reversibility of decisions; and (5) the need for trust. The size and diversification of each partner firm will shape the way the collaboration is structured. Those pronounced effects have been confirmed for the biopharmaceutical industry in diverse empirical settings by Rothaermel.[27]

There have been changes in the nature of these agreements over time. According to Senker and Sharp [26], large firms have gone through three phases in the use of these agreements: (1) a contract research phase, when firms were very uncertain about the development; (2) a source of skill/recruitment/takeover phase; and (3) a source of new product-licensing for development phase. Others have differentiated between three concentrations of strategic alliances; the production phase, the market base and the knowledge base.[20] It appears, in Section 3, that strategic alliance formation was carried forward by complementary assets and driven by broadening and deepening the drug pipeline in order to gain competitive advantages. Most recently, in the strategic consulting business, various factors have been systematized that are identified as driving forces in alliance formation for biopharmaceuticals.[28]

2.9. CONCLUSIONS

The recent history of biotechnology over the past half-century is marked by major transitions. Science has evolved through paradigm shifts forming a new discipline in molecular biology and through discoveries of applications in genetic engineering providing the understanding of the double-helix structure of DNA in 1953 that is connected to the mapping of the human genome celebrated in 2000 and reported in the journal Science in February 2001. Throughout this dramatic evolution, The National Institutes of Health (NIH) has managed the distribution of many billions of dollars for research, much of it directed toward biotechnology and biomedical subjects. Research grants flow largely to universities with gifted scientists equipped to manage the human and capital resources to achieve results

on a rapid response schedule. The dependence on university-based research produced the discoveries that established the United States' world dominance in biotechnology, one offshoot of which was the emergence of the scientist-entrepreneur as a new participant in business formations. Following the formation of the first new biotechnology firm in 1976 was the unleashing of creative and entrepreneurial energies, financed initially by private investment and venture capitalists, and later through public stock offerings and collaboration agreements, that by 2004 had produced over 2,000 existing biotechnology firms in the US. The formative events in biotechnology established a set of relationships that we have been following. Scientific discoveries in the quarter-century following the Second World War led to events that spawned a new industry. Today research and product development continue at the highest levels of national and international capabilities. NIH precipitated early research success and, today, retains its status of the dominant source of research grants for basic and applied biotechnology research in the world. University professors in the biology sciences had the propensities to simultaneously work in the academic and business communities, a pattern that has caused strong connections between the research and business sectors, but not without criticism from many in the academic community.

The locations that excelled in the formation of new biotechnology businesses are expected to be dominated by the presence of agglomeration economies, including a highly skilled labour force, strong universities, high amenity levels, excellent access to national and international markets, and the existence of new technology businesses that stimulated new biotechnology business formation. These same locations would be expected to be major recipients of NIH research grants to universities and local biotechnology firms. Knowledge-based labour mixes with equally or better skilled university or institutional researchers to begin or to staff new businesses. Knowledge based industries, as the term applies to biotechnology, means a dominance of molecular biology and related disciplines and highly specialized abilities in drug development, clinical trial management, regulatory procedures and other specialities to successfully market and sell new drugs. The complexity of these skills and the requirements for success in this industry causes small and large companies to reach collaborative agreements and work cooperatively to move quickly from R&D to successful marketing of a new product.

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Chapter 3

ALLIANCES IN THE BIOTECH INDUSTRY: AN INDUSTRY STUDY OF NETWORK ECONOMIES

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"The number of strategic alliances more than doubled compared to 2005, and potential deal values grew to about US$23 billion, an increase of 69 percent over 2005. The largest share of this increase came from pharma-biotech deals …." Ernst and Young, Beyond Borders, Global Biotechnology Report 2007

ABSTRACT

This section pursues an application of network economics to the formation of alliances in the biotech-pharma industry.The framework analysis provides insights under which firms create hybrid governance forms, integrate strategy and economics into a more holistic perspective on network strategy. Firm network types link network economies, competencies and market structure, creating integration between market participants and change as additional dimensions. The resulting constructs involve the network dimension as a mechanism design for investigating the evolution and life cycles of firm networks. An analysis of alliances within the pharmaceutical and biotechnology industries develops the framework, supported by an event-based tracing.

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3.1. INTRODUCTION

The development of the pharmaceutical and the emergence of the biotechnology industries provide valuable insights into the role of alliances and networking that shaped the synergy between both industries. For example, Powell [1], found that biotech industry analysts explicitly examine the alliances of individual firms and ascribe market value based on the quality and quantity of those relationships. Thus, firms with a higher quality constellation of alliances generally enjoy higher market valuations, a reflection of the market belief that they will perform better in the long run. Goldman Sachs published a comprehensive listing of biotech alliances [2] updated most recently [3]. In a study of the Canadian biotech industry, Baum et al. [4] found that young firms being better able to leverage alliances, in particular R&D alliances, grew at higher rates than those that did not, that much could also be inferred from a comprehensive EU study on the biotech industry in Europe [5]. In particular, the alliance configurations built during the early start-up stages significantly impact early performance. Our overriding objective here is to examine the role of interfirm arrangements in the market performance of large, advanced pharmaceutical firms,using analytical tools derived from principles of industry analysis in network economies [6]. In brief, network economics deals with economic activities that provide more value combined than the sum of their separate activities. They are able to give rise to increasing returns that contribute to the growth of industries and economies. Both biotechnology and large pharmaceutical firms compete in an industry characterized by rapid technological change, in particular, these firms depend on the creation and accumulation of new knowledge [7]. Alliance competencies should be prevalent in any market characterized by fast changing intangible assets, given the challenges inherent in trading intangibles; moreover, in industries with very high rates of technology change, technologies can be introduced that create new market segments, obsolesce existing product lines, and create substantial competitors from previously little known firms. Under such conditions, few firms can afford to conduct research in enough directions to build sufficient R&D options. Alliances offer opportunities for firms, in essence, to outsource R&D efforts, creating options on knowledge developments without requiring mergers or acquisitions. Additionally, under conditions of fast change and high uncertainty, network forms of governance provide preferred access to information, decreasing information asymmetries and allowing firms involved in a network to scan a broader environment. In a time of a deep global business cycle downturn they also provide a cushion to survive with a broader product portfolio and an opportunity to reengineer and restructure their business.

3.2. BIOTECHNOLOGY INDUSTRY AND DRUG DEVELOPMENT

The primary objective of the biotechnology and pharmaceutical value chain relates to the discovery, development and distribution of therapeutics and drug delivery mechanisms. Significant biotechnology industry participants target non-drug based activities, such as medical instruments and diagnostics [8]. We focus on new drug development and distribution, including firms involved in creating and marketing new drugs (e.g, candidate drug discovery,

genomic based therapeutics), or providing tools for the process (e.g.- bio-informatics, combinatorial chemistry, high-throughput screening, X-ray crystallography). Moreover, the majority of the analysis will address publicly traded firms, due to significantly greater access to information compared to privately held firms. The biotechnology and pharmaceutical industries present a complex network of technology-focused firms. Industry analysts define the pharmaceutical industry as firms involved in the discovery, development, manufacture, distribution and marketing of pharrnaceutical therapeutics. The biotechnology industry is more difficult to delineate. In general, the biotechnology industry is including firms that apply technologies to the life sciences. There is an aspect of newly emerging or 'cutting-edge' to the technologies represented within the industry.

Some firms characterized as medical biotechnology firms in the past have increasingly been categorized with pharma companies.(It used to be a joke to say that ' biotech companies are pharma companies without sales' [9,10]. Similarly, along this line, as Powell et al [1] has observed, while biotechnology was 'competence-destroying' in upstream R&D, it was 'competence- preserving' in downstream commercialization activities. This appears to reflect the complementary nature of both industries as symptomatic for network industries. As a few once-biotech firms have matured their activities have expanded to resemble more integrated pharma companies. Some notable examples include Millenium Pharmaceuticals (now acquired by Japan's Takeda), Genentech and Amgen with their product range in biopharmaceuticals. Conversely, there are some pharmaceuticals which became deeply entrenched into biotech early on such as Eli Lilly, Glaxo (GSK) and Roche. Additionally, 'medical' biotechnology as an industry includes firms involved in cutting edge research and development of life sciences-related tools and equipment, some of which support drug discovery and development.

In terms of categories, one could break the biotechnology industry into tiers based on market capitalization [11]. Tier-1 firms include the largest publicly traded firms, with market capitalizations above approximately US$800 m.These firms, such as Amgen and Genentech, generally resemble large pharmaceutical firms, but the nature of their core technologies, as well as history, place them in the biotechnology category. Other Tier-1 firms, such as Celera Genomics and Millenium Pharmaceuticals, are in much earlier stages of development as integrated firms, but the market believes their prospects to be quite good. Tier-2 firms range in market cap from approximately 125 - 800 million US dollars. These firms usually have overcome the early stage challenges of successfully proving the potential of their technology platform, in most cases having products on or near market stage. Almost all of these firms accomplish their trials, distribution and marketing functions through alliances with established pharmaceutical and/or tier-1 biotechnology firms. Even firms with half a billion-dollar market capitalization lack the breadth and depth necessary to bring new drugs to market on their own. Tier-3 firms have made it to the public markets and have gained enough success to achieve market caps between about 20 and 125 US million dollars. These firms may have promising technology platforms, but they are further away from being able to bring drugs to market. Evidenced by the volatility of biotech shares, firms migrate between tiers based on general biotech market conditions, but more often based on milestone announcements. These announcements usually pertain to the status of drugs in the development and trial pipeline, as well as major firm alliances though many of them may not come true. While many tier-2 and tier-3 firms aspire to elevate their status, some end up being acquired. In June, 2001, Celera Genomics acquired Axys Pharmaceuticals for US$173.4 m in

a stock swap in order to accelerate its transformation from a genomics firm to an integrated pharmaceutical company.

3.3. Network Formation Dimension

Three network formation dimension factors--- network economics, competency and market structure---influence the biotechnology-pharma industries, but they do so in differing ways, depending on the sub-segment of the industry.The preponderance of biotech alliances pertain most directly to the competencies category, where firms ally to leverage complementary competencies, such as a small firm's new target drug discovery platform and an established pharma company's clinical trials competency. Most of these biotech-pharma alliances fall into the interface between competencies and market structure, due to the additional value provided by major pharma companies' established distribution channels. Depending on perspective, a purely distribution alliance could fit either on the interface between competencies and market structure, as suggested in this example, or only as part of the market structure category. However, in portions of the biotech value chain where information plays a central role, such as in bio-informatics, genomics and proteomics, network economics factors help incentivize a network strategy [12]. To illustrate how each incentive might impact the evolution of firm networks within an industry, we only need to trace the early history of the American biotech-pharma industries [13] --- in view of its pioneering leadership and precursor of worldwide evolutionary industry development.. Previous alternative explanations of alliance formation such as asymmetry of investment markets or intellectual property flows seem to support this comprehensive incentive structure [14]. Also the link to innovations could be part of a network strategy as it will generate dynamic efficiencies in R&D intensive industries [15], here giving rise to pharma-biotech increasing returns mechanisms [16].

3.4. Evolution of Alliances

The evolution of networks of firms within and between the pharma and biotech industries over the past fourty years illustrates not only the transformative power of the factors addressed by the Network Formation Dimension (NFD), but also their changing nature over time. NFD factors play varying roles, one dominating over a period, to be superseded and/or complemented by other factors as events unfold. Recognizing these ‘strategic inflection points’, as laid out by A. Groves [17] for Intel, suggest when network strategies can be most effective, and in what form. Surveying the history of the pharma and biotech industries since World War II uncovers four primary inflection points in the evolution of network strategy in these industries, as in Table 4.1:

Table 4.1. Four Critical Events that Shaped the Pharmaceutical & Biotechnology Industries

1. The wide-spread production of penicillin for the War effort, and birth of the modern pharmaceutical industry immediately following World War II;
2. The Thalidomide (‘Contergan’) Crisis of the mid 1960s, which led to the expansion of FDA regulation of drug development, trials and marketing, in terms of risk and safety profiles
3. The success of early biotech products, human growth hormones and human insulin, in the 1980s;
4. The advent of the Human Genome Project (HGP).

The first factor, the US government contracted large--scale production of drugs for the War effort, underscores the government's role in disseminating knowledge and enabling investment in capabilities, encouraging the emergence of the contemporary pharmaceuticals industry. While this event did not necessarily engender corporate alliance formation, it exhibits the importance of the public/private partnership that led to the birth of one of our most important industries. The Thalidomide Crisis of the early 1960s led to the rapid expansion of government regulation of all aspects of the pharmaceuticals industry, reinforcing regulatory scrutiny, impacting the market structure [18]. The success of early biotech products in the early 1980s initiated strong incentives for the formation of pharma-biotech alliances based on the need for firms to share complementary competencies. The advent of the Human Genome Project initiated a strong network economic influence to the evolution of these industries. Each of the four factors influenced the nature of governance decisions within the pharma and biotech industries.

During and following World War II, the expansion of pharmaceutical research and production capabilities arose as a result of the US. government's efforts to provide antibiotic production for the military. These defense expenditures vastly expanded the resources available for research, development and production of new drugs.

Concurrently, early life sciences technologies, such as chemistry, biochemistry, microbiology and fermentation, began to emerge as viable development and production processes for a wide variety of products. By the late 1950s, early pharmaceutical research was characterized by extensive university-centered efforts, funded in large part by US, European and, later, Japanese governments. The early pharmaceutical companies such as Merck and Pfizer provided further resources to commercialize the results of laboratory research, scale-up production processes and market these new therapeutics. These early private sector/academic collaborations look primitive compared with arrangements of the late 1990s. The magnitude and depth had transformed substantially.

Until the early 1960s, it was still possible for a small pharmaceutical firm to emerge from university or government lab research and successfully develop and market products as a stand-alone firm. Alliances were very rare, normally existing in the form of intellectual property licenses and manufacturing contracts, where larger producers would provide scaled-up production capabilities and access to distribution and marketing channels. These alliances between emerging and more established pharma companies tended to be less integrated than those of the late 1990s. Moreover, it was possible for small and mid-sized pharmaceutical companies to succeed in developing and marketing therapeutics as independent firms. By the

1990s, it was virtually impossible for any firm, beyond the most established and well capitalized, to bring a drug from research to market on its own. What had occurred in the interim?

The Thalidomide Crisis and Industry Consolidation

Between 1957 and 1961, three German, British and American firms introduced a new drug, Thalidomide, for approval to the authorities in the three major pharmaceutical markets, the US, Europe and Japan. Thalidomide had been shown to be highly effective in the treatment of morning sickness in pregnant women. While European and Japanese regulators approved the drug, US regulators withheld approval. Frances O. Kelsey, at the time a new FDA medical officer, led the team that rejected the drug's application. When the FDA received the application in 1961, as Kelsey explained in a conference on thalidomide held by the FDA in 1997, the new drug application (NDA) process was quite different than after the crisis:

> 'Many of the studies in support of new drugs were written really more as promotions than as scientific studies. The ground rules in those days were that after an application had been submitted and filed with the agency, the agency had 60 days in which to decide that the drug was safe for the proposed use or uses. There was no requirement for efficacy, and this of course was one reason why the applications were so much smaller' [19].

After a few years of successful sale of the drug, in some cases over the counter in Britain, the healthcare community began to recognize a substantial increase in birth defects correlated with the use of thalidomide. Soon after, the drug was pulled from the market. Aside from the devastating impact on the families who endured the crippling effects, the most significant long-term impact of this crisis was to pressure government regulators to increase the rigour of the therapeutics approval process by orders of magnitude. The Kefauver-Harris Act, passed in October, 1962, required both proof of safety and proof of efficacy for NDAs. The FDA dramatically changed its procedures and requirements for applications as a result.. Other developed nations followed suit over the following years, and because of recent concerns on drug safety the issues have reemerged for the FDA.

By the mid 1960s, only large firms could afford the animal and human testing required by the FDA to bring new drugs to market. As a result of this expansion and deepening of regulatory control, the pharmaceutical industry underwent a period of steady consolidation between 1963 and the late 1970s as firms merged, were acquired, or went bankrupt. The incidence of alliances or cooperative agreements between large and small pharma firms also decreased to near insignificance. The remaining pharmaceutical firms found that they required substantial control of the drug R&D process, in order to pass the stringent, time - consuming and costly requirements of federal regulations.

Effectively, the smaller players had been regulated out of the market. Between 1965 and 1970, not a single small pharmaceutical firm emerged as a major or even mid-sized player as a result of its own internal growth. M&A activity remained rapid until the late 1970s, when the pace slowed. This process of marketplace consolidation through firm integration occurred as a result of the market structure factor of regulatory change. The regulatory change

triggered by the thalidomide crisis led to a fundamental shift in the network structure of the industry. Firms that failed to drive consolidation were merged, acquired or forced out of business. By the 1970s, accepted industry wisdom asserted that the development of new pharmaceutical firms was highly unlikely, because of high barries to entry, due to the massive investment and long lead-time required for success. The last new successful pharmaceutical firms had been founded in the 1950s, Syntex and Marion Laboratories, prior to the Thalidomide Crisis. Nonetheless, radically new technologies developed throughout the 1970s would eventually lead to the emergence of new pharmaceutical players enabled by a new collaborative model of competition.

Genentech and the Emergence of a New Alliance Culture

Coincidentally, as the industry continued to coalesce around fewer, more massive firms, substantially new technologies began to emerge from university laboratories. Since the discovery of the double helix structure of DNA by Watson and Crick in the 1950s, and the explosion in basic life science research during the 1960s and 1970s, a number of new DNA-focused technologies arose from within government and university research labs. Despite significant progress in the lab, by the mid 1970s none of these new DNA-based technologies had yet produced marketable products. Researchers required assistance from established pharmaceutical firms in order to fulfill FDA regulatory requirements, develop scalable manufacturing capabilities, and market and distribute new therapeutics. Unfortunately, established pharmaceutical firms were skeptical, and few extended the capital or expertise necessary to help commercialize any of the new DNA-based technologies. The industry continued to focus on the established, 'hit-and-miss' approach of the chemical manipulation of molecules as the primary source for new drug candidates, a sort of 'trial-and-error innovation'. As Comonor [20] reported on the R&D path of the pharma industry during this time much of research in drug discovery was empirical, not systematic, i.e. drug discovery ' arising from a search, more or less informed., among many possibilities', a process much akin to new discoveries in the chemical industry but with new tools originating from 'computational explorations' [21]. The research, development and manufacturing requirements of the "new" biotech required a very new approach, and none of the established players were willing to take the risk. In retrospect, this decision appears shortsighted, but we must recognize the significant time-to-market predicted at the time for most of these opportunities. In many cases, industry experts did not even consider many of the new technologies likely to succeed commercially, if at all. Nonetheless, had pharma companies allocated even a small portion of their R&D budgets to a portfolio of these forward thinking projects, they might not have encountered the "catch-up" condition in which many firms found themselves by the mid-1980s.

A critical event that presaged and introduced the contemporary pharma-biotech alliance culture occurred in 1978 with the announcement of a major research contract between a young biotechnology firm, Genentech, and the US pharma giant Eli Lilly. Genentech emerged out of Herbert Boyer's work with DNA at the University of California, San Francisco (UCSF). While a detailed history of Genentech would be outside the scope of this section, the important points regard the challenges Genentech encountered developing the early alliances necessary to bring products to market. Over the past few decades, UCSF has

gained a reputation as one of the premier life sciences research laboratories in the world. By 1976, the Boyer team's work on recombinant DNA (rDNA) had achieved success sufficient to encourage Boyer and his partner, Robert Swanson, a Silicon Valley venture capitalist, to found Genentech. [22].

The challenge for the company early on was to choose technological paths such that the firm could eventually introduce marketable products, a major departure from the university lab environment. This also meant finding financial backers willing to back unproven technology. Venture capital provided some of the required capital, but which products to pursue? It was not at all clear which products could be most efficiently commercialized with rDNA. Additionally, the young company received very little attention from the established US and European pharmaceutical firms. The Genentech team itself was unsure what alternative protein products they should pursue that would have both high commercial potential and scientific viability. Despite much effort, Swanson and Boyer were having limited success with US and European firms. At this juncture in 1977, Swanson and Boyer began prospecting for partners and financial support amongst Japanese pharma firms. The Japanese firms awash with money for investment at that time had not developed internal R&D capabilities competitive with their US and European counterparts and had found it difficult to enter the market with new, patent protected therapeutics. In most cases, Japanese firms had not been successful in expanding beyond distributing drugs developed by foreign partners, primarily to their home market, or marketing generics [23].Close relationships with a number of Japanese pharma firms over the prior decade were developed to arrange substantive meetings with Genentech. Over a two-week period, the team met with 26 Japanese pharmaceutical firms. Within the year, Genentech had arranged capital investments and development partnerships with a number of Japanese firms including Toray and Kyowa Hakko Kogyo, eventually providing over US$14m in research contracts. The individual leading Toray's life sciences operations, Koichi Kato, had a reputation within Japanese industry, government and academia as an innovator, and had already been considering rDNA as an emerging opportunity. He was an “innovative mind who immediately recognized the promise of what Genentech had to offer.” [11]. These firms recognized Genentech's emerging technology as an opportunity to stake early claims on a potentially useful and valuable technology platform. From Genentech's perspective, the contracts provided much needed capital and additional research direction. In terms of the Incentive Taxonomy, Genentech's Japanese partners hoped to leverage Genentech's new drug development competency to bring new proprietary, higher value added products to market.

Supported by these contracts, Genentech continued to vigorously pursue the support of US and European firms. The Japanese contracts, while important at that early stage, were insufficient to create substantial validating news for Genentech. The young firm still needed an agreement with a leading pharmaceutical firm in the U.S. and Europe in order to drive acceptance within the industry of its developing capabilities. Early on, in 1977, Genentech developed the brain hormone somatostatin as the first useful protein to be produced by recombinant DNA(rDNA) technology, hailed by the National Academy of Science as a ‘scientific triumph of the first order’, and in 1978, human insulin as the only recombinant DNA product. After initial development, the firm was able to acquire an agreement with the Swedish firm, Kabi (that later became Pharmacia&Upjohn and then Fresenius-Kabi) for the development of an rDNA-based production of human growth hormone (hGH). Based on proofs of principle in the laboratory, but not actual production of any hGH, Kabi provided

research funds, stipulating that Genentech must be able to produce hGH through its rDNA process within 24 to 30 months from April, 1978. Genentech accomplished this milestone within seven months of this date. At this point, however, production of hGH remained at the laboratory level. The Genentech team significantly underestimated the challenges of scaled up production. In addition to the problems inherent in any scaling up of a laboratory process, scaleable production is a consistent challenge for pharmaceutical firms. It is often difficult to know demand for a new drug prior to market introduction. A blockbuster requires substantial production capacity, which is difficult if not impossible to bring online on short notice. Genetic engineering based technologies presented a new problem. It had never been executed before on a commercial basis; moreover, accomplishing rDNA production of products at the commercial level necessitates a number of complementary technologies, including fermentation, purification and complex analytical methods. While each of these technologies had existed for sometime prior to the commercial production of hGH, they all required adaptation specific to each new product application. Moreover, none of these techniques had been used to that point for scale production of rDNA based proteins..

As described in detail by McKelvey in Evolutionary Innovations, development of large-scale production posed more substantial challenges than either Genentech or Kabi had anticipated [24]. The two firms were only able to accomplish commercial production after significant, long-term cooperative development, including frequent interaction with members of the general research community. McKelvey explains:

> 'Interactions among specialist researchers corresponding to specific parts of the system helped identify challenges as well as the direction of knowledge-seeking activities. There were a number of specialist groups inside the firm who were organized to work together on the system, but each group was in turn a larger community of specialists in other firms and in universities. They could then draw on established knowledge available in the community' [24].

For example, Genentech's fermentation expert, Norm Lin and his counterpart at Kabi, Björn Holmström, worked closely together to commercialize the hGH production process. During the early stages of the partnership, fermentation was accomplished at Genentech in California, while Kabi purified the result. While this had something to do with regulatory restrictions in Sweden over scale production of rDNA products, Lin asserted that the primary justification for this division of labor was the two firms' complementary competencies. While collaboration helped both firms accomplish their common objectives, they also endeavoured to acquire each other's competencies relevant to their respective long-term objectives. Genentech hoped to develop a broad based, relatively standardized set of production technologies for future rDNA products to leverage across other product initiatives. Kabi endeavoured to enter the field of rDNA drug research. The alliance worked quite well while the two firms worked out the details of the science, commercial production and quality control of hGH. By the time the firms neared pre-clinical and clinical testing stages of the regulatory processes, each firm required much larger amounts of hGH. The two firms stopped collaborating, aside from their agreement to divide the world market, with Genentech exclusive in the US, and Kabi elsewhere. Kabi began sourcing its fermented hGH product from a British laboratory until it could begin production in Sweden, while Genentech accomplished the necessary production.

Effective collaboration between Kabi and Genentech was certainly not the only factor involved in the success of the hGH product; however, another, faded case bolsters the argument that effective competency-based collaboration had been vital. During the late 1970s, the Danish pharma firm Novo Nordisk had decided not to pursue rDNA technologies for human insulin production partly because they were working on improving traditional extraction methods. rDNA presented a disruptive technology for Novo's R&D efforts and product lines, and as such delayed their involvement in genetic engineering approaches to producing marketable products. In 1981, after Genentech and Kabi's success became clear, Novo allied with the Swiss-American biotechnology firm, Biogen, to develop a genetically engineered microbial expression system for insulin. Despite having the scientific competencies necessary to succeed, Biogen proved unable to make the science work in practice. The Seattle-based firm ZymoGenetics ultimately accomplished this task for Novo, after which Novo acquired the firm. McKelvey comments on the Biogen case then

> 'Biogen's failure to make the techniques function indicates that knowledge competencies alone do not suffice. Techniques and practice are as important as knowledge for technological activities. The requirement that technology functions in practice and not just theoretically applies as much to genetic engineering as to machinery'[24].

Biogen had the scientific know-how, but could not translate it into practice. This case contrasts with the close collaboration between Kabi and Genentech in which the two firms successfully overcame substantial challenges. Collaboration was certainly not the only factor, but the breadth and complexity of the complementary technologies necessary to accomplish rDNA production of hGH required a combination of a number of complex competencies. When introducing products based on complex technologies to market, firms often must source competencies from outside firm boundaries. Rarely do single firms have all of the technological capabilities necessary to introduce such products completely on their own. This condition is particularly true with substantially new, developing technologies. Genentech and Kabi were able to bring rDNA produced hGH to market more quickly in alliance than in competition. In fact, Kabi did not own the necessary rDNA patents, and Genentech lacked a developed production competency of any sort outside the laboratory.

Kabi's incentive for collaboration involved the fact that the only source for hGH prior to the introduction of rDNA had been harvest and extraction from the pituitary glands of human cadavers. The demand for hGH far exceeded the available supply, and Kabi found itself with a growth constraint on a significant product. rDNA provided an answer, and Kabi had the incentive to take the risk. Despite the importance of the Kabi contract for the nascent Genentech, the relationship was not considered particularly significant from Wall Street's perspective. Kabi was a minor player with limited visibility outside Europe, and the agreement involved the development of an unproven process to produce a relatively minor product. From Kabi's perspective the alliance was of limited value unless Genentech could deliver. Unlike later high visibility pharma/biotech alliances, the markets paid little attention to Genentech's initial alliance announcements of the US market for insulin, worth a total of US$155 m, Europe and the rest of the world accounted for another US$200 m. Its closest competitor, Novo Industri, had only about 30 percent of the worldwide market. Nonetheless, in contrast to Genentech's contract with Kabi, Lilly was unwilling to invest in an alliance until after the rDNA technology was proven. Concurrent with its discussions with Genentech, Lilly

was investigating several alternatives to Genentech's approach to insulin production. In fact, Lilly had been supporting rival scientific teams, including former colleagues of Boyer's at UCSF. A year prior to the signing of the contract between Lilly and Genentech, the UCSF team received a commitment estimated at US$1.3 m over five years. In return Lilly received right of first refusal for any technologies developed by the UCSF team. Lilly also attempted to acquire a similar arrangement with the Harvard professor Walter Gilbert, but Gilbert committed his technology to his own firm, Biogen. The risk that Genentech would successfully introduce rDNA based production of insulin with another partner was not a sufficient threat for Lilly to bet on an unproven technology.To Lilly's benefit, there were very few major pharma firms willing to consider such an investment risk. It even shows today that Lilly is the only big pharma corporation today with a sizable internal biotech activity and in that respect well ahead of its rivals. Lilly's only major competitor in the insulin market, Novo, never expressed interest.

Thus, Lilly pursued a strategy of attempting to tie up all potential alternative methods for rDNA development of insulin, increasing the likelihood of success. Certainly, such “diversity is beneficial but expensive” [24]. Lilly could have limited investment costs by following one promising path, but the likelihood for success would have been much lower. Within the context of Lilly's entire R&D budget, the cost of this diversified strategy was not that great. Moreover, Lilly was attempting to block competitors' access to the new technology. Tellingly, of the three primary teams involved in the development of rDNA for insulin production, Lilly was least eager to contract with Genentech, ultimately the most successful alternative. Lilly invested research dollars with the UCSF team, actively pursued Gilbert's group at Harvard, and avoided committing to Genentech until after it had proven its technology effective. Nonetheless, Lilly maintained communications with Swanson and Boyer, and signed a research contract with Genentech on August 25, 1978, one day after the firm completed its confirming experiments [25]. The firms have kept the dollar value of the contract confidential, but it is clear that Genentech agreed to transfer the micro-organisms capable of producing insulin, related patent rights and know-how in return for research fees and ongoing royalties of 8 percent of Lilly's human insulin revenues. This agreement set a precedent for future alliances between large pharma and small biotech.

Even after the announcement of the Lilly contract, most large pharma companies continued to ignore biotechnology as an emerging field for substantial investment. Some established pharma firms devoted minimal resources to exploring developments in the field, but direct investment remained modest. Exceptions included Hoffman LaRoche (Roche), which provided research money to Genentech to develop rDNA derived somastostatin and alpha and beta interferon and most recently the anti-cancer blockbuster drug Avastin [26] and Schering-Plough, which contracted with another early biotech firm, Biogen, for production of alpha interferon. For their part, Genentech and Lilly encountered greater than anticipated resistance to regulatory approval of their new product. This all changed in late 1982, when Lilly received FDA approval for rDNA produced human insulin, the first genetically engineered product to reach the market. Genentech's and Kabi's hGH product encountered even more regulatory hurdles, receiving FDA approval only in October, 1985. Ultimately, the two firms benefited substantially from rDNA produced hGH. hGH became the first product to be manufactured and sold by a biotech firm when Genentech marketed the drug under its exclusive rights to the US market. Both rDNA produced hGH and insulin became enormously

successful products, each well surpassing US $1 b in annual world-wide sales across all producers by 1995.

Finally, other pharma firms began to take note. Here were two products that, since their introduction to the marketplace decades prior, had only been produced through highly constrained, living sources. Genentech's rDNA technology relied on bacteria to replicate each product, providing supply to meet market demand. Most pharma firms found themselves caught flat-footed, unprepared to compete in this new arena. R&D structured around traditional chemistry-based approaches was largely incompatible with research focused on DNA and living organisms. Moreover, pharma companies began recognizing that their traditional methods of drug discovery and development were not filling their pipelines quickly enough to satisfy their bottom lines and financial investors. Each blockbuster drug accounts for hundreds of millions or even billions of dollars of annual revenues. When a drug comes off patent protection, the introduction of generics not only impacts margins, but also decreases the magnitude of a firm's revenues from the product. The probability of drug candidates becoming marketable products being quite low, firms must discover and pursue thousands of candidates each year. While recently emerging techniques and tools provided by genomics and bioinformatics are improving the odds of pursuing fruitful paths, these technologies did not exist or were of limited applied value to pharma firms during the 1980s. Bioinformatics and computational molecular biology and systems biology have been a more recent alternative response to replenish dried drug pipelines.

Biotech firms offered a solution to the drug discovery bottleneck. Many large pharma firms began investing in a re-orientation of their R&D operations during the late 1980s, but this process inevitably required substantial time. There is an onerous time compression barrier to entry with regards to substantial redirection of a firm's R&D program and structure. In almost all cases, firms cannot fundamentally re-direct an R&D program in a short period of time, without employing M&A or cooperative agreements with firms already possessing the desired capabilities. This was particularly true in the transition from molecular chemistry to emerging technologies based on DNA. Although much uncertainty continued to characterize biotech investments during the 1980s, large pharma players could no longer afford to operate without a biotech strategy. Some of the new therapeutics under development had the potential to obsolesce existing drugs. Such has been the case with Biogen IDEC Pharmaceutical's drug Rituxan, a monoclonal antibody treatment for cancer introduced to the market in 1997 which has in many cases replaced previous chemotherapy treatments for non-Hodgkin's lymphoma [11], or much more recently with Genentech’s Herceptin for breast and Avastin for colorectal cancer.

While the transformation of the pharma industry during the 1960s and early 1970s occurred largely as a result of market structure issues, the birth of a substantial alliance culture within the industry arose as a result of the interface competencies and market structure incentives. This first wave of biotech-pharma alliances occurred as a result of the need to combine competencies. The biotech firms offered expertise and patents in areas that might eventually produce substantial new products. The pharma firms had large cash reserves and established expertise and relationships relative to the FDA drug approval process, a regulatory regime that continued to, de facto if not de jury prevent small and mid sized firms from independently accomplishing the new drug approval process. Even today, only the largest biotech firms can navigate the FDA process primarily through internal resources. Most firms rely on large pharma partners. Additionally, the extensive distribution and sales

networks of the established pharma firms provided both a market structure and a competency incentive for the smaller biotechs to ally.

Genentech, Amgen and Biogen are three of the most notable survivors from this early period in the evolution of the conternporary biotech industry. Each of these firms successfully balanced the creation of firm specific and network specific assets. A primary component of their strategies included developing long-term alliances with multiple pharma firms, rather than betting on one primary alliance partner. Each of these firms' technology platforms was broad enough to be attractive to, and flexible enough to accommodate, multiple partners. The breadth of their technology platforms allowed each firm to maintain flexibility as their R&D efforts unfolded, increase their share of the value created by cooperative efforts, relative to more narrowly focused competitors, and retain their long-term independence. Although Roche acquired about 40 percent of Genentech in 1988 and a remainder in mid 1999, they did so after Genentech had created a very strong competitive position and substantial market value. Roche's decision to offer 17 percent of Genentech to the public in July, 1999, illustrated Genentech's continued value independent of Roche. The IPO raised US $1.94 b for Roche. Both Amgen and Biogen have continued as independent, top tier-one public firms as of the writing of this document. All three firms continue to maintain an active network strategy. Despite being majority owned by Roche, as of March, 2000, Genentech continued to manage its own strategic alliances and licensing arrangements with numerous pharma and biotech firms [27]. With such a successful symbiotic relationship between Genentech and Roche one might have wondered why Roche attempted and succeeded to completely gobble up Genentech (DNA) in 2009, presumably to squezze out more its profitable future, with Genentech topping the ranking in the number(and possibly value) of US biotech patents in 2007, and as Art Levinson, the CEO of Genentech remarked that ‘the percentage of Roche drug sales based on Genentech-derived products increased from 21 percent in 2000 to 66 percent in 2008 [28].

Above all, Roche appears to engage in consistent alliance dealmaking in a clear strategic sense to strengthen its product portfolio in the fast growing cancer drug market building now a network with about 75 biotech partners and counting [29,30] setting itself on an alternative path to mega-mergers in the industry [31].

3.5. Genomics and Network Economics

The competencies and market structure dimensions have played the predominant role in explaining the transformation of the pharma and biotech industries' network structure and behaviour. Network economics will add a leading role in this discussion. After the point where an academic-like openness to basic research is no longer essential, research into new therapeutics becomes highly proprietary. Researchers become much less willing to share information, patents are dominant and intellectual property strategy restricts information flow between researchers. This not only applies to research conducted in for-profit settings, but extends to many academic settings as well. As suggested in the introductory discussion of the social nature of knowledge creation, this lack of openness retards intellectual and technological progress. Nevertheless, individuals and firms must be provided an incentive to

innovate, which in almost all cases requires proprietary ownership of intellectual property in some form.

This issue presents fewer problems in the identification and creation of new drugs under the traditional R&D model. Traditional molecular chemistry offers the ability to create a vast number of compounds that firms can investigate and develop as marketable drugs. The fact that another firm owns a patent on a particular compound has limited impact on another firm's efforts. If one firm is aware of the patent, it might decide to pursue an alternative direction. Moreover, once a firm achieves a patent on a particular compound for a specific condition, that firm is reasonably assured of proprietary rights to profit from the sale of the drug, assuming the drug passes FDA muster.

The situation became much more complicated with the introduction of genomics, proteomics, its more complex sibling, and the broader field of bioinformatics and systems biology. As the application of information technology increasingly transforms the drug discovery process from primarily a matter of chemistry and biology to an information-intensive pursuit, as IBM's 'Blue Gene Project' appears to indicate, network economics plays an increasing role. A shift toward 'priority review drugs'against 'standard review drugs' showed an increasing share of new molecular entities (NMEs) at the expense of new chemical entities (NCEs), and reflects the paradigm shift toward biopharmaceuticals [32]. This fact presents crucial implications for the nature of network strategy in the industry. To understand why, we will investigate the relationship between the Human Genome Project, private efforts focussed on the human genome, and the emerging race to understand the proteome.

The United States Government began funding for the Human Genome Project (HGP) in the 1980s, coordinated through the National Institutes of Health (NIH) after years of lobbying by the scientific community. Many sources, academic and popular, provide extensive coverage of the detailed background of the project, as well as the much publicized controversies surrounding the competition between public and private efforts to map the genome. We will focus on the implications of the HGP for the alliance culture and structure of the pharma and biotech industries.

Using genes as targets for new therapeutics existed well before the HGP; however, prior to the availability of an effective gene map, researchers would start from a particular observed pathological condition and attempt to work backwards to identify the culpable gene or genes. This represented an unacceptably slow, cumbersome process.

Since the introduction of technologies capable of accelerating the mapping of the genome and the identification of specific genes related to diseases or pathologies in subjects, the pace of progress has intensified by orders of magnitude. Nonetheless, neither the substantial public investment in the HGP, nor the advance of gene mapping technologies has been enough by itself to encourage the activity witnessed in the field over the past two decades. Certainly, know-how is not enough to create a new private-sector industry, as has arisen with genomics and related fields. Firms must be able to profit from their knowledge.

As the HGP progressed, internal conflict arose between various research entities over the preferable methods for gene sequencing. Craig Venter, a scientist at the National Institutes of Health (NIH) advocated a substantially more efficient, but not widely accepted, technology for sequencing. In fact, Venter had become increasingly isolated by the NIH establishment as a result of his unorthodox views [33]. When he was unable to convince the HGP leadership to adopt his approach, Venter accepted an offer in 1992 from the late W. Steinberg, chairman of the venture fund HealthCare Investment Corporation, to head up a nonprofit research center,

The Institute for Genomic Research (TIGR). With an US $85 m grant from Steinberg, Venter was able to conduct research without interference from the venture fund. In order to profit from the work of TIGR, Steinberg founded Human Genome Sciences (HGS) and in 1993 hired William Haseltine away from his post at Harvard to lead the new company. By mid-2000, HGS had become the largest genomics-based firm by market capitalization. Later, in 2004, it shrank to roughly a tenth of it. TIGR used its grants to sequence the genome, while HGS's mission was to capitalize on TIGR's discoveries. Haseltine's ultimate objective was to eventually build an integrated pharmaceutical firm based on proprietary genomics technology. As Haseltine reminisced more recently, modern medicine and supporting pharmaceuticals are overwhelmingly based on a body's anatomy, not genetics [34], reaching its limits. In order to survive in the near to mid-term, Haseltine and Steinberg approached Pharma firms with the prospect of buying proprietary access to HGS's genomics discoveries over a period of years. Many firms turned them down, such as Glaxo and Rhone-Poulenc Rorer, but the (then) British firm SmithKline Beecham (now Glaxo SmithKline Beecham, GSK) accepted in 1993, providing US $125 m in exchange for 7 percent of HGS and exclusive commercial rights to the gene portfolio.

This represented the largest alliance between a pharma and biotech firm up to that point in industrial history. The announcement encouraged a number of other deals, most notably a US $70 m agreement between Hoffman LaRoche and Millennium Pharmaceuticals.

Venter parted company with HGS in 1997, waiving US $38 m of the US $85 m originally committed to TIGR. Soon after, he founded his own firm, Celera Genomics, in order to focus on sequencing the genome. He announced, to much surprise, that Celera would succeed in mapping the human genome significantly earlier than the publicly-funded HGP. As well, Venter intended to provide the resulting information to researchers in a more open and timely manner than his former partner, Haseltine's HGS. While Venter's firm succeeded in proving the superior efficiency of his chosen approach to sequencing, the entry of private firms such as Celera and Human Genome Sciences introduced a proprietary, competitive dimension to the field of genomics [35]. Clearly, competition from the private sector accelerated the completion of the gene sequencing project. The profit motive also encourages the search for marketable products as a result of the genome project, benefiting consumers and the economy in the long run; however, the search for profits encourages firms to maintain proprietary ownership of new knowledge. As such, they often attempt to pursue new knowledge without the relative openness of most academic or public research. A look at the next major mapping effort, the human proteome, will elucidate how these new information intensive aspects of the drug development process exert a substantial influence on the alliance culture of the pharma and biotech industries.

3.6. Information and Drug Discovery

Despite the hype and the value of a complete genomics database, the human genome map alone provides an insufficient platform with which to create the next generation of highly targeted and valuable therapeutics. Soon after co-announcing the end of the race with the public Human Genome Project to map the human genome (which ironically both parties celebrated prior to completion), Celera announced substantial new investments in attempting

to map the human proteome. A proprietary understanding of the proteome could arm a competitor with a substantial competitive advantage; however, the task presents a challenge order of magnitude greater than mapping the genome. Rather than simply representing the order of nucleotides, as in the genome, understanding the proteome requires mapping the three-dimensional structure of proteins and the behavior of their structuration with respect to functions and activity. Proteins consist of 20 naturally occurring amino acids. The sequence of these amino acids partly determines the shape and behaviour of the proteins they create. Mapping each human protein independently requires such a long time as to be impractical; however, local structures within proteins, known as domains, reflect consistent behaviour between different proteins. Much like the root structures of ideographic written languages, such as Chinese, these root structures manifest in a relatively consistent manner. Once a domain is identified, that part of the protein structure is considered understood.. Moreover, proteins group into families as a result of common ancestry. As a result, biochemists can predict protein structures of subject proteins based on resemblance to known protein families.

Here is where demand side economies of scale, or network economics, become important., not the least to reduce the uncertainty on scale and dimension of drug discovery [17]. As further explained by The Economist,

> 'Since knowing the structure of one member of a protein family lets researchers guess what others will look like, the most efficient strategy for choosing protein targets should cover as wide a diversity as possible. That is not, unfortunately, what is happening. At the moment, laboratories are competing to work out the same protein structures, rather than collaborating in the way they did to produce the human genome' [36].

The Human Genome Project began as a worldwide, publicly-funded collaborative effort. Mapping the human genome resolved as a competition between proprietary and public rights to genes that offer targets for therapeutics. Celera's proprietary effort benefited from the publicly available HGP database. In the case of the proteome, "the days of happy collaboration... are gone, not least because a lot of money is now at stake. Proteins are drug targets, and some may become drugs in their own right." [36]. As a consequence, many researchers jealously guard the results and methodologies of their protein research.

In the June, 2001 issue of Nature and Structural Biology, a team from MIT, Harvard, the University of Maryland and Millennium Pharmaceuticals reported on its efforts to understand the costs associated with this lack of cooperation among researchers in this proteome effort. They estimate that 16,000 targets would provide enough information to survey 90 percent of all protein domains, if all were widely available. Lacking a coordinated approach, the team reckons an equivalent survey would require "around 50,000 experimental determinations of structure" [37]. The coordinated approach achieves higher efficiency by allowing researchers to target domains for study based on more complete information. The non-collaborative model requires a substantial amount of random target selection. Assuming the ability to define ten structures per week, the going rate, an independent research team could expect to work nearly a century. Even though technology will continue to improve throughput, 'a bit of collaboration would speed things up to end' [36]. Here we see the conflict between proprietary ownership of knowledge and cooperation for the common benefit. Access to an inclusive lexicon of protein domains does not, by itself, enable the development of new therapeutics. There would clearly be substantial common benefit from a coordinated mapping

effort, while the identification of protein function relative to diseases or disorders, and the development of targeted drugs, could be kept proprietary. As by then, open collaboration appeared unlikely, largely as a result of the competition over the results of the human genome map. Barring broad collaboration, cooperation between specific firms and research organizations could present a more effective solution than operating as insulated actors, while maintaining proprietary benefits. The cooperative efforts of the HGP and the associated competition that ensued provide a precedent for building a viable strategy around proteomics. Celera's strategy to leverage its position in genomics to create an integrated pharma company, evidenced by its acquisition of Axys Pharmaceuticals in mid-2001, partly reflects the fact that the majority of the value created by the pharma industry accrues to those firms that successfully develop and market new proprietary drugs. Celera's aspiration to become an integrated pharma company also suggests some concern over the viability of a firm completely focused on providing information to the rest of the industry. Succeeding in the genomics and proteomics space requires a network specific strategy built around a strong core of firm specific resources. All of the major genomics firms by market valuation employ an extensive network strategy, leveraging their proprietary firm-specific resources across multiple firms (see Table 4.2). The value accrued to all increases substantially with the breadth and diversity of minds addressing the application of the new knowledge; nonetheless, all organizations involved must be able to appropriate enough value to justify cooperation.

Table 4.2. Alliance activity of the three top Genomics firms on record as of June,2004

Firm	Market Capitalization	# of Alliances
Human Genome Sciences	US$9.3 billion	34
Millennium Pharmaceuticals	US$8.7 billion	67
Celera Genomics	US$3.0 billion	35

Source: Recombinant Capital Alliance(2004) data together with Wall Street Journal Reporting (2004).

It would be incorrect to suggest that collaboration equates to market performance. Clearly, success in the marketplace reflects numerous factors. Nonetheless, the three genomics leaders as of mid-2001 had each acquired significant partnerships early in their development: HGS's US $125 m deal with SmithKlineBeecham during. its first year of operation, Millennium Pharmaceuticals' US $ 70m deal with Hoffman LaRoche, the 80 percent position of PE Corporation (formerly Perkin-Elmer) in Venter's founding of Celera.

As these firms have matured, they have become able to command increasingly advantageous partnership positions, most importantly appropriating a larger percentage of the value created by their discoveries. Millennium Pharmaceuticals completed deals with Monsanto and Bayer in 1997 and 1998, worth US $343 m and US $465 m respectively. Over the life of the original US $125 m agreement between HGS and SmithKline, the HGS's R&D program produced more medically important genes than the pharma giant could use. The two companies licensed targets they decided not to pursue internally to other firms. SmithKline was able to recover its entire original investment simply through these licensing deals. As a result of this success, HGS has been able to demand better terms from its partners. On June 30, 2001, its original agreements were scheduled to expire, allowing HGS to form new partnerships. Even more important, HGS raised US $1.8 b between June, 1999 and December, 2000. this enables the firm to accomplish the development and clinical trials of

new drugs on its own resources. While HGS is able to maintain a larger ownership of its products than almost all other biotech firms save the largest and best established, even Haseltine seeks partnerships with which to leverage its resources and intellectual property. HGS pursues a broad network strategy, including 24 alliances with pharma companies, other biotech firms and universities listed in the Recombinant Capital database of pharmaceutical and biotechnology alliances.

Celera and Incyte, another prominent genomics firm, originally planned to profit by providing data and data analysis tools to other firms, rather than pursuing their own therapeutics. Following HGS and Millennium's lead, both firms have moved increasingly toward developing their own drug development competencies. Celera's purchase of Axys Pharmaceuticals in June, 2001, provides the most compelling proof of its emerging strategic direction. To some extent, Celera, Milleninum and HGS's relative valuations (see Table 4.2) reflect the substantial challenges inherent in deriving firm-specific value from information that many participants and observers believe should be a communal resource, in this case the human genome. Beyond philosophical arguments and basic science, a complete, widely available map of the genome increases the likelihood of the development of new therapeutics, consumer well being, and the overall profitability of the pharmaceutical industry. The actions of pharmaceutical firms to block genomics firms' attempts to convert the human genome map into a firm specific resource evidence the industry's concern over ceding control of a crucial resource to a single firm. The compelling network economics implications of the genome database, allied with the combined market structure influences of the major pharmaceutical firms, government regulators and the scientific research community compelled Celera in particular to make many substantial strategic changes in course. A robust network strategy might provide the only viable way to profit from the genome database, for which Celera has invested hundreds of millions of dollars. The same might prove true of the proteomics database. The nature of knowledge compels cooperation.

As evidenced by the contrasts between the strategies of major genomics players, there is no single solution to understanding the proper balance between network specific and firm specific resources. The objective should be to achieve the most advantageous sustainable, profitable balance. Firms can co-exist and compete, applying contrasting strategies, as in the case of VISA and American Express in the bank card industry. Nonetheless, any case where network economics exerts a strong influence requires a careful consideration of inter-firm cooperation. HGS relies for a substantial part of its future success on network specific and network flexible resources, even given its financial and intellectual power. The breadth of its collaborations provides strategic options, while the depth of its intellectual property and capital reserves allows the firm to appropriate substantial value from collaboration.

Conspicuously, the introduction of genomics and proteomics to the drug discovery and development process further encourages large firms to seek biotech partners. According to the Industry Standard

> ‘Pharmaceutical companies have begun to realize that matching the breadth and technological sophistication of genetic research ongoing at biotech firms would require a massive, time-consuming internal investment. Machines to decode, classify and interpret genetic information often cost well into the millions of dollars, and recruiting people to run them can be a challenge. Instead of doing it all themselves, large pharmaceutical

companies that once fiercely guarded their privacy have begun crafting long-term and largely equal partnerships with biotech' [38].

By the late 1990s and early 2000s, biotech firms perceived likely to enjoy success were able to pursue agreements with pharmaceutical companies on much more advantageous terms than had been previously possible. The introduction of information intensive technologies to drug discovery proved different enough from traditional methods that the large drug makers were compelled to seek partnerships rather than build the competency internally.

To the future, it will be important to monitor the extent to which big pharma successfully acquires genomics and proteomics players and competencies, as opposed to remaining allied with independent genomics firms, as well as the extent to which the industry creates information sharing capabilities. Traditionally, the pharmaceutical industry has been averse to sharing information between companies. The collaborative nature of knowledge creation has compelled the industry to place more emphasis on R&D efforts outside the boundaries of the individual firm. In perhaps the most compelling example of pharma-biotech collaboration over genomics, in January, 2001, Bayer, the German pharma giant, allied with the U.S. genomics firm CuraGen in an effort to discover drugs targeting obesity and diabetes. Worth US $1.34 b, the deal redefined "mega-deal" within the industry, and, most notably, included an agreement to split profits from products developed roughly 50-50. Whether Bayer overpaid for this relationship can only be determined as the relationship progresses; nonetheless, the agreement suggests the increasing bargaining power of genomic s firms.

3.7. Recent Pharma and Biotech Alliances

As the biotech industry expanded their product pipeline in the US [39],alliances continue to proliferate through the early 2000s, a very recent spade of activities centering around RNA chemicals, involving Roche, Astra Zeneca, Merck and Bayer, cover alliances with biotech platform providers or biopharmaceuticals [40]. Some equities analysts suggested consolidation might ensue in biotech, which dominated the pharmaceutical industry in the late 1990's and early 2000's, but the creation of new firms has far outstripped any consolidation [2]. The diversity of research and technology platforms encourages the use of alliances as a preferred mechanism over internal development. A very good example in this regard is the Roche Holding which uses partnering and licensing to strengthen its overall product porfolio around a defined set of its perceived core competencies [29] Even the largest and best financed pharma companies cannot afford to pursue all, or even most, emerging technology platforms through in-house R&D. Moreover, big pharma cannot afford to be left out, in the event that an emerging technology proves to be a major marketplace winner. A single technology platform may be able to turn out numerous drugs over a period of years. These new drugs could potentially be used to treat diseases in competition with a firm's existing products. Even a large pharma firm can require many years to recover from the loss of a major drug. Bringing a new drug to market requires upwards of 10 - 15 years from concept to revenue. Even after a new therapeutic enters clinical trials, the likelihood of the drug reaching the market remains low. As a consequence, the success of big pharma firms requires a deep and diverse pipeline of new drugs.

Most of them plan to achieve this through mergers with some questionable results to date [31]. The renewed consolidation of the pharma industry during the 1990s and early 2000s has occurred to a great extent as a result of the need to expand drug development pipelines. As problems with drier drug pipelines proliferate across the industry it appears that pharmaceuticals based on chemical combinations have failed to produce significant product innovations in recent years. It shows that in 2006 the US pharma industry received FDA approval for just 18 new chemical based drugs, down from 53 only 10 years ago [41]. One of the more recent factors for such a slowdown is possibly enhanced public scrutiny of drug safety issues as recently encountered by Merck and Pfizer among others. These events have raised the stakes for pharma companies to ensure the safety of their products. On the other side, the biotech industry is also concerned that regulatory and legislative reaction to these events could reverse the significant reduction in FDA approval times that has been achieved since the 1992 enactment of the Prescription Drug User Fee Act (PDUFA) which allowed speeding up the process of high priority drug applications.

Filling the pipeline through acquisitions of other pharmaceutical or biotech firms has not been enough, even as many merged firms have been seeing their pipelines become even drier, prompting a leading Economist article claiming 'Big Pharma needs a new Business Model' [42]. In fact, the acquisition of biotech firms by large pharma companies tended not to be very effective. As Robbins-Roth [11] explored in his book, acquisitions of biotech companies by large pharmaceutical firms just don't work. He cited the substantial differences in culture and approaches to R&D between large firms and their smaller counterparts that impede the innovative advantages of smaller firms. In retrospect, an exception may be Genentech, acquired by Roche in two transactions between 1990 and 1999 and recently accomplished itscomplete acquisition of Genentech (DNA) (against strong headwinds from Genentech's board) in March 2009. Genentech is filling up Roche's drug pipeline with a couple of promising cancer drugs Avastin and Herceptin [26]. In this case, however, Genentech was already a well-established, large organization before acquisition, and Roche has provided Genentech with substantial freedom, to the extent that 17 percent of Genentech was publicly traded. For the record of science business, American Genentech is the source of inovations for those drugs (the originator) and Swiss Roche the financial investor and drug distributor.

The overall commercial success of the Roche-Genentech model points to a tentative implication that strategically a broad based platform portfolio and shift toward biopharmaceuticals could help in replenishing drug pipelines and effective risk management with the added advantage that those would be less prone to generic reproduction. This approach is also more likely to come to grips with increasing safety concerns and regulatory scrutiny of drug approval which lead to larger and therefore higher cost of clinical trials [43].

The European biotech sector, in general, is lagging in strategic alliance and M&A activities because of earlier stage product cycle and smaller size though by 2005 the sector has a flurry of initial public offerings (IPOs)(23 v. 13 in the US,2005). But there are stark differences within Europe. The UK and Scandinavia having the largest share of alliances, Switzerland playing a special role being the home of Novartis and Roche, two of the world's leading pharmaceutical companies [44]. Novartis claims to manage hundreds of alliances with diverse biotechs and academic centers (for example, Morphosys, Myogen, Xenon, Cellzome AG), over the past years it has continously expanded their drug pipelines to cover 25 percent biologics, as well as it has their bottom line to embrace generics (Hexal). German Evotec and Roche form a global alliance to jointly discover novel drugs, and Roche has a large network

of global alliances, increasingly with European biotechs. The typical agreement (as with Evotec) involves joint projects up to clinical development, at which stage Roche will have exclusive rights to the development of drug candidates. The biotech will be eligible to receive upfront milestone payments plus royalties on the sale of any products.

It is even much harder to make assessments on alliance formation in Japan, given the fragmentation of the industry over an extended period and its relation to the pharma companies. Even as of today Japanese pharmaceutical companies remain small by global standards. So when two Japanese drug makers, Yamanouchi and Fujisawa, had a recent merger (now Astellas) that would rank globally in sales only 17th even when they were Number 2 (after Takeda Pharmaceuticals) in Japan [45].

Market analysts identify the breadth and depth of firm pipelines as one of the most important valuation factors for pharmaceutical firms, along with the projected value of existing products and a firm's ability to navigate the FDA regulatory process. The proliferation of pharma firms allying with other pharmas and, more prevalently, with biotech firms, reflects the need to keep pipelines full. Consequently, equities analysts pay close attention to the quality of pharma firms' alliances (46,2]. Roland Gerritsen van der Hoop, vice president of clinical operations at Solvay Pharmaceuticals, a US-based firm, comments that, “Any pharmaceutical company that wants to maintain its presence needs to both supply new compounds from its research pipeline as well as actively look for in- license candidates” [47]. The president of R&D for Pharmacia Corporation (now Pfizer-Pharmacia) explained that over the last several years, “basically all of our R&D growth has been external.... In 1995, our external research budget was 4 percent; in 1999, it was 21 percent” [48]. Sidney Taurel, the former CEO of Eli Lilly reported a similar figure of 20 per cent of total R&D expenditures for its external R&D investments. According to a study by McKinsey & Company, 14 of the 55 drugs categorized as blockbusters were acquired through some form of licensing arrangement [49]. The same study found that for the top 10 U.S. pharmaceuticals firms in 1998, revenues from products developed externally and licensed to the firm increased from 24 percent in 1992 to 32 percent in 1998. This translates into a 15 percent compounded growth rate, compared with a 9 percent compounded growth rate for internally developed drugs. The study predicted that 35-45 percent of typical firm revenues will derive from licensing arrangements by the year 2002. From the perspective of biotech firms, many of these partnerships are working. Recombinant Capital, an industry consulting firm, reports that earned revenues for 100 pre-commercialization biotech firms they track totaled US$ 5 b between 1997 and 1999.

While all large pharma firms engage in externally focused R&D activities, the level of external R&D varies. Merck represents a major firm that has traditionally focused its R&D efforts in- house. While its strategy has helped create the world's largest pharmaceutical company with revenues ofUS$ 40 b in 2000, in 2001, the company has encountered increased uncertainty over its ability to continue to fill its pipeline predominantly through internal development, and in 2004 ended up with a dry pipeline. In early 2001, Merck hired Professor Peter Kim from MIT to lead its research efforts, which includes 6,500 research professionals. Merck has avoided mergers with other large pharma, licensing drugs from smaller firms, and copying blockbuster drugs of its competitors, all standard strategies to build a strong pipeline. As from 2001, even more so in 2005, Merck had a “pipeline problem”. Five of Merck's best-selling drugs come off patent protection in 2001, probably eliminating between four and six billion dollars in annual revenue and most analysts doubt that there are any blockbuster drugs in the firm's pipeline anywhere near market-ready. While Merck sources technology and

development externally, the firm suffers from a bit of the "NIH" (Not Invented Here) syndrome.

As of the end of the 1990s and early 2000s, the large pharmaceutical firms faced a condition known by a number of observers and insiders as the blockbuster quandary [50]. Throughout the 1980s and 1990s, large pharma had increasingly structured its R&D, marketing, sales and distribution efforts around the development and introduction of blockbuster drugs. These large firms had become so reliant on high grossing drugs that they were often unwilling or unable to pursue drug targets representing good opportunities with small to mid-sized market potential. One way to attempt to ensure a large market potential for a new drug is to target chronic conditions affecting a large population of potential patients; however, a limit exists to the number of such ailments capable of supporting a drug with blockbuster revenues. The number of potential blockbusters in the pipelines of the large firms appears to limit the susrainability of growth on this basis alone. A few smaller, emerging pharma firms have structured their efforts around niches within which they could pursue these high margin, smaller market drugs. Allergan, the eleventh largest U.S. pharma firm by revenues in 2000 represents an example.Validating the severity of the situation, the massive European pharma firm Novartis announced in 2001 its intention to re-organize in order to allow the firm to pursue a greater number of midsized market opportunities in an attempt to offset the need for continual introduction of blockbusters, it also pursued toward diversifying further into generic drugs. The firm intends to organize itself around a number of specialties, much as Allergan has done with ophthalmologists and dermatologists.

In terms of the incentive taxonomy, the blockbuster quandary represents a manifestation of a Market Structure motivation for inter-firm relationships. Novartis not only intends to leverage its new structure to pursue R&D in-house, but also to ally with related biotech firms in the development of drugs serving markets with more modest revenue potential. In essence, Novartis is attempting to create an internal structure mimicking a number of smaller, more flexible firms with different economic requirements for knowledge creation and new products. Allying can mitigate the risk of pursuing targets with smaller revenue potential, enabling large pharma firms to overcome the quandary. Allergan has leveraged its relatively small size (nearly US $2.0 b ytd, June 30, 2001 revenues) by licensing drugs for niche markets that its larger pharma brethren cannot efficiently market. Johnson and Johnson(J&J) and Pfizer have both provided profitable drugs to Allergan under such conditions. Conversely, when Allergan introduced Ocuflox, an antibiotic for eyes, they partnered with Johnson and Johnson to access J&J's sales and distribution network with pediatricians, a segment of the healthcare community in which Allergan has not established its own sales network.

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Chapter 4

ALLIANCE PROPENSITY OF BIOTECH-PHARMA: AN EMPIRICAL PERSPECTIVE

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" … it is evident that the underlying forces driving biotech and pharma companies deals show no signs of subsiding…" Ernst and Young, Beyond Borders, Global Biotechnology Report 2007

ABSTRACT

Based on the conceptual framework in Sect. 3., an empirical examination of the relationship between collaboration rate and market performance of major globally operating pharmaceutical firms is conducted. Case examples, supported quantitavely and qualitatively, provide evidence for the efficacy and market implications for the network dimension.

4.1. COLLABORATION AND MARKET PERFORMANCE

The search for new drugs requires massive long-term investments in R&D. Because of the unpredictability of innovative activities, drug firms build broad, diverse R&D portfolios to spread risk across many projects. Given that both industry participants and observers pay close attention to the alliance activity of pharmaceutical firms, and that these alliances play a major role in supplying pharma firms' primary products, a firm's ability to build and execute an effective network strategy might reasonably correlate with that firm's marketplace success.

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When pharma and biotech firms create co-development, in-sourcing, marketing and/or licensing agreements, they are creating a form of intellectual property (IP) based network specificity. Such alliances convert firm specific assets to network specific assets that each firm believes might lead to competitive advantages, based on IP protection and know-how.

Industry analysts relate the future prospects of pharmaceutical firms to the quality and defensibility of their product offerings and drug pipelines. Even those firms with profitable lines of drugs currently on the market require constant diligence to replace drugs as patents mature. Despite a range of strategies for drug franchise extension, patent protection eventually runs out. Moreover, the low success rate of any given drug candidate from discovery to market requires firms to pursue a broad portfolio of R&D activities in order to ensure a robust supply line of new products. The expansion of collaborative relationships in the pharmaceutical industry over the past twenty years illustrates the recognition by pharma leadership that collaborative arrangements represent an important mechanism with which to broaden and deepen product pipelines. It should be possible to test this notion quantitatively by examining the relative performance of large pharma firms with respect to collaborative activity. While the simplest hypothesis would suggest that pharma firms with broader portfolios of inter-firm relationships should exhibit superior performance, certainly other possible correlations exist. One could argue that pharma firms that ally more often are doing so to make up for some real or perceived inequity in their internal R&D programs. The data could show a negative correlation between a firm's collaborative activity and its performance. Alternatively, both firms performing above as well as below the mean within the industry might exhibit high rates of collaborative activity. Finally, it is even possible that the data will exhibit no particularly strong or statistically significant correlation. Numerous factors influence the market value performance of pharma firms, so the possibility exists that the extent to which a firm engages in collaborative activity has little to do with its success. This final possibility seems unlikely, due to the strong anecdotal and historical evidence discussed in the previous sections, as well as the proliferation of alliances within the industry since the early 1980s.

It should also be possible to examine whether there seems to have been an increase in recent history in the relationship between the frequency of firm collaborations and the marketplace's valuation of individual firms. Many inter-related factors impact firm performance, and market analysts evaluate firms by examining a broad range of issues to arrive at rational valuations. When evaluating pharma and biotech firms, analysts consider each firm's collaborative portfolios and effectiveness at successfully monetizing these relationships. As such, any increase in the correlation between collaborativeness and market valuation over the past decade might directly reflect analysts' increased recognition of the importance of these relationships. Nonetheless, if collaborative relationships had not at least appeared to create value for firms over time, analysts would be unlikely to afford these arrangements such importance. If firms have not found value in creating these alliances in terms of improved performance over time, these relationships would have been unlikely to have proliferated so conspicuously over the past twenty years.

In order to examine the role of alliances in the performance of large pharma companies, we will explore the correlation between a firm's relative level of collaborative activity and two important market metrics, total return and the price-to-earnings (P/E) ratio. First, we will investigate whether a correlation exists between collaborative activity and total return over the period from 2000 – 2005 (Test I). Second, we will examine whether a statistically

significant change occurred during this period with respect to the correlation between collaborative activity and P/E ratios (Test II). The first test provides a decade long picture of market performance that accounts for the long period of time that collaborative relationships typically require to produce market value results. The second test begins to examine whether change has occurred in the correlation between valuation and collaboration over the latter half of the decade under consideration. Both tests considered the top nine US pharmaceutical firms by revenues, ytd through June 30, 2006, taken from the Fortune 500. The following table lists the firms with their ticker symbols and revenues for the benchmark period

Table 4.1. The Nine Largest US Pharmaceutical Firms by Revenues, billions, ytd, June 30, 2001

Merck	MRK	$45.3
Johnson & Johnson	JNJ	31.2
Pfizer	PFE	30.8
Pharmacia	PHA	18.8
Bristol-Myers Squibb	BMY	18.7
Abbott Labs	ABT	14.7
American Home Products	AHP	13.7
Eli Lilly	LLY	11.6
Schering-Plough	SGP	9.8

The Fortune 500 for 2001 also included Amgen and Allergan; however, these firms are orders of magnitude smaller than the next smallest pharma firm, Schering-Plough (US $9.8 b), with Amgen at US $3.8 b in revenues (ytd 6/30/01), and Allergan at almost US $2 b. Amgen, as a large biotech firm, and Allergan as an emerging pharmaceutical company, operate differently than their large pharma rivals, subject to different growth and valuation expectations. As such, we will only examine the top 9 US pharmaceutical firms.

4.2. Collaboration Rate

The proxy for the level of collaboration used in both tests as the independent variable was defined as the collaboration rate (CR). Here it defines the number of collaborative agreements into which a particular pharma company entered during the period commencing January 1, 2000, through the end each year considered (2000 -2005).

The CR for the first test of total return included the total number of collaborative relationships of each pharma firm for the period from January 1, 2000 through December 31, 2005, coinciding with the period used to calculate Total Return to investors, the dependent variable of Test I. The CR was based on detailed information compiled from the ReCap database, managed and maintained by the consulting firm Recombinant Capital [1], perhaps the most complete repository of information on inter-firm agreements in the biotechnology and pharmaceuticals industries (as US data sources). The term “collaborativeness” will be used to refer to the relative level of collaboration between firms, as represented by the CRs. Using this variable as proxy for some notion of the collaborativeness of a firm requires some caution. The absolute number of agreements of a firm could misrepresent the relative level of

collaboration between firms if the distribution of contract sizes varies substantially across firms. For instance, a firm with many small agreements would have a higher collaboration rate than another firm with fewer much larger agreements.

The CR under such a circumstance might not accurately compare the two firms' collaborativeness. Nonetheless, collaborative agreements have achieved a level of consistency across the pharmaceutical and biotech industries as they also extend to other areas such as EU Europe [2].We found that as agreements between pharmaceutical and biotech firms have become more sophisticated, they have also become more standard in form and substance. This bolsters the assumption underlying the variable that the absolute number of collaborative agreements can be compared between firms as proxy for a firm's relative level of collaboration. Additionally, Recombinant Capital pays close attention to ensuring that agreements are properly categorized by agreement type. Attempting to control for the distribution of differing sizes of agreements, or calculating the total monetary value of agreements executed by a firm as an alternative measure of the CR does not appear feasible. Regarding the reliability of the data itself, a number of researchers have earlier employed the ReCap database with very satisfactory results [3,4]. G. Pisano corroborated the ReCap data on over 260 bio-pharmaceutical projects against other industry-focused sources. He observed that, “The Recombinant Capital database proved to be remarkably accurate when compared against these secondary sources” [4]. Given these caveats and the positive precedent regarding the source of data, the CR presents a reasonably accurate picture of the collaborativeness of the sample firms. A good deal of insights resides in outliers, one of them is Schering Plough (SGP), the smallest of the large US Pharma firms. At around US $9.8 b in revenues as of year-end 2000, it is one quarter the size of the largest firm in the industry, Merck, at US $40 b.

What accounts for SGP's outstanding performance during the 1990s? SGP successfully introduced Claritin, a high visibility blockbuster drug early in the decade that accounted for approximately a third of the firm's revenues by 2000. Claritin alone generated US $2.3 b of revenues in 1998, compared with the firm's total revenues of US $8 b for the year. During the third quarter of 2001, Claritin posted revenues of US $828 m on firm revenues of US $2.4 b [5]. While other firms introduced blockbuster drugs during the same period, the success of this single drug significantly enhanced the firm's visibility and relative size within the industry. The timing of this product's introduction to market coincided favourably with the total return calculation for 1990 - 2000, substantially increasing the firm's performance during the period (the drug was approved by the FDA in 1993.) The company made a successful assault on the top tier and avoided acquisition by larger firms largely as a result of the astonishing success of C'laritin. Schering-Plough's performance illustrates an important characteristic of research and development driven industries. In addition to the factor of size, SGP's unique success with Claritin reflects the unpredictable nature of R&D and the FDA approval process. All of the large pharma firms pursue a portfolio of research in order to manage risk and enhance the likelihood of successful introduction of new patentable products. The frequency of a firm's collaborative relationships reflects to some extent the breadth and depth of its R&D program. Nonetheless, having the broadest and deepest such portfolio does not alone ensure success in innovative activities. Innovation is quite unpredictable, particularly seminal innovation of the type often required by the development of new drugs. Incremental innovation can be managed quite successfully as a process. Although an effective culture and management process can enhance the success of seminal

innovation, it will always remain an unpredictable endeavour. Schering Plough's predicament as of late 2001 further illustrates the importance of the unpredictability of R&D for understanding the strategic requirements of competing in pharmaceutical markets. In early 2001, SGP was assailed by questions regarding the suitability of some of its manufacturing capacity. The company announced that it was working with the FDA to resolve the issue; nevertheless, the company's market capitalization plummeted. More important, the business media began drawing increasing attention to SGP's lobbying attempts in Washington, aimed at further extending the Claritin patent franchise for what many observers considered questionable reasons [6,7]. Questions also surfaced regarding the true efficacy of the drug, putting further pressure on the company's primary product. SGP failed to receive further patent life extension, underscoring a crisis long in the making.

Despite significant spending on R&D during the latter half of the 1990s, SGP posted a relatively low Collaboration Rate for a top pharma firm during the same period. While it is impossible to assign a direct relationship, some analysts and other observers question the ability of SGP to successfully replace Claritin as it comes off patent [8]. The loss of Claritin revenues as a result of generic competition typically eliminates up to 80 percent of a product's revenues, and most of its margins. Schering-Plough's solution as of the end of 2001 has been to introduce an improvement drug (i.e.-similar to the existing drug, with incremental enhancements) for Claritin, known as Clarinex..

4.3. Some Empirical Findings

The firms in the sample exhibit a high correlation between CR and total return over the decade (Test I). In order to delve deeper, another test (Test II) includes an expanded set of data points reflecting relative market valuations as opposed to investor returns. Moreover, it will examine the extent to which correlation between collaborativeness and market valuations might have changed over time.

Test II entails a set of simple statistical investigations of the relationship between the CRs of each firm and their Price-to-Earnings ratios (P/E ratios) during the five-year period January 1, 2000 - December, 2005. Both the P/E ratios and CRs are normalized in order to enable comparisons across years. All the results are relegated to the Appendix.

The introduction of P/E ratios as the dependent variable emphasizes relative market valuation of the firms in the sample, as opposed to total return used in Test I. A firm can perform quite well in terms of total return, while having a P/E ratio generally higher or lower than its industry over the same period. Comparing firms within the same industry, - against “comparables” in investment banking parlance- P/E ratios suggest the market's relative valuation of a firm's prospects. Comparing firms in different industries or market segments presents additional issues. Different industries have different average P/E ratios, reflecting overall prospects for the industry's future. As such, we must remove American Home Products (AHP), now Wyeth, from consideration in Test B. The market confers lower overall P/E ratios to firms in OTC drug products and medical instruments in comparison to pharmaceutical firms. (It was appropriate to include AHP in Test I, given that Total Returns can be compared across industries, regardless of differences in valuations.) Throughout the 1990s, AHP underwent a radical transformation from a firm engaged in the manufacture and

marketing of products as diverse as over the counter (OTC) drugs, food products and agricultural chemicals to a firm focused primarily on therapeutics. Reflecting a radically different strategic direction than that pursued by the company in the late 1990s, AHP acquired the over the counter consumer products firm AH Robins in 1989 and the agricultural chemicals firm American Cyanamid in 1994. As a result of a substantial strategic shift during the late 1990s, AHP divested itself of its food division, American Home Foods, its Storz Instruments and Sherwood-Davis & Geck divisions, focused on medical instruments and disposable medical equipment. In 2000, AHP sold Cyanamid Agricultural Products to BASF. In 1996, AHP's pharmaceuticals division accounted for barely 50 percent of the firm's revenues. During the first nine months of 2000, pharmaceuticals contributed over 83.5 percent of the company's revenues [9].Test II plots the P/E ratios against each firm's CR for the end of year of each year 2000 - 2005. The trend of the plot appears clear, and a t-test of the x-coefficient confirms statistical significance at α =0.01. Clearly, correlation exists between these two variables, though the R2 fit is somewhat weak. Firms engaged in more collaborative activity tended to be valued more highly by the market.

4.4. R & D AND M & A

Two factors were transforming the structure of the pharmaceutical industry from 2000 – 2005 that might account for its performance. First, rapid consolidation manifested as many high profile mergers and acquisitions occurred or commenced during this period. Firms merged in order to combine pipelines and R&D programs in an attempt to deal with the "pipeline dilemma" described earlier. A few notable examples include Pfizer's acquisition of Warner-Lambert and the Pharmacia&Upjohn merger with Monsanto's life sciences operation to become Pharmacia (in 2003 acquired by Pfizer). European firms consolidated during this period as well, resulting in GlaxoSrnithKline,Aventis and Novartis, although these events would not appear directly in this data set. This consolidation would have had particular impact on the firms in this sample, given that these firms are the results of this consolidation.

Mergers often prove traumatic and costly; at the least, mergers distract firms from their core missions over the near term. The second factor relates to a cause of the underlying pipeline problem. Large pharma firms had spent most of their post-war history pursuing small molecule drugs. The acceleration in alliance formation during the 1980 and 1990s to a large extent occurred as a result of pharma firms' interest in- and eventually, requirement for – converting their R&D efforts to include an ever-expanding set of new biotechnologies, as improving their chances to revive increasing returns to scale in R&D. In particular, by 2000 - 2001, firms were intensifying their alliance formation with genomics and bioinformatics in order to accelerate their discovery of new drug targets for development. Prior to the addition of genomics and bioinformatics to drug development, the discovery of new targets presented a bottleneck in the process. Firms began allying in earnest to pursue the application of these new approaches to drug discovery. While it will require some time to determine how beneficial these relationships will become, there are some early indications of success. The alliance between Human Genome Sciences (HGS) and SmithKline, begun in 1993, initiated a new and financially more significant round of pharma/biotech alliances with a commitment of

US $125 m. By the completion of the agreement in mid 2001, both firms believed that the value they had appropriated from the relationship far surpassed their investments [10].

Consolidation typically accompanies market saturation, as growth rates slow and competitors expand, merge or exit and market share becomes concentrated in fewer dominant firms [11]. In contrast to many other industries, saturation in this case did not coincide with a deceleration of R&D. Rather, R&D expenditures increased dramatically over the 1990s as a percentage of revenues. Maturation occurred, and continues, in the industry's development platforms and product lines. However, the pharmaceutical industry has experienced, and continues to undergo, not just one but two fundamental changes to its technology platform:

1. The intensive application of information technology (‘parallel processing techniques’) to drug discovery and development; related to this, new drug delivery mechanisms and targeted therapeutics through nanotechnology.
2. The conversion from small molecule chemistry to DNA-based biopharmaceuticals.

The transition exhibited by the collaboration to P/E ratio data to some extent reflects the conversion of the pharma industry's traditional drug development processes to new development paradigms. Rather than accomplishing this transformation internally, pharma firms have been forced to look externally for new capabilities and research directions. Those that have been more prolific and successful at leveraging external resources and competencies have been rewarded by their valuations and total returns.

Over the past decade, the pharmaceutical industry has experienced a challenging period of transition to consolidation concurrent with expansion and increased diversity of technology and competency requirements. Although the echelon of industry leaders has been rapidly consolidating, thousands of firms have been founded with new approaches to drug discovery and development. Many of these firms will remain successful niche players or be acquired, some will fail, but a few will emerge as the next generation of industry leaders. We have begun to witness this with such early firms as Amgen, the 10th largest pharmaceutical firm in the US (in 2000), deeply rooted in biotech, and Millennium Pharmaceuticals and Human Genome Sciences, the latter of which began their ascent to the ranks of large biopharmaceuticals in the past few years. Large pharma has consolidated as a result of the pressure to maintain robust growth in the face of pricing pressures (such as from HMOs and government payers) for which traditional drug development paradigms proved insufficient. In response, large pharma has both partnered with other firms offering emerging development technologies, such as genomics and bioinformatics, as well as invested resources in building these new competencies internally.

As these new development platforms mature and large pharma becomes more adept at leveraging these capabilities internally, might industry change decelerate and intra-firm arrangements become less prevalent? This appears unlikely for some time, given the pace of innovation required to compete successfully in the pharmaceutical industry. Even as pharma firms acquire new development capabilities in-house, the diversity of research at university and government labs, government funded initiatives and small biotechnology firms will continue to compel competitive pharma firms beyond their boundaries in search of new knowledge.

4.5. NETWORK DIMENSION

This exploration of data most directly addresses the role of network specific investments within the competencies incentives. However, as presented in our brief history of the pharma-biotech relationship, the changes in the alliance culture of the two industries have also been heavily influenced by the market structure (regulatory and economy of scale requirements) and network economics (genomics and the introduction of information technology to the industry). Simple total return or P/E ratio data plots such as presented here fail to differentiate substantially between the distinctions presented by the network dimension. Despite the broad nature of the tests, the results present an intriguing challenge to the notion that a firm's core competencies should not or cannot be outsourced or achieved in a collaborative fashion. No one would contest the assertion that drug discovery and development represent core competencies of the major pharmaceutical firms. All of the major firms maintain an extensive in-house competency. Market analysts assign valuations partly based on the quality of this in-house capability-, nonetheless, valuations are also assigned as a result of big pharma's ability to develop and manage alliance-based drug discovery and development effectively, the large pharma and biotech firms are outsourcing a significant portion of their R&D.

Given the superior performance of most firms with relatively high collaboration rates, collaborative efforts must be considered a best practice within the industry. The results certainly do not invalidate the care with which firms must accomplish those competencies they define as core. Rather, the results suggest that hybrid organizations can successfully accomplish core competencies through collaborative effort. It appears from this analysis that, in the pharmaceutical industry at least, collaborative organizational forms can outperform more integrated strategies.

None of the firms in the sample lack an extensive network of alliances and cooperative arrangements but they show differential performance of firms in terms of their success at managing and garnering value from inter-firm collaboration. The high-level data analyses presented herein lacks the specificity to address firm differences in selection processes of agreements, contractual types, collaborative governance systems and execution success. The fact that collaboration can at the very least be described as an industry best-practice correlated with market success encourages further study. However, simply creating and maintaining a large portfolio of inter-farm agreements cannot by itself confer success. Managing inter-firm arrangements can be a challenging, resource-heavy affair. It is possible that a point of diminishing return or even a “diseconomy of scope”of sorts could impede the progress of a firm with too many and/or too diverse a set of hybrid organizational arrangements. Such corporate promiscuity might decrease a firm's effectiveness at leveraging these relationships.

Additionally, a reputation for extensive collaboration, combined with lower overall corporate performance might impede a firm's ability to entice the most eligible biotech, pharma and academic partners. As in mating games, higher quality opportunities target more attractive partners. Less attractive, or more risky, biotech ventures might be more likely to ally with less effective partners on less attractive terms. Conversely, firms better able to coordinate and leverage multiple external relationships might over time develop a competitive advantage built on strategic flexibility and access to a broader range of technological and market opportunities. More attractive pharma partners might also be able to command more advantageous terms from their partners. Understanding network strategy from an operational

standpoint requires investigation into these and many other issues at the applied level of the manager and the enterprise.

4.6. COLLABORATION AND PERFORMANCE IN THE PHARMACEUTICAL INDUSTRY: SEMINAL VERSUS INCREMENTAL INNOVATION

Innovative capacity clearly plays a central role in the success of pharma and biotech firms; however, innovation takes many forms. Differentiating innovation based on the distinctiveness of technology and/or application offers useful insights. Much research suggests that large, integrated firms can be quite successful at driving incremental innovation over long periods of time. As Christensen pointedly argues, large firms often become too successful at driving incremental innovations in response to existing customers at the expense of recognizing potential threats from disruptive technologies [12].

Pharma companies regularly pursue incremental innovations in both new and existing drugs. “Me too” drugs are common, such as TAP Pharmaceuticals' Prevacid, a number two competitor to AstraZeneca's acid pump inhibitor, Prilosec. Improvement patents can address changes such as dosage size and frequency or reformulation of an existing drug, such as AstraZeneca's Nexium, a reformulated version of its blockbuster drug Prilosec. Additionally, drug firms can introduce their own generic versions of patented drugs prior to patent expiration in order to acquire a strong position in the generic drug market prior to the entrance of generic competitors as more recently shown by Swiss Novartis.

Nonetheless, successful incremental innovation alone cannot support the strong shareholder value growth required by the market over the long term, particularly as competitors continually pursue potentially disruptive technologies. Successful incremental innovation can be pursued through an ‘open-source’ approach to invent drugs or vaccines for rare or infectious diseases in poverty stricken developing regions. But still large pharma firms must pursue seminal innovations leading to drugs with the profit potential to support acceptable growth. The most valuable patents underlying the most valuable therapeutics go to firms capable of developing truly seminal therapeutic innovations. First-to-market firms in a new drug market segment generally win over 60 percent of the total market for like drugs. Successful new drugs in new areas can create billions of dollars of revenue for the patent holders. Eli Lilly owes over a third of its revenues over the past decade to Prozac, one of the most successful drugs in history. But the rewards of introducing seminal new therapeutics come at great cost. Pursuing seminal over incremental innovations substantially increases the risks associated with R&D. In any field, most very new approaches to problems just don't work. A portfolio approach provides the dominant solution! An extensive external network of firm relationships spreads these risks over many firms pursuing alternative paths to new drugs. Firms in regular pursuit of seminal innovations should be more likely to develop an active network strategy in order to decrease risk and increase the likelihood for success. This has clearly been a factor driving the network strategies and competitive environment of the pharmaceutical industry. While our empirical analysis does not compare this phenomenon across industries (e.g.- whether firms engaged in incremental innovation are less likely to engage in inter firm collaboration), it does support the assertion that a strong network strategy supports success over the long run for firms engaged in seminal innovation.

4.7. IMPLICATIONS FOR FIRM GOVERNANCE

The predominance of alliances within the pharmaceutical industry presents a compelling endorsement for the importance of firm networks in industries where the pursuit of new knowledge represents the primary value creating activity. A simplistic application of the resource-based view of the firm would argue that pharma firms (with sufficiently 'deep pockets') should pursue all research in-house, as the benefits of innovations created internally need not be shared with others. The behaviour of most pharmaceutical firms prior to the early 1980s reflects this approach. Prior to the market success of radically new rDNA technology, firms almost exclusively conducted internal research, or research with university or government labs. Alliances were quite rare. After it became clear that seminal innovations produced through emerging biotech research could provide profitable new markets, alliance frequency accelerated markedly. Established pharma firms knew that re-tooling R&D from traditional small molecule chemistry to biotech would be time consuming and costly. Moreover, firms recognized they could not pursue enough new directions internally. Interfirm relationships became essential.

If firm competencies provide a notion of boundaries of firms, as competency proponents argue, then these boundaries appear quite permeable. In the case of core competencies shared across multiple firms, defining core competencies as boundary markers appears problematic. The pharma-biotech industry exhibits firms with significant overlaps in core competencies allying to accomplish similar objectives. Our discussion of the pharma and biotech industries also challenges the traditional view of transaction costs as the primary determinant of firm boundaries. Merck, as used to be the largest pharma firm by revenues, avowedly pursued a strategy based on economies of scale and internally focused R&D for organic growth, yet the firm consistently performed below the mean from a P/E perspective within its industry. As suggested by Zajac and Olsen, hybrid organization of resources can be more costly from a transaction cost perspective than internal or market organization, while creating greater value [13].

These reservations regarding the firm boundary conditions of the competencies and transaction cost literatures reflect to a great extent a need to reconsider each perspective in light of fundamental changes in economic organization and firm strategy. Transaction costs and competencies both provide powerful approaches to understanding firms but, there appears to be something more at work here. The challenge presented by these results to established theories of the firm reflects evolution in the fundamental nature of firms. Echoing Chandler's 1966 treatise on the railroad industry and the emergence of the modern corporation (Section 1), the advance of technology and the resultant acceleration of marketplace change of recent decades has encouraged, and been encouraged by, the emergence of new organizational forms. It is impossible to separate these three phenomena. Technology change, marketplace change and the evolution of organizational forms exist as mutually reinforcing, interdependent developments shaping economic realities. As we entered the 21st century, ever-widening sets of industries are becoming dominated by the creation and exploitation of new knowledge. In order to garner the benefits of new knowledge, firms must in some manner own the benefits of their creation. Whether through intellectual property rights, trade secrets or simply the ability to better leverage competencies, firms must have some proprietary ownership of knowledge resources in order to successfully compete. Conversely,

knowledge creation by its nature requires the open interaction of human beings with varied perspectives, backgrounds and capabilities. This conflict between proprietary ownership and the social nature of knowledge propels the evolution of new organizational solutions. Nowhere is this dynamic more evident than in those industries consistently in pursuit of seminal innovations. Examining the evolution of the pharmaceutical and biotech industries offers three strong endorsements for the emergence of hybrid organizational forms as vital components of the strategic success of pharma firms:

1. The proliferation of alliances from the early 1980s through the present day;
2. Strong anecdotal evidence from industry participants and observers regarding the competitive value of alliances; and,
3. The statistically significant correlation between the collaborativeness of large pharma firms and their long run market performance, a correlation which increased over the course of the late 1990s and early 2000s.

Clearly, pharma firms ally with biotech firms primarily in order to search for new products across a portfolio of R&D activities. The seminal nature of much of new drug research compels this behaviour, given the high risks involved and the competitive pressure of so marry firms pursuing such a vast technological horizon. The highly unpredictable nature of innovation makes its practice risky. Network strategies provide large pharma firms with a portfolio approach to managing risk and expose the firm's researchers and managers to more diverse information sources and perspectives on developments within the industry.Toward the future, the incentive taxonomy suggests that the pharma industry offers additional opportunities for expanding efficiency through cooperative agreements.

For instance, the development of new drugs and the manufacture of drugs each require substantially different competencies. R&D efforts require innovative technological solutions to market needs, while manufacturing requires a focus on reliable, high efficiency. R&D and marketing-driven pharmaceutical firms will likely increasingly look to firms focused on drug manufacture, entering into long term contracts rather than producing drugs in-house. Such an evolution would mimic that of the electronics contract manufacturers such as

Solectron and Flextronics, who produce products for brand name firms like Gateway and Dell. Ultimately, the most effective combinations of competencies across companies will define the boundaries of firms involved in the pharmaceutical and biotech industries.

4.8. Evolution of Firm Networks

Based on a framework of network dimension, through a history of the biotech/pharma relationship and a simple empirical analysis we summarize a number of observations and conclusions. At identifiable points in the history of the pharma and biotech industries, critical events encouraged the transformation of firm networks within and between both industries. Understanding critical events in light of an incentive taxonomy deepens insight into the impact of such events on the structure of inter-firm relationships within an industry, market or economy.

A strong, statistically significant, positive correlation exists between the Collaboration Rate of large pharma firms and their performance in terms of market valuation and total return over the long-term.

Explanations provided for these results include:

[1] during the period from 2000 to 2005, the pharmaceutical industry began a significant evolution in the platform technologies necessary to develop new drugs (e.g. functional genomics, combinatorial chemistry), strangely,combinatorial chemistry recently being blamed for drier product pipelines [14].

Alliances offered a successful strategy for incorporating these emerging capabilities into pharma firms' R&D portfolios.

[2] The search for new drugs requires a substantial degree of seminal innovation. In contrast to incremental innovation, large firms find seminal innovation to be much more difficult to accomplish internally [12]. The challenges presented by seminal innovation including a high degree of unpredictability, encourage large pharma firms to pursue collaborative relationships.

[3] Given the unpredictability of seminal innovation, an effective alliance strategy provides firms with a broader portfolio of options on R&D efforts than that which internal R&D alone can accomplish. The expanded options provided by collaborative relationships appear to have translated into superior market valuation performance for large US pharma firms during the period under consideration.

An alternative explanation for the correlation between collaborativeness and market valuation could be that firms seeking partners tend to ally with more successful firms. However, this hypothesis, if it turned out to be valid, would not invalidate the assertion that a high rate of collaboration positively impacts market valuation performance of pharma firms. It is quite likely that performance and collaboration rates are mutually reinforcing. Firms exhibiting superior performance might experience higher demand as a potential partner, leading to access to more, higher quality, deals. Higher quality deals, on the other hand, would presumably lead to superior performance of collaborative projects, improving the performance of the firm's overall R&D portfolio. Superior performance of the R&D portfolio likewise reinforces superior performance in terms of market valuation.

Perhaps the most important characteristic of the incentive taxonomy has been its applicability to change.

The co-evolution of the biotechnology and pharmaceutical industries industries underscores the importance of understanding the impact of critical events and trends. These events not only impacted the nature of the relationships between firms, but also transformed the structure and direction of each industry. Industry consolidation as a result of the FDA's regulatory changes following the Thalidomide Crisis, a Market Structure influence in terms of the taxonomy, resulted in very few small firms pursuing cutting edge research. It might be useful for researchers to investigate whether industry consolidation during this period resulted in decreased diversity and variety of research efforts in the private sector. Life sciences research continued at the academic level, eventually leading to the founding of the early biotech firms, however, small firms could no longer independently navigate the drug trials

process. The agreement between Genentech and Eli Lilly represented the nascence of successful alliances between biotech and pharma firms, and remains representative of many practices to this day. Throughout the 1980s and 1990s, pharma and biotech firms evolved in varied forms of inter-firm relationships in order to combine the innovativeness of smaller firms with the resources of their mammoth counterparts. Finally, the introduction of genomics, proteomics and bioinformatics during the late 1990s began to transform the industry into one dominated by information. As access to broad, diverse information became increasingly important for pharma and biotech firms, network economics began to play a role in defining the competitive and cooperative relationships between firms and, as such, the competitive dynamics of both industries.

Further, this discussion suggests insights regarding the importance of firm networks for firms pursuing innovation competencies under varied conditions. For instance, firms competing in very mature industries tend to pursue incremental innovations (whether or not this is the optimal strategy). Firms in fast changing industries where new knowledge drives value creation must pursue more significant, even seminal, innovations. Firms pursuing patentable therapeutics offer a compelling example. Useful future research could investigate whether industries requiring more seminal as opposed to incremental innovation are indeed more likely to exhibit a stronger correlation between collaborativeness and market success than those industries more concerned with incremental innovation. Relative to the biotech and pharma industries, changes in the institutional environment represented by regulatory events, and the introduction of dramatically new technologies to market initiated periods of punctuated change, followed by periods of adjustment. The network dimension's distinctions by regulatory events (market structure space), and the introduction of new therapeutic technologies (competencies), and the introduction of genomics, proteomics and bioinformatics (competencies and network economics) to the industry underscored varied implications for inter-firm alliances and competitive dynamics. Related to punctuated equilibrium, Christensen's notion of 'disruptive technologies' describes situations in which technologies present a disruptive challenge to existing products provided by established competitors [12]. Firms introducing disruptive technologies to market are typically new competitors, and are often new firms. Their original products normally target a market space, entering into competition with established competitors. Clearly, the biotech industry has offered a number of potentially disruptive challenges to traditional approaches to drug development.

Genentech's first two products, insulin and human growth hormone, both introduced substantially new technologies that replaced prior products. The insulin product proved disruptive for Novo's and Lilly's traditional insulin products, despite both firms' active pursuit of alternative production methods. Novo did not ignore the need to innovate, it simply chose the wrong direction for research. By contrast, Eli Lilly sought to lock-in three research teams pursuing rDNA produced insulin, resulting in its access to Genentech's successful version. While the new product obsolesced Lilly's existing animal-derived product, increased sales and supply far outweighed the loss.

Many other disruptive technologies have arisen in the pharma industry, such as Prilosec and Prevacid's replacement of histamine H2 blockers such as Tagamet and Zantac. The pharma industry, however, has used alliances as a useful mechanism to deal with an ever-expanding universe of new drug technologies

Beginning with Eli Lilly's successful leveraging of multiple relationsships to acquire the insulin product, the industry has evolved in extensive inter-firm networks. Nonetheless, it took large pharma firms a while to recognize the potential of their biotech competitors. In this sense, the entire field of biotech that emerged during the late 1970s and 1980s can be viewed as disruptive.

Due in part to denial and skepticism, the pharma industry succumbed to the myopia that enables new competitors to thrive from disruption. It might be too strong, however, to assert as quoted in Robbins-Roth [15] that 'If big pharma had had half a brain, there never would have been a biotech industry'. This argument implies that had the massive pharma firms pursued the technologies of the biotech firms on their own, there might not have been an opportunity for the upstarts to develop. This assumes that large pharma companies could have succeeded in developing the relevant emerging technologies primarily through in-house research. This is probably an erroneous assumption.

Even after the biotech/pharma alliance culture began to expand following the success of Genentech's insulin product, the industry required many years to adjust. Alliance competencies do not occur over night, particularly alliance mindsets.The development of the alliance culture in the life sciences industries, particularly during the 1980s and 1990s is revealing. During these years, the industry evolved in highly successful network strategies that fulfilled the needs of large and small firms alike. Understanding developments in this sector could provide useful insights for other industries undergoing substantial technological change largely driven by smaller emerging firms. The large pharmaceutical producers could provide a model for other companies facing disruption. Moreover, it is important to take action against disruption before recognition of a specific threat. By the time a competing product reaches a critical mass in the maketplace, it is probably too late. Firms in any industry can monitor the technological and market horizons and construct a portfolio of access to new technologies through alliances with new firms pursuing potentially relevant technologies. Such outsourcing of R&D can provide insurance against being caught unaware, and helps introduce a successful product pipeline.

4.9. Summary of Empirical Analysis

Based on the Appendix we provide a summary of the detailed empirical analysis.

- A strong, statistically significant, positive correlation exists between the collaboration rate (CR) of large US-based pharma firms and their performance in terms of market valuation and total return over the long term. The magnitude of the market value correlation increased markedly between 2000 and 2005.
- During the period from 2000 – 2005, the pharma industry began a significant evolution in the platform technologies necessary to develop new drugs (e.g. genomics, combinatorial chemistry). Alliances offered a successful strategy for incorporating these emerging capabilities into pharma firms' R&D portfolios.
- The search for new drugs requires a substantial degree of seminal innovation. In contrast to incremental innovation, large firms find seminal innovation to be much too difficult to accomplish internally. The challenges presented by seminal

innovation, including a high degree of unpredictability, encourage large pharma firms to pursue collaborative relationships.

- Given the unpredictability of seminal innovation, an effective alliance strategy provides firms with a broader portfolio of options on R&D efforts than that which internal R&D alone can accomplish. The expanded options provided by collaborative relationships appear to have translated into superior market valuation performance for large US pharma firms during the period under consideration.

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APPENDIX

Table A.1. Test I: Collaboration Rate & Total Return Data, Major Pharma Companies 2000 – 2005

Company	Collaboration	Total Return Rate (percent compounded)
PFZ	139	32
PHA	117	24
AHP	92	21
JNJ	92	21
LLY	75	21
MRK	74	23
ABT	60	18
BMY	56	20
SGP	40	29

Table A.2. Test B: Collaboration Rate Data, Raw and Normalized

2000	Adjusted CR	Normalized	2003	Adjusted CR	Normalized
MRK	34	1.06	MRK	65	1.02
JNJ	41	1.28	JNJ	76	1.19
PFE	37	1.16	PFE	61	0.96
PHA	40	1.25	PHA	105	1.65
BMY	25	0.78	BMY	47	0.74
ABT	20	0.63	ABT	52	0.82
LLY	46	1.44	LLY	70	1.10
SGP	13	0.41	SGP	34	0.53
Mean	32.00		Mean	63.75	
2001			2004		
MRK	44	1.09	MRK	74	0.91
JNJ	48	1.19	JNJ	92	1.13
PFE	41	1.02	PFE	139	1.70
PHA	48	1.19	PHA	117	1.43
BMY	32	0.80	BMY	56	0.69
ABT	28	0.70	ABT	60	0.74
LLY	58	1.44	LLY	75	0.92
SGP	23	0.57	SGP	40	0.49
Mean	40.25		Mean	81.625	
2002			2005		
MRK	50	1.01	MRK	67	0.78
JNJ	61	1.23	JNJ	95	1.11
PFE	51	1.03	PFE	140	1.64
PHA	63	1.27	PHA	119	1.39
BMY	40	0.81	BMY	58	0.68
ABT	37	0.75	ABT	86	1.01
LLY	65	1.31	LLY	78	0.91
SGP	30	0.60	SGP	40	0.47
Mean	49.63		Mean	85.375	

"Adjusted CR" refers to the adjustments made to raw data from the ReCap database (www.yahoo.com/finance) in order to account to acquisitions and/or divestitures during the period of the study. For instance, if a firm's total number of agreements listed on the ReCap database for 2000 includes those of a firm acquired at a later date, these agreements were subtracted from the company's total for 2000.

The CR figures were normalized by taking the ratio of each company's CR for a given year to the mean CR for all companies during that year. In this way, CRs can be compared between all firms, across all years.

Table A.3. Test B: Price-to-Earnings Ratio Data, Raw and Normalized P/E ratios are stated as of the end of the year, December 31, of each year.

Company	P/E	Normalized P/E	Company	P/E	Normalized P/E
2000			2001		
MRK	25.54	1.01	MRK	28.37	0.73
JNJ	23.69	0.94	JNJ	32.77	0.84
PFE	31.09	1.23	PFE	54.39	1.40
PHA	36.33	1.44	PHA	68.85	1.78
BMY	19.45	0.77	BMY	30.14	0.78
ABT	21.31	0.84	ABT	24.81	0.64
LLY	25.14	0.99	LLY	39.09	1.01
SGP	19.84	0.78	SGP	31.83	0.82
Mean P/E 25.30			Mean P/E 38.78		
2002			2003		
MRK	34.30	0.74	MRK	27.42	0.83
JNJ	39.94	0.87	JNJ	45.44	1.37
PFE	82.02	1.78	PFE	41.22	1.24
PHA	36.26	0.79	PHA	34.98	1.05
MY	49.41	1.07	BMY	34.34	1.04
ABT	32.75	0.71	AST	23.13	0.70
LLY	47.58	1.03	LLY	28.89	0.87
SGP	46.82	1.01	SGP	29.84	0.90
Mean P/E 46.14			Mean P/E 33.16		
2004			2005		
MRK	32.3	0.71	MRK	23.59	0.72
JNJ	37.63	0.83	JNJ	31.72	0.97
PFE	78.77	1.74	PFE	39.73	1.22
PHA	81.66	1.81	PHA	37.93	1.17
BMY	36.05	0.80	BMY	26.60	0.82
ABT	27.21	0.60	ABT	48.58	1.49
LLY	33.4	0.74	LLY	28.16	0.86
SGP	34.56	0.76	SGP	24.15	0.74
Mean P/E 45.198			Mean P/E 45.198		

Table A.4. Test II: Collaboration Rate to P/E Ratio, Normalized Data by Year and Firm

Company			Company		
2000 MRK	1.06	1.01	2003 MRK	1.02	0.83
JNJ	1.28	0.94	JNJ	1.19	1.37
PFE	1.16	1.23	PFE	0.96	1.24
PHA	1.25	1.44	PHA	1.65	1.05
BMY	0.78	0.77	BMY	0.74	1.04
ABT	0.63	0.84	ABT	0.82	0.70
LLY	1.44	0.99	LLY	1.10	0.87
SGP	0.41	0.78	SGP	0.53	0.90
2001 MRK	1.09	0.73	2004 MRK	0.91	0.71
JNJ	1.19	0.84	JNJ	1.13	0.83
PFE	1.02	1.40	PFE	1.70	1.74
PHA	1.19	1.78	PHA	1.43	1.81
BMY	0.80	0.78	BMY	0.69	0.80
ABT	0.70	0.64	ABT	0.74	0.60
LLY	1.44	1.01	LLY	0.92	0.74
SGP	0.57	0.82	SGP	0.49	0.76
2002 MRK	1.01	0.74	2005 MRK	0.78	0.72
JNJ	1.23	0.87	JNJ	1.11	0.97
PFE	1.03	1.78	PFE	1.64	1.22
PHA	1.27	0.79	PHA	1.39	1.17
BMY	0.81	1.07	BMY	0.68	0.82
ABT	0.75	0.71	ABT	1.01	1.49
LLY	1.31	1.03	LLY	0.91	0.86
SGP	0.60	1.01	SGP	0.47	0.74

Table A.5. Significance Tests for the Regressions Two-tailed t-tests

Significance Tests for All Regressions					
Two Tailed t-tests					
			Significant at alpha =		
Test		degrees of freedom	t-value	0.1	0.01
CR to Total Return, all firms		7	1.18	No	No
CR to Total Return, no SGP		6	4.34	Yes	Yes
CR to P/E, 2000	- 2005	46	4.14	Yes	Yes
CR to P/E, 2000	- 2002	22	1.63	Yes	No
CR to P/E, 2003	- 2005	22__	4.29	Yes	Yes
CR to P/E, 2000	- 2001	14	2.02	Yes No	No
CR to P/E, 2002	- 2003	14	0.52	No	No
CR to P/E, 2004	- 2005	14	4.53	Yes	Yes

Chapter 5

EUROPEAN BIOTECH-PHARMA INDUSTRY DEVELOPMENT

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"The conventional fallacy is that the cost of R&D drives prices. In reality, it's the other way round: prices drive costs. The more a company can charge for a drug, the more it will spend on developing and marketing it" – Frederic Scherer, Industrial Market Structure and Performance (1990)

ABSTRACT

A review on industry evolution in EU Europe attempts to benchmark industry development both in pharmaceuticals and biotechs to the US, overall tracing a slower, delayed and catchup growth and a more diversified path in biotech (joint) ventures.

5.1. INTRODUCTION

The pharmaceutical industry has been one of Europe's success stories. Emerging in the late 19th century as an adjunct to the chemical industry, it was for many years dominated by German and Swiss firms. After World War II the American industry emerged as a strong player, taking advantage of the incapacity of the German industry in the aftermath of the war and establishing itself, via subsidiaries, in many European markets. By the 1960s German companies had re-established themselves, but failed to regain their pre-war market share. Since the 1960s it has been British and Swiss firms that have seen the strongest gains and this has helped to restore the European position. In 2005, out of the 20 top ranking companies in terms of sales, including two out of the top three, 10 were European, eight were American and two Japanese.

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In conjunction with its American counterpart the European industry recently has become more pessimistic about its future. Briefly, the main reason for this is that costs, especially R&D, are rising, and revenues are falling resulting in a squeeze on profits. For an industry which has enjoyed above average profits for a considerable period of time, this is an uncomfortable situation. This has given rise to talk about the declining research productivity in the pharmaceutical sector which otherwise could be just a temporary cyclical downturn for a few years. It is worth exploring the developments which lie behind these trends starting from the roots of development on the background of previous reports [1,2]

One major indicator is R&D intensity in the industry since the early 1970s. While there are significant differences between countries which can to some extent be explained by market structure, more specifically, by the degree to which the industry in that country is dominated by leading firms in the industry, a notable feature is the rise in R&D intensity over time.

In producing countries (USA, Germany, Switzerland, UK and France) by the 1990s it averaged about 10-12 per cent.

On the basis of previous analysis in Section 3 two main explanations can be offered:

1. *Increased regulatory requirements.* Over time safety checks on drugs have become more and more rigorous and time consuming. In the 1960s many compounds being tested were anti-infectives whose efficacy was readily apparent within a short time frame. Drugs now being developed increasingly target chronic long term diseases such as cancer, heart disease and ageing, where efficacy and safety takes time to judge and, more importantly, where side effects sometimes take years to become apparent. Regulatory authorities are becoming tougher; in response to public and media becoming more sensitive in cases of more risk failures; tests are more complicated and the time required to bring the drug to market is longer. The US FDA and the European EMEA acting on public pressures and court rulings have become increasingly more restrictive in drug approval on safety issues sometimes at the expense of speed and timeliness of new drug approvals [3,4].
2. *Diminishing returns to drug discovery.* In the 1950s and 1960s, in the so-called 'golden age' of drug discovery, new compounds for testing suggested themselves fairly readily and a number of major breakthroughs emerged from the exploitation of the properties of families of compounds such as the histamines, steroids, penicillin and the cephalosporins. As time went by all the ready targets had been investigated and the search had to be extended over a wider field and was therefore necessarily more expensive. The more targeted approaches to drug discovery, pioneered by James Black with beta-blockers and cimetidine, helped to stave off diminishing returns, but the hope that biotechnology would short circuit the process and open up a whole new range of cheap and easy targets proved ill-founded. On the contrary, biotechnology has to date proved an even more expensive route to drug discovery it is likely to result in more ‘platform’ drugs with a larger treatment scope (as could be shown with Genentech’s Avastin). Yet with a slowly evolving shift toward more genetic based medicine instead of one originating from anatomy and biochemistry and with drug discovery directed toward these objectives we may turn from a diminishing to an increasing returns regime in the future.

For now, recent reports followed by the Economist [5] suggest that R&D costs have become unsustainable for the health care system. It was calculated that it now costs in the range of US $ 800 m to US$ 1 b to launch a successful ‘blockbuster’ new drug. If allowance is made for R&D which goes into drugs which fail to make the grade, then the cost goes up even further. To break even requires profitable sales for 10 years with annual peak sales of at least US$ 500 m. By assuming a 15 per cent rate of return on the total R&D spent by the pharmaceutical industry on R&D in 2003 /2004 would require revenue growth of at least the same order of magnitude per annum. As such growth rates are not feasible under current market conditions, the conclusion has to be that current levels of R&D are untenable and that some way has to be found to cut the costs of new drug development and/or increase its effectiveness.

5.2. MERGERS AND ACQUISITIONS

The response of the pharmaceutical industry to these pressures has been to look on the one hand for savings, particularly in R&D expenditures, and on the other for unexploited areas of profitability. The first has led to a number of different directions:

1. *Extending patent life.* As regulatory procedures lengthened the time needed for clinical trials the effective life of patents had been eroded. In the 1960s when a 5-7 year period of discovery/development was common, a 20 year patent enabled the company introducing a new drug to reap 'premium' profits for 13 years provided no major competitors emerged. Development times of 10-12 years cut 'effective patent life' back to 10 or 8 years. A concerted campaign by American companies in the 1980s secured an extension of patent life by 5 years for products affected by such delays, and this was followed by similar moves in Europe. GATT and WTO rules harmonized US patent laws (USPTO) with those of other countries and make the patent start from the time when the patent is filed (previously in the US it had been from the time it was granted). However, the provision for the five year extension remains where there are undue delays in the patenting process.
2. *Parallel trials and simulations.*In seeking savings in the R&D process, many drug companies have experimented with ways of short circuiting the lengthy development period. Increasing use is being made of molecular modelling techniques, combinatorial chemistry and bioinformatics which enable companies to simulate the effects of drugs. Such developments have been particularly useful in the early phase of development but of course cannot substitute for clinical trials at later stages. It has, however, provided for effective screening and companies making extensive use of the process claim that it is highly cost effective in helping to slim the number of drugs under development. It may also increase the likelihood to hit a blockbuster unlike finding a ‘needle in a haystack’. At the same time, companies moving into clinical trials, which have normally been undertaken on a sequential basis, are 'doubling up' and running two trials in parallel. This, too, seems to have been effective and companies are reporting a time saving of up to three years on development times.

3. *Collaborations* - An increasing number of products are being licensed-in by pharmaceutical companies as a response to the emergence of biotechnology and the need to cut R&D costs. Where two companies cooperate in the development of a new drug, development costs are shared. As previously shown in Sections 3 and 4, large public pharmaceutical companies have only slowly and reluctantly engaged in such collaborations.In the past few years, 'vertical collaborations' between large companies and small specialist firms (e.g biotech companies) have become more common. At the same time cost pressures are now making 'horizontal' collaborations between companies at the R&D stage of development much more routine.
4. *Mergers* - The logic that underlies collaborations leads inevitably to mergers. Given the relatively small (world) market share enjoyed by even the largest companies, pressure on profit margins has been the underlying factor in the large number of mergers in the sector in recent years. In 1989 the first of the 'mega-mergers' involved mainly US companies: Bristol Myers with Squibb, Smith Kline with the UK's Beecham, and Dow with the mid-size US company Marion Merrell, and in 1990 Rhone Poulenc acquired Rorer. After the mid nineties we have seen a renewal of merger activity with European companies, the largest being Glaxo's take-over in early 1995 of their fellow UK company, Wellcome for US$14.5 b and the agreed merger of Sandoz with Ciba Geigy to form the new Swiss company, Novartis. Germany's Hoechst with French Rhone Poulenc, forming Aventis which itself was gobbled up by Sanofi to form Sanofi Aventis.

The overall result of all this merger activity has been a considerable increase in concentration and impact on market structure. The top ten companies now control 40 per cent of the world market, nevertheless there is considerable skepticism as to how far mergers will lead to cost savings. Many commentators point to the relatively higher profit record of the non-merged companies, the transaction costs caused by merger and conclude that there may be few if any gains from merger, In particular, there remain doubts as to how far merger can lead to real savings in R&D.

5.3. THE BIOTECH PHARMA LINK: HISTORICAL RECORD

The biotech firms were more than just a convenient route to research. If they were to flourish they needed markets for their research and it was the large companies which provided the market. Back in the nineteen-seventies companies such as Dow Chemical, DuPont, Shell, Eli Lilly and Hoffman LaRoche were amongst the earliest to place contracts with these small firms, many for as little as US$1m or US$2m which was but a small amount for the large companies but vital for the finances and credibility of the small. In this essential contract research role the biotech firms performed two very useful functions. First, they acted as intermediaries between the large companies and the academic base. Because of close academic links they were able quickly to get together the cross-disciplinary teams required to develop new products in this new technology, whereas the big firms, with their traditional contacts in chemistry, not biology departments, found it difficult to find the right people [6]. Second, they helped the large companies to hedge their bets. Research contracts for US$5m,

US$10m even US$20m were limited commitments which might yield substantial prizes but, at a minimum, would provide the contractor (i.e, the large company) with useful research results and avoid long term and expensive employment commitments at a time when it was still uncertain where biotechnology was going.

In Europe biotech firms have not flourished in the same way, partly because the institutional framework (high funding/leading edge research in the life sciences, active venture capital market) was underdeveloped, partly because the academic entrepreneur was alien to much of the European academic tradition [7]. Earlier studies [8,9] suggest that the total population of small firms in Europe was small and grew only slowly. However, recent research suggests that the early 1990s was a period of rapid change for this sector in Europe and there are now more than 1400 firms in EU –Europe (2004), more than in the US though on average smaller, less mature in the product pipeline, less profitable and less likely at the leading edge of research, with a significant North-South divide: more advanced in the North (Scandinavian countries), less so in the South (Italy, Spain) [10] In view of product pipelines, in distinguishing between public and private biotech companies with altogether fewer public than private companies, we see a robust growth of the biotech sector more recently with the UK ranking first in the public and Germany in the private group [11]. A string of recent EU reports on life sciences and biotechnology, laying out possible political strategies for accelerated industry development of biotechs in Europe, was largely preoccupied with all sorts of policy, ethical and risk constraints,but completely missed out on the complex entrepreneurial dimension of science//technology entrepreneurship as the most important single source where Europe lags in the development of the industry. Though the EU Lisbon agenda predicted to surpass the US in competition, innovation and technology by 2010, at this stage, in 2008, if ‘no miracle occurs’, it appears that the biotechnology gap between the EU and the US will be even larger than before, and ‘leapfrogging’ in the sector is increasingly unlikely [12].

A most recent report [13] laments the fact that new expanding markets in the EU are often not in the forefront of development, e.g. in the case of biopharmaceuticals, biologics and recommends an integrated industrial policy emanating from the EU Lisbon Strategy (European Research Area) in conjunction with its Sustainable Development Strategy, Health Care and Food Safety, and quality of life enhancement.

Comparisons with the US biotechnology industry are made throughout. In the United States, biotechnology was the motive force behind the first large-scale entry into the pharmaceutical industry since the early post World War II period. Entry rates soared in 1980s and remained at a very high level thereafter, with waves linked to both the stock market performance and to the appearance of successive new technologies. One notable difference between Europe and the US in the 1980s and at the beginning of the 1990s has been that, while in the US a new research-intensive industry in the life sciences has continued to develop, there has been no equivalent specialization in entrepreneurial biotechnology in Europe. Partly reflecting this difficulty to develop a biotech industry the perception has emerged that the US will keep a competitive advantage over Europe in biotechnology.

As earlier in the US, with a few exceptions, none of Europe's large traditional chemical/pharmaceutical companies played much part in the first decade of 'the new biotechnology'. Most of the companies were uncertain what to make of the new technology and especially of the hype surrounding its development that grew with the small firm sector in the US. Some had experience of fermentation technology through the production of biological

pharmaceuticals such as penicillin, or with the use of enzymes and the techniques associated with immobilization of enzymes that had been developed during the 1960s. The latter, however, had tended to be the preserve of medium-sized specialist companies such as Gist Brocades (Netherlands, acquired by Shell) or Novo Nordisk (Denmark) rather than big firms. A number of the larger companies had also dabbled into single cell protein research, including Shell, BP, Hoechst and ICI [14].

This combination of uncertainty, skepticism and inexperience led to what might be called a minimalist strategy on the part of most large firms. While avoiding large investments most of the companies built up teams of researchers large enough to keep abreast of the science and to monitor developments and competitors. Thus, in the 1980s, Bayer, ICI,Ciba Geigy and then Glaxo Wellcome all established small research teams in their corporate R&D laboratories with some exploratory undertaking in biotechnology [15]. Other companies, for example BASF, left even these moves until the early 1980s, having only minor interest in pharmaceuticals and being very uncertain whether biotechnology would have any relevance to their main interests in areas such as plastics and fibres.

One consequence of this strategy of 'watching and waiting' [16] was that it conceded leadership in the development of the new technology to American biotechs which were so closely linked to the academic base. In this phase of development relatively few of the major European chemical firms were to be found as partners to the biotechs, although some, such as Ciba Geigy and Hoffman LaRoche, acknowledging that the US science base in this area was much stronger than that available in Germany or Switzerland, threw tradition to the winds and placed research contracts with a number of biotechs as mentioned in Section 3. Hoechst, in placing a US$67m, 10 year contract in 1981 with the Massachusetts General Hospital (MGH), also linked itself directly to the US academic base and made arrangements for its researchers to be trained at the MGH, thereby implicitly acknowledging the limitations of its indigenous science base. Other companies, among them Glaxo, Wellcome and Bayer, chose instead to expand their own research base into the US, setting up laboratories which were able to link directly to the US research base.

By the mid-1980s the period of watching and waiting was over. Most companies recognized that, whatever their original reservations, biotechnology had established itself as an important enabling technology (i.e, a route to new product development) that would be essential for future product innovation.

The strategies chosen by the large companies varied from company to company. All were concerned to build up in-house competence. Some chose to do this internally, using existing and new linkages into academic science; others bought in competence through the acquisition of new biotechnology firms or through merger (and a subsequent reshuffling of assets) with American counterparts; yet others chose to retain external linkages with American and/or European biotechs. (see 5.4). Initially many of these researchers were grouped together in special Biotechnology Divisions but as time went by these were disbanded and the biologists and biotechnologists within them disbursed among project based multi-disciplinary teams. The investments in new plant and capacity brought the regulatory issues to the forefront for the first time. Most companies were prepared to accept the strict containment principles laid down by OECD guidelines of best (laboratory) practice [17] but the problems encountered by Hoechst in trying to bring their genetically engineered insulin plant on stream in Frankfurt in 1987 and the discussion of a five year moratorium on genetic research in (West) Germany caused uncertainty and raised fears about the future.

Given the need to build up in-house competencies, the pressure from companies on government at this time centered on improving the indigenous science base and on issues of linkage into the science base. Governments, for their part, were anxious, insofar as funding was increased, to see it linked to technology transfer schemes which would ensure that companies used academic research, and that the research was 'relevant' to industrial needs. Hence the various Science & Engineering Research Council (SERC) schemes in Britain, the CRITT (Regional Centers for Innovation and Technology Transfer) in France and the German Government Biotechnology Centers, all aimed at establishing university/industry linkage.

The more recent phase of the development of the new biotechnology starting in the 1990s sees products beginning to appear on the market and companies, both large and small, becoming more selective in targeting activities. Given the increasing emphasis on bringing products to market, the issues of regulation and intellectual property rights suddenly become very much more pressing and from the company point of view take precedence over all other issues of public policy.

The design of industrial development speaks much in favour of the American focus.

The US have pioneered the emergence of an effective division of labour between new, small companies, large corporations and other research institutions, which have different comparative advantages in the “exploration” and “exploitation” of new innovation opportunities [18]. Europe has been less effective in facilitating the growth of research-intensive ‘Dedicated Biotechnology Firms’ (DBFs).

While large multinationals, such as biopharmaceuticals and agro-food, may not need local technology suppliers, the presence of a local industry of research-based firms and technology suppliers is critical. On the one side, despite tendencies towards a wider internationalization of research, high technological performances tend to be linked to home-based research capabilities. On the other side, the biotechnology industry is, by itself, a powerful source of growth and social progress. The US biotechnology industry has generated, over the past two decades, a large number of new jobs and at least a dozen new world-class companies (e.g. Amgen, Chiron, Genzyme, Gilead and others), along with several new others of new general purpose technologies (e.g. Incyte, Human Genome Sciences, Millennium, Celera, and others). It has also produced a stream of revenues, most frequently in the form of royalties from licenses or R&D contracts and collaborations though it had over some years consistent losses [19].

Given the impact of biotechnology on social and economic progress, as well as its effects on downstream industries, both national European governments and the European Commission have developed a strong anxiety about European competitiveness in this field and have promoted the birth of a new industry of dedicated biotechnology firms.

5.4. Corporate Alliances

By exploring type and scale of corporate alliances in the European pharmaceutical industry we notice an interesting phenomenon of a biotechnology base pointing to evidence of a relatively deep penetration of the US biotechnology base by European pharmaceuticals such as GSK, Novartis, Roche, Bayer, Sanofi-Aventis, Astra Zeneca. Examining the extent of alliances we notice that there has been a shift over the course of the last ten years from R&D

agreements, which dominated in the early years, towards marketing and licensing agreements. In other words, whereas ten years ago the alliances were to supplement internal research work, today they fulfill a more important role, namely as a key supplier of potential new products. This suggests that in spite of their substantial investments in in-house biotechnology since the mid-1980s, these companies are still short of key biotechnology products for their new product portfolios. It also illustrates the complementary nature of the investments vindicating network economy impacts as detailed in Sections 1 and 3. In order to be able to exploit the new product ideas coming from biotechs, the large companies also need in-house capabilities. Without such capabilities, they would not be in a position to license and market the new generation of biopharmaceuticals.

To the extent how deeply some of these European companies are networked into the US biotechnology system gives little perspective of the relative position of European firms vis-a-vis those from other parts of the world. In particular, given fears in the early 1980s of the growing challenge from Japan it is interesting to compare European collaborations with those of Japan. The Biotechnology Reviews of Ernst and Young in the late 1990s [20],suggest that European firms have considerably been more active than Japanese firms in forging alliances with US biotechs but of course the latter are somewhat smaller and more preoccupied with Japanese pharmaceuticals as followed in Section 6. In general, we have seen a structural shift in transborder mergers and acquisitions activity, in view of pharma-biotech deals, as EU-EU transactions have increased their share at the expense of EU-US and US-EU pharma-biotech deals [21], among them British companies took a major share. However, it comes as no surprise that the value of transatlantic deals was usually larger.

5.5. INNOVATION TRENDS

This section provides an overview of the innovative performance of medical biotechnology in Europe. It looks first at the general structure and trend in innovative activities, as measured by patent data and patent citations. Second, it examines in more detail the localisation of inventive activities in biotechnology across macroregions and countries, always relying on patent data.

The use of patents as an indicator of innovative output is largely justified by the peculiarity of the technology and the widespread patenting practices at all levels of the industry. While in other industries patents are a highly imperfect indicator, in biotechnology they closely reflect innovation output.

Using OECD patent statistics over the last decade [22], the available empirical evidence shows that the US are and continue to be the overwhelming locus of innovation in biotechnology, both in number and value, followed by Japan, Germany, UK, and France in that sequence. From 1990 to 2000, the United States increased by 9 percentage points its share of all biotechnology patents granted by the USPTO (US Patent and Trademark Office). The share of Japan declined by 11 percent. A modest increase occurred in the case of Denmark (+ 1.1percent), while Germany lost a little ground (- 1.2 percent). The patent shares of all other European countries have remained relatively stable over the last decade. Between 1990 and 1997, national shares of biotechnology EPO (European Patent Office) patent applications were relatively stable, with the exception of Japan, which saw a decline of 6

percent. The UK shows the strongest performance (+ 2.1 percent). The shares of the other European countries have remained relatively stable over time.

Comparing the US with the EU-25 (EU 25 member states) over the last decade until 2005 we observe a consistent gap in patent counts though with a diminishing trend in favour of EU-25 though US patents still have a higher commercial value per patent measured in terms of leading products in the market [23].

Patent citation data provide a better measure of the technological and economic potential value of innovative activities than patent counts. Citations are a measure of the importance or impact of inventions and a proxy for knowledge flows among patenting institutions. Widely-cited patents tend to be 'seminal' patents, i.e. key inventions which further patents must refer to. Moreover, high citation rates have been shown to correlate with the economic value of patents. Thus, a high number of citations received by a given firm or country can be interpreted as a measure of the quality and relevance of its innovative activities. The data also show that the share of citations referring to US patents is substantially higher (around 55 percent) than the share of simple counts, suggesting that on average US patents are relatively more important. Moreover, among European countries, only UK patents show a higher share for citations than for patent counts. Citations received by a given firm or country can be interpreted as a measure of the quality and relevance of its innovative activities. On the basis of a subset of 'highly cited' patents (i.e., patents receiving at least 10 citations in the period 1978 - 1995 (with citations up to 1997), the US lead increases further to 65.4 percent.

DBFs account for more than 80 percent of DBFs' highly cited patents. In EU Europe (including Switzerland), around 65 percent of the highly cited patents belong to large incumbent firms and around 20 percent to DBFs (almost all of them British). Considering the top twenty institutions in terms of patent citations (i.e. institutions having the higher number of patent citations), 11 are American (4 DBFs,,3 incumbents, 4 universities and other research organizations), 2 are, respectively, German, British and Japanese, while Switzerland, France and Denmark appear with one institution. Almost all of these European institutions are large corporations, with the only exceptions of one British DBF and one French public research organization. At a more aggregate level, however, it is important to notice that Sweden turned out to have the highest share of highly cited patents in the life sciences filed in 1994-1998 [24].Patent data show also that the US are relatively more specialized in the pharmaceutical segment of biotechnology. Their share of highly cited agro-food patents is 13.5 percent as compared to a total of 17 percent. Only two European countries have highly cited agro-food patents, namely Germany (35 percent) and the UK (33 percent) of their total highly cited patents. The growth and impact of biotechnology is affected, to a certain extent, by the size and the growth of `downstream' industries, which demand biotechnology products and technologies [25].The countries that recorded the highest growth in the GNP share of pharmaceuticals are the US and the UK, while Germany and Japan experienced a much slower growth. As for chemicals, UK, Germany and France have the highest share in GNP.

To assess innovation trends one has to take into account the major facilitating factors for Europe.

First, markets for technology and networks of collaborative agreements are important in biotechnology.

Second, the biotechnology patents by US assignees invented in Europe are more interdisciplinary than those of the European assignees. This finding is specific to biotechnology and suggests that they are also potentially more valuable.

Third, US biotechnology patents developed in Europe are the outcome of teams of inventors located in different regions. This suggests that US biotechnology patents enhance international and inter-regional collaboration in Europe.

Fourth, small firms produce a large amount of inventions in biotechnology.

Fifth, the network (hub) of the biotechnology collaborative projects is largely US based, despite a recent increase in the participation of European biotechnology organizations. European DBFs tend to be less active in the networks and they do not seem to be able to attract US established pharmaceutical companies as developers of projects originated in Europe. Rather, they turn preferentially to European partners.

Sixth, public research organizations (PROs) in Europe tend to be focused on the generation of new research opportunities, while they tend to be absent from the downstream stages of product development. Moreover, European companies tend to access markets for technologies in biopharmaceuticals later on during product development (clinical research and marketing), and they are less active in the early stages of research. In synthesis, product innovation in biopharmaceuticals is highly dependent on the capabilities of US companies.

Recently, open-source approaches have emerged in biotechnology. Sequencing the human genome resembled an open-source program; it placed all resulting data in the public domain rather than allow activities to patent results separately. Open source is also merging in bioinformatics and systems biology. Apparently, an open-source approach works in biological research tools and pre-competitive platform technologies though it may be more challenging in downstream product development where competitive rivalry between firms becomes more dominating.

5.6. THE EUROPEAN BIOTECH INDUSTRY IN DIVERSITY

The lack of a general and commonly accepted definition of biotechnology affects the reliability and the comparability of official analyses and statistics, making any measurement extremely difficult. Historically, the definition criteria adopted from different national and international sources have been heterogeneous. Here we follow the definition of biotechnology developed by the OECD [26]. This definition focuses on techniques (tools, manipulation and know-how) that either modify existing living organisms/part of them, or transform material, of living origin or not, by the use of processes involving living organisms, for the purpose of producing new (scientific) knowledge or developing new products or new processes.

The following classification is referred to:

- DNA (the coding): genomics, pharmacogenetics, gene probes, DNA sequencing/synthesis/amplification, genetic engineering;
- Proteins and molecules (the functional blocks): protein/peptide sequencing/synthesis, lipid/protein engineering, proteomics, hormones, and growth factors, cell receptors/signaling/pheromones;
- Cell and tissue culture and engineering: cell/tissue culture, tissue engineering, hybridisation, cellular fusion, vaccine/immune stimulants, embryo manipulation;

- Process biotechnology: Bioreactors, fermentation, bioprocessing, bioleaching, bio-pulping, bio-bleaching, biodesulphurisation, bioremediation, and biofiltration;
- Sub-cellular organisms: gene therapy, viral vectors.

In addition to `core' biotechnology organizations identified according to the OECD definition, we take into account those firms which are focused on the development of tools, instruments, and devices that apply directly and prevalently to biotechnology product development, such as bioinformatics, high-throughput screening, parallel processing, combinatorial chemistry.

Most of the dedicated biotechnology organizations, especially in Europe, are young and small that they hardly show up in any survey. They are deeply involved in set up and early-stage R&D activities that do not provide any externally visible signal, be it a scientific board, a deal, or a first-round of financing.

A third limitation of currently available statistics is a consequence of the fact that organizations active in biotechnology are typically heterogeneous and embedded in complex proprietary and collaborative networks. They range from public research organizations (universities, hospitals, research labs, foundations, and institutes), to large pharmaceutical, agro-chemicals, food and chemical companies (typically, highly diversified multinationals with several divisions and intricate proprietary and control links). DBFs play a pivotal role in connecting heterogeneous components and actors. As a result, boundaries among different organizations are often blurry and it becomes hard to count the number of independent units. In order to take into account the existence of these complex systems of innovation, production, and control, the organizations monitored in the survey have been classified according to four main categories:

Independent dedicated biotechnology firms (DBFs): (i) core biotechnology firms: European private and public firms specialised in biotechnology product and process development; (ii) specialized suppliers, e.g. firms active in combinatorial chemistry, bioinformatics, DNA sequencing instrumentation, and in the production of tools and techniques which are used by `core' biotechnology companies.

Established companies active in related fields (ECs): large companies that do have asound research position in modern biotechnology. Although the core business of firms in this category is not in biotechnology, they are actively involved in biotechnology research and development;;

Biotechnology divisions: units that operate in biotechnology and are controlled either by established companies or by DBFs; Public Research Organizations (PROs): research institutes, universities, hospitals and other public organizations with relevant scientific results in molecular biology and in fields and disciplines related to biotechnology.

According to an Ernst & Young Biotech Report for 2004 [5] there are 1730 independent dedicated biotechnology firms (DBFs) in Europe, which constitute core biotechnology firms (according to the OECD classification). Detailed data for each of these has been collected. Germany leads the league with about 400 small independent DBFs, followed closely by the UK. Taken together, Germany and the UK account for about one half of the total number of DBFs in Europe. France ranks third with over 200 biotechnology companies, followed by Sweden [27].

If one calibrates the number of DBFs using population or GDP numbers, a clear representation emerges, with Sweden ranked first according to both measures, followed by

Switzerland, Ireland, Finland, and Denmark. The UK, Germany and France have similar values while Italy and Spain have the lowest ratios. There are important differences in the composition of the industry across European countries. In particular, the UK and, to lesser extent, France, differ from Germany, both because of the high number of divisions of companies focused on biotechnology, and because of the higher number of large firms. Moreover, in the UK one can observe a higher number of non-industrial research institutes in the fields of molecular biology and biotechnology. In Italy and Spain the number of DBFs is particularly low when compared to the number of large firms or of divisions of large firms but at least in Spain efforts are underway to make a change [28].

Looking at the dynamics of entry, entry of most European DBFs peaked in 1997 and 1998. After 1999, in a four-year period of most intense entry, in which the overall number of EU DBFs almost doubled the rate of company formation decreased. This slowdown seems similar in nature to the one observed in the US at the beginning of the 1990s, and it could anticipate a period of stabilization, consolidation, and selection, with mergers, acquisitions, and exit offsetting new company formation. Here again there is much diversity in Europe. Scandinavian countries like Sweden and Denmark have experienced a relatively stable pattern of entry of new firms, while other countries, such as Germany, experienced an upsurge in the last five years precursing 2000 [29]. Germany accounts now for a third of the total number of new European firms (among those which entered the industry after 1995), followed by the UK and France.

As further explanation one should note that the dramatic increase in the number of European DBFs after 1995 to 2000 reflects to a large extent a flow of new DBFs associated with therapeutic applications of genomics, proteomics and new techniques, such as combinatorial chemistry and bioinformatics.

5.7. CONCLUSIONS

Overall, barriers of growth in European biotech have been to a varying degree: (i) the dominant role of public (state) organizations in scientific activities with fewer linkages to commercial enterprises, (ii) a risk averse environment with a conservative attitude toward failure and a lack of science/technological entrepreneurship, (iii) a critical public, media and political opinion toward the growth of biotechnology, in particular, toward agricultural biotech. All these factors still present today are slowing a catch-up with the US for some time to come.

What conclusions emerge in relation to the innovativeness of Europe's pharmaceutical industry?

- From a comprehensive perspective innovation is not easily measured in the pharmaceutical industry. It is a research intensive industry, but R&D does not necessarily lead to innovative drugs. Indeed, given the oligopolistic nature of the industry and the need to block and counter advantage gained by competitors, too much R&D is devoted to producing ‘me-too’ drugs and duplicating research undertaken by others. The same problem affects both patenting (too much defensive patenting) and counts of drugs under development (does a large count mean poor

management or real innovation?). The best measure, which effectively leaves it to the market to 'pick the winners', is to take numbers of drugs in the top selling 25 or 50 bracket on the market, but even this has its drawbacks, measuring past rather than present innovation and future potential.

- Using this measure, US companies, with slightly less than half of the top 50 best selling prescription drugs, including bio-pharmaceuticals prove to be the still in innovative lead with companies such as Johnson and Johnson, Merck, Eli Lilly and Pfizer [5] though lately faced with a decline in research productivity and drier drug pipelines to cope with, reinforced by the phasing out of major drug patents.
- Europe, with about the same level of best selling drugs is coming close though one has to admit that some of the drugs licensed to European pharmaceuticals come from US biotech firms through licensing.(A case in point is Roche's stake in Genentech's drug pipeline in cancer drugs (Herceptin, Avastin)). Japan holds only 8 to 10 in the pipeline but their market share over the past 15 years has been expanding, Within Europe it is the British companies, notably GSK and AstraZeneca increasing their share. Their position in world rankings has risen steadily over the last two decades, they have a larger market share of the highly competitive US market than most of their European counterparts and they have been steadily increasing their share of European and South East Asian markets. Britain is also host to a large number of overseas laboratories for American pharmaceutical companies. These are almost wholly staffed and managed by British personnel and in this sense both reflect and reinforce innovative capabilities in this area. The German and Swiss companies, traditional market leaders in Europe, fare above average, with Bayer, Novartis, Sanofi Aventis (now French with a German base) and Roche varyingly improving their share. It is notable, however, that it is Swiss and German companies that top the lists in terms of R&D and numbers of drugs under development. As a portfolio strategy they have recently been buying themselves into the generics market as counteracting a decline in R&D productivity which apparently plagues the entire industry.
- The key to the future lies with the biopharmaceuticals and biotechnology where European pharmaceutical companies were slow to develop in-house capabilities allowing the leading edge of the technology to be developed in the United States by the small, specialized dedicated biotechnology companies (DBFs). In contrast to the position in the 1950s and 1960s when the innovative new drugs were coming from the in-house research laboratories of the major pharmaceutical companies, today's innovative drugs have been 'discovered' in academic laboratories or the quasi academic laboratories of the DBFs.
- In some sense Europe's large pharmaceutical companies have shown surprising flexibility in this shift from chemistry to biology. Swiss and German companies have broken with tradition and bought into external research, both through linkages with the DBFs and through agreements of one sort or another which have given them access to the American science base. The French too have been active in developing such links, for example, by Rhone Poulenc's merger with Rorer providing that company with an American base for the development of pharmaceuticals. These linkages, combined with heavy in-house investments in the new technologies, means

they are now in a position to exploit developments in biotechnology. In the last few years in particular there has been a notable shift towards deals with DBFs which replenish product portfolios with drugs in development rather than the early deals involving exploratory research.

- The exception, until recently, have been the British drug firms which have chosen to exploit linkages with the British rather than the American science base. British capabilities in molecular biology and molecular genetics, combined with a more mature venture capital market mean that Britain also has had a stronger and more active small firm sector in biotechnology than any other country in Europe. Substantial investments in the public science base and the development of venture financing in other European countries, means that Britain is no longer as distinct in this field as it was in the 1980s.
- Significant changes have taken place in the last few years (from 2005). The emergence of a new 'generation' of bio-pharmaceutical research with developments in genomics, functional proteomics, bioinformatics,combinational chemistry and medical nanotechnology have seen Swiss and British companies, such as GSK, investing heavily in US capabilities. Also German-French Aventis, now Sanofi-Aventis, is following suit. These developments suggest that all companies are now shifting from the old model of concentrated in-house R&D to one which accepts a new extended division of labour, with specialist companies performing specialist roles.
- These changes reinforce other cost cutting pressures on the major pharmaceutical companies, especially pressures from governments anxious to limit the public sector liabilities on drugs expenditure. The spate of mergers already seen in the industry, which seek to reinforce research and rationalize distribution systems, are likely to be followed by others as companies reassess capabilities and reposition themselves in the market.
- The US are more specialized in biotechnology research compared to Europe and Japan. However, some of the smaller European countries (in particular, Scandinavian countries) meet or surpass this advanced level of innovation [30]. The share of biotechnology patents invented in the US and assigned to European organizations is higher than that of other chemical sectors, This suggests that the US are an attractive location for biotechnology research conducted by European organizations
- Strategic alliance formation between pharmaceutical and biotech firms is still largely US based with European based pharmaceuticals tapping into American biotechs while US pharmaceuticals are less attracted to European biotechs.

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Chapter 6

EMERGING ASIAN BIOTECH-PHARMA INDUSTRY - ANALYSIS AND TRENDS

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"The growth of the Asia-Pacific biotechnology sector in recent years has been fueled by increased public and private sector focus." Ernst and Young, Beyond Borders, Global Biotechnology Report 2007

ABSTRACT

Emerging Biotech-Pharma Industry in Asia reviews the current strong emergence of the bio-pharmaceutical industry in both mature and emerging Asian regions amid severe pressure to innovate and to improve competitive positioning beyond domestic markets. It shows how the emerging, small and underfunded bio-pharma companies in Asia form alliances domestically and across national borders as part of their business strategy and industrial policy.

6.1. INTRODUCTION

The biotech industry in most Asian countries is lagging in development, share and size to that in the US and Europe. It is relatively small in terms revenues and expenditures on R&D. But governments of some countries like Japan, Taiwan, Singapore, South Korea, India and China strategize that the biotech sector would be one of the next engines of growth for their economies. The substantial surge in R&D investments, 25.5 percent on average in 2004-2006, Ernest & Young [1,2], reflects the drive in Asia to innovate which is the lifeline for

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companies in the industry. However, there is a significant diversity in scale and scope of biotech ventures, for example, not counting China, the number of biotech ventures was highest in South Korea (300) and lowest in Malaysia (4), as by 2003 [3].

Biotechnology is profoundly changing the health care industry with the emergence of biopharmaceuticals, bioinformatics and bioservices. We will focus on diverse companies in Asia that are involved in development and applications of biotechnology as well as analyze their strategies to survive and thrive in the regional and global competition. New biopharmaceuticals for the treatment of diseases common in Asia such as respiratory and infectious diseases, cancer and cardiovascular ailments are the focus of many biotech firms [4]. Expensive and novel medicines may still be unaffordable to the majority of the population in India and China where health insurance is poor or non-existent and price is very important for consumers; hence generic drugs are in great demand. So it is left to Japan, South Korea, Singapore and Taiwan, the more advanced countries in Asia that have advanced health care systems, to serve as important research based lead markets for innovative but costly medicines. India has a strong bulk and generic manufacturing of vaccines, recombinant therapeutics, and diagnostics most of which are to meet the domestic health needs (such as hepatitis B, typhoid, diabetes, cancer, cardiovascular, malaria, cholera, encephalitis, HIV) of the 1 Billion population. The same is true for China where most of the drugs for sale are generics used for treatment of hepatitis, cancer, stunted growth, diabetes and cardiovascular diseases. With China intensifying its efforts in genomics and stem cells, they have also developed biomedical products for the treatment of hepatitis B, SARS, cancer, anemia, cardiovascular ailments and hepatitis B, the more common diseases in the country [5]. According to Ernst and Young [6] there have been close to 700 (public and private) companies in the Asia Pacific market, most of them small,emerging and some being used for offshoring to top Western pharmaceutical companies [7]. A reverse flow of western educated Chinese nationals has the potential of building a new generation of biotech startups in their home country. In some countries such as South Korea and Japan much of biotech has been conducted within the conglomerates and by companies in related but established industries (pharmaceutical, chemical, food, beverages and others). This section will study how biopharmaceutical companies in the region are pursuing multiple sources of competitive advantage in an industry that has become more global and where competition has become more fierce and pressure for cost, time and novel drugs are high.

6.2. Fledging Biotech Industry in Asia

Japan's traditional strength in biotechnology is in enzyme production and food fermentation. In the early 1980s, some large Japanese firms in the chemical and food sector had been involved in biotech research in collaboration with foreign companies. Nevertheless, the biotech sector became fragmented and did not grow as expected. For example, Mitsubishi Kasei (which merged with Mitsubishi PetroChemical to form the Mitsubishi Chemical in 1994) was already engaged in biotechnology research and in 1982 allied with Genentech.

Under license from Genentech, Mitsubishi Chemical brought into the market two rDNA drugs: issue plasminogen activator for coronary thrombosis and hepatitis–B vaccine. Likewise they have collaborated with IDEC, now Biogen IDEC, a US biotech company for

the development of therapeutic monoclonal antibodies for auto-immunity and transplant rejection [8]. Kirin Brewery, the largest beer company in Japan, established in 1982 a drug division and did research on anti –cancer, cardiovascular and immuno/allergic medications. (After a few years of having a strategic partnership, Kirin took over a key DBF, Kyowa Hakko Kogyo, in 2007). At that time Kirin was able to launch its first gene recombinant drug erythropoietin (EPO), sold as Espo(EPO), used to treat anemia of patients undergoing dialysis with technology from Amgen. EPO is a hormone used to increase the production of red blood cells to cure renal anemia, a drug which recently got scrutinized for risk on potential tumor growth by the US FDA. Kirin and Amgen also co-developed a G-CSF (granulocyte colony stimulating factor), commercialized as Gran. G-CSF promotes the production of white cells and is used to treat cancer patients that are suffering from leucopenia caused by chemotherapy and bone marrow transplants. Kirin successfully marketed EPO and G-CSF in Japan as well as in Taiwan and South Korea in the early 1990s. The big Japanese pharmaceutical companies in spite of consolidation did not venture into the area of biotechnologyunlike some non-pharmaceutical companies, and opted to concentrate on chemical and small-molecule drugs. For this reason, the biopharma industry in Japan has grown only 2.5 percent during the past two decades compared to more than 10 percent in the US and Europe [9].

China on the other hand has a strong traditional indigenous and herbal based product sector and the biotech sector, notably the medical part started to emerge in the 1980s. In the mid -1980s most of the drug companies in China were publicly funded, state-owned or spin-offs of public research institutions that produced generic drugs [10]. In China, the best high standard research is done by scientists in publiclaboratories and universities which hold 80 percent of the patents for therapeutics and vaccines [5]. Since 1947, India has created a strong foundation in terms of science and technology which contributed to the growth of its biotechnology sector, more specifically to a strong pharmaceutical industry. But the expertise of the sector relied for a long time on the production of generics and with Ranbaxy and Dr. Reddy among the leaders in the field. India houses world champions in generic pharmaceuticals even after accounting for recent product quality concerns. It has a process patent law enacted in 1970 (amended in 2005 thus insuring more IP protection) that allowed pharmaceutical companies to manufacture drugs of other pharmaceutical companies provided they vary the manufacturing procedure. Using their own process they could then manufacture more affordable generic drugs. The biotech industry in India started in 1978 when Biocon, the first biotech company in enzyme production was founded. In the 1980s and early 1990s, however, public institutions were the ones mainly involved in biotech research in rDNA, immunology, molecular biology and genomics. In 1996-1997, private biotech firms (e.g. Bharat Biotech and Shanta Biotech International) introduced their first recombinant Hep B vaccines. Overall we learn that Indian companies such as Wockhardt, Biocon, Shanta, Bharat and Dr. Reddy are busy to manufacture recombinant drugs and vaccines but almost all of them are generic biopharmaceuticals that are low-priced and useful in addressing India's health needs [11]. It appears that thesecompanies will plow their profits into R&D and drug discovery may thus be the future leaders of research based biopharmaceuticals.

Though the biotech sector in the more advanced Asian countries started decades ago it has remained lagging vis-a-vis their Western counterparts. Most R&D in biotech is still done in public laboratories and national universities, some headed by first class scientists that have access to state-of-the-art research facilities and infrastructures and these institutions often own the patents. In most Asian countries, with a partial exception of India and South Korea,

there has been an almost complete lack of science/technology entrepreneurship. Indian biotech entrepreneurship was partly initiated by Indian expatriates (mainly from the US) some of whom lately have been returning to their country to start biotech ventures. The other part resulted from spin-offs of well-established pharma companies, or IT related corporations (such as Infosys and Tata) expanding to biotech areas as in bioinformatics [12].

The sluggish growth of the biotech sector is attributed to insufficient incentives to commercialize biotechnology therapeutics, lack of a structure to connect scientific research with business objectives, hence limiting the transfer of technology to the industrial sector. As a consequence, with the lack of entrepreneurial engagement and venture capital, start ups were minimal. Few bioventure spin-offs from universities and public research institutions existed. Venture capital shied away from the more risky biotech sector because of a low rate of R&D success reaching the commercialization stage though clinical trials costs are comparatively low compared to rivals in western countries. But recently with bioventure funds established by the government, there has been an increase in spin-offs that are nurtured by the government run biocenters recently resulting in more IPOs. From 2002-2004, there were 11 biotech IPOs in Japan, two years after the government allowed university professors to be actively involved in biotech firms. As of 2005, there were 387 biotech startups half of which are into medical R&D, not to mention the 300 already established biotech firms. The small biotech firms in Japan have to work on their own with their limited capital since unlike in the US and Europe, the big Japanese pharmaceutical companies would rather do in-house R&D than form alliances with or acquire small local biotech companies.

China aspires to be a lead country for biotech not only in Asia. As of 2005 there are 300 biopharma enterprises in China. The government wants to develop home grown biotech firms as more state and local governments are financing quasi-venture capital companies as well as encourage multinational biotech firms to invest through foreign direct investment (FDI) in the country with low cost and easy market access as its main investment incentive.

6.3. Innovation Capacity

Many drug companies in India, China, South Korea and Japan have depended on and generated much of their revenues in the manufacture and distribution of “me-too” drugs for bulk manufacturing or on what is commonly called generics which do not require substantial R&D investment. This has given them increased revenues.However some Asian pharma firms have exhibited innovative capabilities. They have come out with innovative drugs that are marketed by more well–known and internationally operating pharmaceutical companies such as those onceived in Japan.

In 2001, two new drugs, Radicut (Edavarone) for acute stage celebral infarction and Cleanal (Fudosteine) for chronic obstructive pulmonary ailments [13] were developed by Mitsubishi Pharma. The company raked success in these two drugs used to cure ailments where there are not that many alternate medicines available.

Nevertheless, Japanese companies for some time have been slow to develop blockbuster innovative drugs. In contrast to manufacturing Japan lags behind the West in terms of drug discovery and development. In the US, it takes drug companies an average of 10 years to develop and commercialize an innovative drug while in Japan it takes 15-17 years [14]. In

terms of biopharmaceuticals, recently Japanese companies are active in fermentation techniques and monoclonal antibody (Mab) manufacturing.

Table 6.1. Japanese blockbuster pharmaceuticals

Product name	Medical application	Company that developed the drug	Company that markets the drug	Product name in foreign market
Pravastatin	Cholesterol	Sankyo	Bristol-Myers Squibb	Pravachol
Lansoprazole	Anti-ulcer	Takeda	Tap	Prevacid
Resuvastatin calcium	Lipid-lowering	Shionogi	Astra Zeneca	Crestor
Aripiprazole	Schizophrenia	Otsuka	Bristol-Myers Squibb	Abilify
Donepezil Hydrochloride	Alzheimer	Esai	Pfizer	Aricept

Source: Kermani, F., L. White and C. Gooch, (2001)Japanese Pharma Looks West, Business Briefing, Pharma Outsourcing, http://www.chiltern.com/_data/articles/8.pdf and Nakamoto M., and D. Pilling (2001) Pharmaceutical 2001/Japanese Focus, Financial Times, April 26.

For the former, Bipha Co. (now 51 percent owned by Mitsubishi Pharma) produces recombinant human serum albumin (rHSA) which is a recombinant protein derived using yeast fermentation. For the latter, Chugai (now 51 percent owned by Roche) has taken the difficult task of manufacturing Mab needed in the development of Actemra(r), a genetic recombination injection for the treatment of cancer, inflammation and rheumatoid arthritis.

In South Korea where a majority of drug companies manufacture generics, some have developed the top selling drugs in the country such as Easyef for diabetic foot ulcers(Daewoong Pharmaceuticals) and Balofloxacin, an oral active fluoroquinolone antibiotic (Chongwae Pharma) [15]. South Korea is a late comer in life science products but the "Biotech 2000 " program of the government aimed to catch up. The following companies are now doing R&D for innovative drugs and vaccines : LG Life Science (Hepatitis B), Korean Vaccine (typhoid), Dong Shin Pharmaceutical (bacterial meningitis), Cheil Jedang (renal cell cancer), Daewoong Pharmaceutical (anti ulcerant for diabetics), Callontech (cartilage damage) and Samyang Genex (cancer and diagnostics), LG Life Sciences (Hepatitis C), Dong Shin Pharmaceuticals (osteoporosis); and bioinformatics and functional genomics: Bioneer (DNA synthesis), Macrogen (Genotyping) and Lifecord (Cryopreservation of cord blood stem cells) [16].

6.4. GOVERNMENT INITIATIVES IN BIOTECHNOLOGY

The governments' role to develop the biotech sector comes in many forms. For one, the Korean government has invested around US $4.4b from 2000-2007 into the biotechnology sector. Funding goes to the country's best universities and public laboratories to do adult and embryonic stem cell research whereas the Ministry of Commerce, Industry and Energy subsidizes and provides fiscal incentives to the private sector to indulge in the applications of

biotechnology R&D. One good example is Macrogen which is a spin-off business venture of a Seoul National University laboratory in 1997. The company designs DNA sequencing and is mapping the "Korean" genome structure. It has mapped 100,000 bacterial artificial chromosomes of Koreans containing the whole genome of a Korean person which it utilizes to develop DNA genome arrays [16].

Public research institutions, laboratories and universities are known for their leading roles in R&D, usually in line with the government's overarching goal of safeguarding the basic needs and health of the local people. Some of the research centers are arms of the government ministries and some small biotech companies are spinoffs from these public and university laboratories. The main purpose of the collaboration between the public institutions and the biotech companies is to find solution to diseases prevalent in the country/region. An example of this public-private alliance is the Novartis Institute for Tropical Diseases (NTD) in Singapore which Novartis is pursuing in partnership with the Singapore Economic Development Board on an initial US $122m budget to discover medicines for the treatment of tropical diseases like malaria, dengue fever and tuberculosis. Merlion Pharma, Singapore's first homegrown enterprise, was founded in 2002 with the privatization of the Center for Natural Product Research (CNPR) in partnership with Fujisawa (Japan), Johns Hopkins (Singapore) and the National Cancer Center to discover and develop new therapeutic drugs from natural sources. Merlion boasts of the following assets and capabilities of CNPR which it is capitalizing on: advanced drug discovery techniques, efficient screening of natural product samples in search of various new bioactive compounds, and the biggest and most diverse collection of natural product samples in the world [17]. Singapore appears to be the only case where biotech development goes beyond indigenous incubation and where foreign know-how, entrepreneurship and capital is encouraged as part of a fast development strategy.

In China, meanwhile, Novartis formed a partnership in 2004 with the National Shanghai Institute for Materia Medica which developed expertise to identify compounds derived from traditional Chinese medicine that Novartis may be able to develop into new drugs. Sinovac Biotech in collaboration with the Center for Disease Control of China are actively engaged in the research and development of a vaccine for Avian flu which is a recent phenomenon in Asia.

6.5. Genomics and Stem Cell Research

Genomics and stem cell research are biotech areas where Asia, with its heterogeneous gene resources is trying to carve out a niche. Stem cell research has received a lot of attention lately due to its potentials in the treatment of diabetes, Parkinson's disease, cancer, and spinal cord injuries. Stem cells are elementary cells which can form a spectrum of human cells and can differentiate into multitudes of cells. These cells have the healing potentials by forming cells which replace cellsthat do not function due to disease or accident [18].

For stem-cell researchers, Singapore offers one of the world's most liberal legal environment. The law permits stem cells to be taken from aborted fetuses, and human embryos to be cloned and kept for up to 14 days to produce stem cells (though the usefulness of the paradigm recently has changed). This is one field the Biomedical Research Council (BMRC) wants the city state to have a niche market. The government thus provided US

$600m to fund startups in stem cell and life science research, US$22m of which has been put into ES Cell International. Stem cell research in Singapore was pioneered by Prof. Ariff Bongso. He successfully isolated stem cells from a five day old embryo in 1994. Eight years later, again he was able to culture human embryonic stem cell lines without the assistance of mouse feeder cells [19]. ES Cell International is a spin-off of this work. The company now owns 6 of the human embryonic cell lines that are supplied worldwide. Currently the research focus of ES Cell International is on the use of stem cells as cure for diabetes. According to the Stem Cell Research Foundation, embryos are the source of the most versatile stem cells.

Due to ethical considerations, research has been directed on cord blood as the source of stem cells. In this regard, Cell Research Corporation in Singapore has successfully differentiated the outer amniotic lining of the umbilical cord into specific cells such as skin bone and fat. Stem cell research results are now being tested for their applicability in Singapore. Leukemia patients at the Singapore General Hospital are being treated with haematopoietic stems cells taken from the umbilical cord blood [19]. Cognizant of the market potentials of the stem cell research results, CyGenics was established in 2004 in Singapore. The company markets adult stem cell related products, services and technology with the assurance that they will make the technology safe for human use. The company has a blood bank that stores the frozen umbilical cord blood for possible use for lymphoma, anemia and bone marrow cancer [20].

After the series of regulatory and economic reforms in China, the country has started to develop its medical biotech industry only in the 1980s. One sector where China is making a mark globally is in the area of genomics. Among the developing countries China was the only nation to join the Human Genome Project and thereby paved the way for the establishment of the Beijing Genomics Institute and the Chinese National Genome Center [5]. The country is also gaining headway in gene therapy. At a cost of US $9.6m, Shenzhen Sibono GenTech was able to develop Gendicine, a recombinant ad-p53 gene therapy type for the treatment of head and neck cell carcinoma. Moreover, Chinese researchers were the first to research on adult stem cells from blood and umbilical cord. One advantage China has is its many homogenous subpopulations which are important for clinical trials and good for functional genomics and disease gene identification.

6.6. Interindustry Convergence: Bioinformatics and Nanomedicine

Various high tech industries are converging or intersecting and have diverse applications.The technology and skill demands of those firms go often beyond the individual firm’s capability. The better option to pursue amid the fast changing demands of the times and global business environment in biotechnology is to collaborate and cross-license technology. Biotechnology has become so advanced that it has become virtually a multi-disciplinary industry. The convergence of complementary industries are warranted due to the pressure of time,risk, and costs. Bioinformatics is one case in point. The levels of information technology and expertise in Japan, Singapore, South Korea, Taiwan and India are very high. These countries have top ranked and highly competitive IT companies.

This gives them leverage in areas where IT and biotechnology converges, e.g., bioinformatics which is the interface between experimentation and computation [21], especially in the field of gene sequencing and stem cell research. This relates to the important role of bioinformatics due to the complex computations needed in basic research and experimentation. Japanese IT firms are forming partnerships on their own with domestic and international biotech firms to combine their complementary expertise. Hitachi formed a synergy with Yamanouchi (now merged into Astellas) in genomic research. Itochu using its discovery platform for high level protein research has allied with US Proteomics, a bioinformatics firm. Unlike Japan where highly competitive IT firms seek their partners at home and abroad, in Singapore where segments of the biotechnology sector are still in its nascent stage, the government leads the initiative to develop bioinformatics in the country by creating the Center of Systems Biology and together with Eli Lilly will apply bioinformatics in the study of biological systems [21].

Japan's advanced development of nanotechnology could always give it competitive edge in the application of nanotechnology for pharmaceutical applications. Japanese companies are now gaining headway in putting into clinical use nanotechnology as a new drug delivery system targeting cancer cells. The concept simply involves the cancer drug, Paclitaxel, being encapsuled in ultrafine special polymers. The minute capsule is injected into the blood vessels which then move through the veins, passes through the openings in the blood vessels and attaches to the cancerous cells [22].

The procedure is still in a Phase I clinical trial in Japan. This new drug delivery system was developed by NanoCarrier, a biotech start-up and Nippon Kayaku, a chemical and pharmaceutical company. Japan is making a lot of progress in nanotechnology and its functionality in terms of nanomedicine and bioimaging. A group of researchers from Kyoto University, Terumo and Nippon Shinyaku are developing a technology to treat malignant tumors by injecting patients with peptides (an amino acid compound). The peptide that dissolves when there is oxygen has a nano biological probe with particles that send out lights, attached to it. Cancer cells develop and metastasize in areas where oxygen is scarce. The peptide dissolves only in healthy cells and not in cancerous cells, hence, the peptide accumulates where the cancerous tumor is. Scientists were able to attach light emitting particles for identification and cancer cell killing therapy for cure, to the peptide [23].

6.7. Firm Strategy in Alliance Formation

Many pharmaceutical companies are under pressure to improve productivity and to maintain their leadership. Asian pharma companies receive some of their revenues from the production of generic drugs or in-licensed products. But as recent developments show the dwindling of new products in the pipeline and with patents of blockbuster drugs soon to expire they are much concerned about their long term profitability. The cost of developing innovative drugs is very high and the rate of success from development to commercialization of the drug is rather low, so pharmaceuticals companies have to review their business strategies. On the other hand biotech companies, most of them small, are gaining ground in the heath care sector competing with established pharma. In this light, there are now consolidations in the bio-pharma sector characterized by more mergers, partnerships and

alliances between domestic pharmaceutical and biotech companies, as well as those that transcend national borders to rationalize their activities and bring together complementary competences and assets [24] which each of the company lacks, facilitate entry into a foreign market and increase market presence; and spread and reduce costs and risks in the costly development of new drugs. In what follows, case studies of how bio-pharma companies in Asia build strategic alliances to fulfill these objectives will be presented.

Horizontal Alliances in Biotech Industry, Economies of Scale and Scope

Actual competitors and companies in the same line of business (horizontal alliance) merge and ally together to have more market power and new economies of scale and scope which are very evident in the Japanese pharmaceutical sector. Japan is (country-wise) the second biggest drug market in the world worth US$ 64.7b in 2004 hence is an attractive market for the big and well-established pharmaceutical companies such as Pfizer, Novartis, Bayer and AstraZeneca. During the time when the Japanese market was protected from multinational drug makers, domestic pharmaceutical firms relied on the domestic market and enjoyed high profitability mostly from licensing deals with foreign companies. In 2003, Datamonitor reported that sales from drugs that have been developed a decade ago and many whose patents will expire (referred to as long-listed drugs) are the main sources of revenues of 60 percent of drug companies in Japan [25]. With sales growth remaining stagnant or declining for these mature and disappearing pipelines, companies then had to resort to in-licensing.

Recently, the Japanese government has been exerting pressure on drug pricing through limitations in their public insurance reimbursement schemes and restricted coverage. To enhance competition non- Japanese pharmaceutical companies face fewer regulatory (legalistic) constraints to market entry. With the aging population in Japan, the government under the national insurance system would like to scale down ever increasing medical expenses. This will have bigger repercussions on the revenues of small and medium sized pharmaceutical companies such as Tanabe, and Shionogi since 92 percent and 90 percent of their sales, respectively, are from the domestic market unlike the big pharmaceutical companies like Takeda and Astellas that derive 40-50 percent of their sales from overseas markets. The recent revisions in the Pharmaceutical Affairs Law which took effect on April 1, 2005 made it easier for foreign pharmaceuticals to do business in Japan with regard to product registration, industry standards, clinical trials, labeling, advertising, product classification, and intellectual property. From now on, foreign multinationals can market the imported drugs themselves and can use contract manufacturing instead of having to build their own manufacturing facilities in Japan. The increasing presence of multinational pharmaceutical firms in Japan is evident by the rise in the market share they hold from 18 percent in 2002 to 27 percent in 2003. GSK, Pfizer, Novartis and AstraZeneca now market their products using their own sales forces. These companies are offering their local rivals in Japan tough competition with the adoption of aggressive marketing strategies and more importantly the continuous introduction of novel drugs that they have sold successfully in other overseas markets than license their products to Japanese pharmaceutical companies [26]. The Japanese drug companies are now faced with two dilemmas: no new drugs in the

pipeline and no resources to have international reach. To counter the size of these big pharmaceutical firms in the US and Europe and the drug price regulation in the domestic market which impacts on their profits, pharmaceutical firms in Japan are consolidating and rationalizing their operations through mergers: Yamanouchi and Fujisawa merged to become Astellas in April 2005, Sankyo and Daiichi Pharmaceuticals merged to become Daiichi Sankyo in October 2005 and Dainippon Pharmaceuticals and Sumitomo Pharmaceuticals merged to Dainippon Sumitomo in October 2005. These mergers seek to improve their products in the pipeline, streamline their R&D and expand their sales force. But the ultimate purpose of these actions boils down to being able to compete with well-established foreign firms amid a stagnant domestic market and increasing global competition [25]. These consolidations however capitalize on their complementary strengths and broaden their product offerings of chemically based but not bio-pharmaceutical drugs. Likewise in China mergers between domestic pharmaceuticals are evident with the recent acquisition of Shanghai Pharmaceuticals of Shandong, Xinhua Pharmaceuticals and Topsun Group of Hubei Qianjiang Pharmaceuticals. The buyout of one domestic pharmaceutical company by another in the same line of business in the same market, like what is happening in Japan and in China, is one recent development in the industry.

In some cases a pharmaceutical company acquires a biotech company and in other cases a biotech company acquires a pharmaceutical company or still in other cases a biotech company acquires another biotech company. In these transactions, both parties involved are home grown companies and one company may have a promising drug candidate or a competence in hand that the other company needs. Avesthagen, an Indian biotech company has signed a joint venture agreement in 2004 with Cipla, a pharma major in India combining the prowess of the two companies in the development of biotech drugs for auto immune disorders, cancer, and cardiovascular ailments. The collaboration includes R&D of new technology platforms for expression of recombinant or genetically engineered proteins. In 2006, as Australia's largest pharmaceutical company, CSL, advances into protein based medicines (e.g. monoclonal antibodies), it merged with Zenyth Therapeutics, a local biotech company that has been developing antibody based medicines for inflammation and cancer treatments. Meanwhile Peptech another Australian-based biotech company bought the local biotech company, Promics in 2006 as part of its aggressive strategy which entails having immediate access to Promics' product that is already in clinical trials (e.g. anti-inflammatory drug candidate PMX53) and other compounds that are already in preclinical trials [27]. There is expectation of quicker returns because the deal reduces Peptech's R&D costs and risk since the product acquired is already nearing the end of the development process. Amid the rapidly changing global market, collaborative deals between companies that transcend national borders, where one of the parties involved can be a foreign company, will inevitably maintain competitiveness.

Cross Border Alliances

Learning –by- doing economics suggests that the more the firm produces it can exploit the benefits of the accumulated knowledge as it moves down the experience curve resulting to more efficiency and cost reduction. There will be more specialization and creation of dedicated assets and systems giving the firm competitive advantage. Hence, small biotech

firms who want to develop global scale medicines, can share and leverage on their unique strengths and capabilities or core competences with other firms by forming horizontal alliances across national borders. Merlion Pharmaceutical is a small home-grown pharmaceutical company in Singapore which was a spin off from a public institution, Centre for Natural Product Research (CNPR), a unit of Singapore's Institute of Molecular Biology. The core assets of Merlion include the world's largest and most diverse natural product sample library with potential pharmaceutical applications not to mention the high throughput (HTP) screening of natural product samples to discover an array of new bioactive compounds and natural product chemistry, skills for which reason many biotech foreign companies would like to collaborate with Merlion [28]. Banking on these prime competences Merlion has formed strategic alliances with foreign pharmaceutical and biotech companies capitalizing on its collection of natural compounds: (i) Sankyo (Japan) 2005: Discovery, clinical development and commercialization of new therapeutic drugs from the natural product chemistry [29]; (ii) NovImmune S.A. (Switzerland) 2003: Discovery and development of drugs for immunosuppression and immunomodulation using natural products [30] ; (iii) Athelas (Switzerland) 2003: Discovery and pre-clinical research of a new class of anti virus and anti infection drugs from natural product samples [31]; (iv) Genome Therapeutics (US) 2003: Discovery of anti infectives using natural occurring compounds [32]; (v) Abbott Laboratories(US) 2002: Drug discovery for therapeutics in the fields of oncology, antivirus, immunology and neuroscience using natural compounds [33]. Merlion formed only in 2002 sought quick expansion by acquiring stocks of two German biotech companies, Combinature and Athelas. Merlion expertise is in screening microbial, fungal and plant sources for new compounds but does not possess its own internal drug pipeline and clinical development capabilities for biopharmaceutics. Rather than allocating substantial time and resources in conducting in-house drug development, the acquisition of Combinature have provided them outright two novel antibiotics that were about to enter clinical trials already [28].

Japanese pharmaceutical companies would rather invest in foreign biotech firms abroad to invigorate their dwindling pipeline of new drugs. Takeda, Japan invested in 2006 US $230m in Xoma, an American biopharmaceutical company for it to take the lead in the discovery of therapeutic antibodies for Takeda, and Astellas put in US$815m into FibroGen, a biotech company in the US to develop drugs candidates for anemia [1]. For another, in 2004 Kirin Brewery has invested around US $45-65m into Merix Bioscience (now Argos Therapeutics) of the US, to do joint activities from research to commercialization of dendritic cell vaccines. With competition in the home market getting severe with foreign multinationals' market share in the increase due to the deregulation of the pharmaceutical market as well as their aggressive marketing strategies Japanese companies are collaborating with Western biotech companies. In 2003, Yamanouchi has inked an agreement with Phytopharm, UK, and Takeda with Evotec, Germany for drug discovery alliance for Alzheimer. And in 2004, Mitsubishi Pharma signed a deal with Vertex Pharmaceuticals to develop and commercialize Oral HCV Protease Inhibitor VX-950 for Hepatitis C in Japan and the Far East, and Takeda has an agreement with Andrx Corporation to jointly develop drugs for Type 2 diabetes.

Biocon, a leading biotech company in India has partnered with American drug development company Nobex to develop oral insulin for the global market and with a biotech company based in the US, Vaccinex. The Biocon-Vaccinex tie-up involves a joint R&D on therapeutic antibody products for the treatment of cancer, inflammation and autoimmune

diseases, combining Biocon's strengths in clinical research and biologic production and Vaccinex's expertise in human monoclonal antibodies, a move that would allow them to identify the antibody candidates and proceed with the clinical development posthaste and introduce the new anti-body products in India and in America and Europe. Not only Biocon but other biotech companies in India notably Avesthagen, Serum Institute of India, Biological E have taken the same business model of collaborating with foreign biotech or pharmaceutical companies to strengthen their positions in the biopharma industry and achieve their financial targets.

Outsourcing: Contract Manufacturing

For a considerable number of years now, outsourcing production (or what is referred to as contract manufacturing) of chemical-based pharmaceuticals to low cost countries in Asia has been a common practice but not biopharmaceutical production although this tendency is already changing. The biopharma industry in Asia is still in its infant stage and biopharma companies are still finding their niches but in no time some are proving their track records in terms of capability, cost and quality. In dire need of more resources to fund future R&D activities speedily, companies in Asia resort to contract manufacturing. Moreover, government regulations in Asia such as the revisions of IP protection laws in India and China serve as incentives for outsourcing.

In 2004 Biocon (India) launched a low cost human bio-insulin, the recombinant insulin (Insugen ™). Diabetes is a chronic disease worldwide and in India alone it is affecting 32m people in 2004 and is forecasted to reach 57m people in 20 years so there is the urgent need to offer insulin at affordable prices. The pressure to meet these local demands worked to the advantage of Biocon. Now it possesses the largest insulin manufacturing plant in India that gives it economies of scale and enables it to sell insulin as low as US$2.80/40iu/ml (international unit per milliliter). Cognizant of Biocon's insulin product and manufacturing capability, the company has agreed to supply Bristol-Myers Squibb its low priced recombinant insulin requirements. Under this partnership, Biocon can also benefit from the economies of scope when Bristol-Myers Squib markets the insulin in foreign markets.

Recombinant DNA (rDNA) technology or Genetic Engineering is an umbrella term for a set of experimental techniques that enable individual genes and DNA sequences to be manipulated resulting in genetically modified organisms (GMO) and products. There have been many potential applications of rDNA in medicine, agriculture and industry. Production of therapeutic products using the rDNA technology has several advantages such as provision of drugs that could not be produced by conventional methods, manufacture of sufficient quantities of drugs and provision for manufacture of safe drugs [34].

In 1996, the global sale of recombinant pharmaceutical products was approximately US$607b. In India, the commercialization of nine recombinant products has been approved – insulin (diabetes drug), alpha interferon (cancer drug), hepatitis B vaccine, GMCSF, G-CSF, blood clotting factor 7, erythropoietin (drug used in kidney failure), streptokinase (drug administered in heart attacks) and human growth hormone. All these products except Hepatitis-B are being imported at a cost of Rs 237 crores (US$53m). The four major recombinant products with high market potentials in India are human insulin, alpha interferon, and erythropoietin (EPO). Domestic and foreign pharmaceutical companies are

vying for the rising niche market for recombinant DNA Erythropoietin (EP0) in India. With the prevalence of kidney failure and anemia in the country, there is a big market for EPOs estimated at Rs 75 crores (US$17m) in 2005. The first to develop EPO was Wockhardt in 2001 under the brand name, EPOX. In 2005 after spending Rs20 crores (US$4.4m) Shanta Biotechnics launched its own version under the name, Shanpoietin. Other competitors and their corresponding EPO brand names are: LG Life Sciences (Espogen), Ranbaxy(Ceriton), Johnson and Johnson (Eprex), Emcure Pharamceuticals (Vintor), Intas (Epofit), Zydus Biogen (Zyrop) and Hindustan Antibiotics(Hemax). Most of these r-EPOs are rather expensive hence their usages are limited. To make the drug more available to treat cancer and kidney ailments, Wockhardt is now selling it at a lower cost of Rs 798 (US$18)/2000iu/ml. For its part, to compete in the EPO market, Janssen-Cilag CRF, the Indian division of J&J successfully introduced, Eprex by staging a different kind of competitive strategy: contacting the patients directly, educating the nurses and scientific marketing. Competition in the EPO market in India is very severe but in spite of the presence of several biopharma companies that offer EPOs, prices of the product has not gone down. Cognizant of this, Hindustan BioSciences (HBSL) has a manufacturing contract to produce lower priced Eposino (recombinant human erythropoietin) at the Shandong Kexing BioProducts Co. facility in China. This is another case where price pushes one low cost country (India) biopharma company to buy from a lower cost country (China) biopharma to get a bigger share of the EPO market, targeting people in the middle and low income echelon.

Vertical Alliances in Biotechnology: Fast Access to Local and International Markets

Companies can choose either to internalize some downstream activities or collaborate with another company who can distribute the products for them (vertical alliance) based on efficiency gains. The reason behind the formation of across the border vertical alliances among biotech specially biopharma firms is to secure fast and reliable access to the global market or to previously closed markets utilizing the partners distribution expertise and established network. LG Life Sciences of South Korea develops and commercializes new anti-infection drugs, medicines for cancer, diabetes, etc. Some of its well-known drugs are Euvax-B for the treatment of Hepatitis B, LG HCD3.0 for Hepatitis C and Factive (Gemifloxacin), an antibiotic of the quinolone family which LG Life Sciences jointly developed with GSK. In 2005, Sinovac Biotech of China and LG Life Sciences of Korea have agreed on a sales and distribution alliance. LG Science's known prowess is its knowledge of overseas market development and its international marketing network. It already has well-developed global sales and distribution networks for its HepB vaccine, including UNICEF programs and distribution to 67 countries [35]. Sinovac Biotech Ltd. specializes in the research, development, commercialization and sale of human vaccines for infectious illnesses such as hepatitis A and hepatitis B, influenza, "SARS" and avian flu. The two vaccines of Sinovac approved for commercialization are: Healive ™ for Hepatitis A and Bilive ™ for Hepatitis A and B combined; both seen to have big market potentials in China. Given this, LG Science will sell Sinovac's Hepatitis A vaccine (Healive™) and for its part of the deal Sinovac will introduce LG's HepB vaccines in the Chinese market. Sinovac and LG believe that there is tremendous potential for selling LG's HepB vaccine in China. LG will register its

HepB vaccine in China through Sinovac. They will also work together on Sinovac's influenza vaccine (Anflu™). Sinovac is the global forerunner in the research and development of SARS vaccine which is already awaiting approval. LG thus seeks to collaborate with Sinovac in the development of the vaccine cognizant that it is a novel drug with worldwide medical application.

Clinical Trials and Cost Advantage

Firms perform value creation in optimal locations to achieve location economies.

Thus firms will locate in areas where there are relatively cheap and high quality factor inputs to reduce the cost of value creation. One advantage of Asia aside from the skilled manpower relates to cost. It costs around US$ 800 m to develop a drug [36]. The innovation and manufacturing costs as well as biotech services in India are less costly by international standards. For example, the price of Shanvac B, a hepatitis B vaccine produced by a local company, Shantha Biotechnics costs only 50 cents/dose while the imported vaccine costs US$16/dose. Biotech services are being outsourced to biotech companies such as Syngene and SIRO Clinpharm in India which can offer cheap and yet highly skilled labor force. Costs of R&D in India for Streptokinase is US$1m whereas in the US it is over US$20 m; clinical trials (Phase 1-111) for Rotavirus cost US$5m in India and over US$150m in the US; development and production of 3-Gmp tablets of new molecule-malaria cost US$1m in India and more than US$20m in the US (Bharat, 2004). Chinese scientists with doctoral degrees get a yearly salary of US$25,000, a mere 10 percent of what scientists earn in the West. Hence complicated R&D such as biological testing can be performed less expensively in China since salaries account for 80 percent of total R&D costs. The savings then can be used to expand their pipeline of potential blockbusters. The screening process of compounds with medical application to novel drugs which has to be verified many times over is very labor intensive. To save on cost Roche inaugurated an US$11m laboratory in Shanghai to screen different compounds that have potential use in anti virus and cancer drugs, and at the same time access to the big Chinese market. For labor intensive services and yet requiring high level skills, China can offer low cost bioservices such as necleotide sequencing and synthesis, protein expression and library construction [37]. Multinational pharmaceutical companies conduct clinical tests in China where recruitment of patients is not difficult and the related hospital fees are cheaper. For these reasons, Germany's Mologen is having Starvax of Beijing test the efficacy of a certain compound for a colon cancer drug now undergoing clinical trials in Europe for the treatment of other forms of cancer. WuXi Pharma Tech Co. (China) was approached by TargeGen, a US pharmaceutical company that is developing small-molecule drugs for cardiovascular ailments to perform chemical screening of various compounds that can be used for further development [38].

6.8. Conclusion

The growth and development of the biotech sector in Asia have been quite unique in a way. For one, government support and initiatives were imperative for it to develop to where it

is now. Many R&D were done in universities and public laboratories the results of which could not be commercialized rapidly. There was no system to transfer technology to industry and venture capital was not as popular as in the West. Asians in general are risk averse so they were hesitant to invest in risky bioventures. Hence the government had to establish bioventure funds to compensate for the lack of private venture capitalists. Since most of the researches have been done in public institutions and laboratories, researches were focused on the treatment of local/regional diseases due to immense political, social and economic implications of not doing so. Although many firms in Japan, India and Korea had been involved in biotech since a few years ago, they depended more on the manufacture of generics or licensed drugs since these brought them assured revenue without time-consuming, risky and expensive R&D to come out with innovative drugs. Soon many countries in Asia have to abide by the IP right law in consonance with WTO's regulations that will ban the production and commercialization of patented new drugs which implies that local drug companies have to pay licensing fees affecting their profitability. Due to the globalization of bio- pharmaceutical industry, firms have to rethink their business strategies. For example pharmaceutical and biotech companies are merging to rationalize their operations and product lines and cut R&D costs. Some drug /biotech companies banking on their core competences are forming strategic horizontal alliances with American and other Western biopharmaceutical companies, while others form cross border vertical alliances for clinical trials and commercialization of the drugs. Moreover, biotech companies are now actively involved in new technology like genomics and stem cell research. The advantage of Asia in this regard is its diverse population which is vital to clinical testing and relatively cheap cost of doing clinical trials. Other areas of biotechnology where Asia can have a niche is in bioinformatics and nanotechnology. The recent increases in the number of venture capitalists, bioventures and IPOs are good indications that more people now see that the bioeconomy can be a potential driver of economic growth.

Asia is seen to be the next biotech hub for contract manufacturing, contract services, bioinformatics and genomics. Biotech companies in Asia are small in size and capitalization compared to their Western counterparts and are still in the nascent stage. Amid the ever increasing global competition pharmaceutical companies in the region are developing innovative drugs derived from the biotech sector and pursuing global medicines for the maintenance of the company rather than count on the manufacture of generics for most of their revenues. To survive the competition and takeover from the more powerful Western pharmaceutical companies and given the fact that after the costly R&D only 15 percent of the drugs developed reach the commercialization stage [36], they form synergies using each partner's strengths and share the R&D costs. Alliances can lead to increased market (international) presence that will bring about economies of scale and scope. Biopharmaceutical products and services have big market potentials in Asia specially for novel drugs for the treatment of diseases common in the region such as respiratory and infectious disease and cardiovascular ailments which have been the focus of many biotech firms in Asia, aside of course from the other therapeutical medicines that have already been tested in the West for common ailments and licensed to drug companies in Asia. Moreover, Singapore, South Korea and China hope to have an important niche in genomics and stem cell research as well as their applications. Japan, India and South Korea meanwhile can leverage on their strengths in IT and emerge as strong in bioinformatics. Japan now puts its know-how in nanotechnology into practical use (nanomedicine) considered as the next generation drug

delivery system. Overall, local and international biotech and pharmaceutical firms can bank on Asia in terms of market and location economies, and on Asian bio-pharma companies to form production, clinical trials, and marketing alliances, and for innovation in genomics, stem cell research, bioinformatics and nanomedicine.

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Chapter 7

EMERGING ASIAN BIOTECH-PHARMA INDUSTRY - COMPARATIVE PERSPECTIVES

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"The centre of the global pharmaceutical industry is shifting. Not only is Asia set to be the largest pharmaceutical market in the world but many Asia territories will be powerhouses of the industry." PriceWaterhouseCoopers, Gearing up for a global gravity shift, 2007

ABSTRACT

In Asia India, China and Singapore are emerging as potent hubs of pharmaceutical industry and potential partners of Western Big Pharma. Biotech-Pharma stands to benefit at least as much as other industries from the opportunities that Asian and Asian alliances and expansion present, since its real value lies not just in simple cost savings but also in the faster development of new compounds and in penetrating huge new markets. The reality of shrinking profit margins, drying pipelines, patent expirations, intense generic proliferation and increased R&D costs has made partnership and offshoring an attractive strategy. The business models applied are manifold, mostly by acquiring local companies, strategic partnerships and increasingly by setting up wholly owned Asian R&D subsidiaries.

7.1. INTRODUCTION

Whilst section 6 of this publication in particular deals with the biotechnology part of the life-science industry in Asia and related alliances between Western and Asian firms, this section 7 is focussed on the pharma part and in particular on the impressive domestic capabilities in the emerging hubs India, China and Singapore.

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The shift of global biotech-pharma, i.e. away from North America and Europe towards Asia, started as Asian economies grew and low cost manufacturing in the region expanded. Now, Western companies, are increasingly, also seeking to site research, development, analytical services and clinical trial activity in Asian territories. This reflects both increased capabilities in the region and a changed business model of pharmaceutical multinational companies (MNC).

Part of that change is the recognition that one of the key challenges of biopharmaceutical industry is to improve R&D productivity. So development organizations are targeting the drivers of cost and value aiming to increase R&D productivity and retooling their R&D engine through a series of lines of attack – expansion in Asia and forming alliances with Asian partners is one such approach. For obvious reasons as strategic importance, market size, and their increasing potential in biotech-pharma relevant R&D capabilities the Asian countries of choice are particularly China and India. So India, China but also Singapore are poised to become leading countries in the Asia pharmaceutical space – other territories, notably South Korea, Malaysia and Thailand are also building strong domestic pharmaceutical bases although so far only multi-national companies (MNC's) currently dominate these markets.

Only to mention in that context, because it's so illustrative for the emerging pharmaceutical powerhouses India and China: 80 percent of the currently used API's for drugs made in Europe are manufactured in India and China. In addition, 30 percent of bulk drug manufacturing - worth around US$ 31 billion - and US$ 25 -30 billion of Pharma R&D is already outsourced by global majors. It doesn't need a lot of imagination to predict that in particular India's and China's share in that outsourcing business is continuing to increase.

After a long period of superior financial performance Western pharmaceutical industry is now confronted with challenges which can be summarized as below:

- increasing cost of drug discovery & development due to …
  - tougher regulatory demands
  - competition for patients
  - larger clinical studies
  - high rate of failures
  - new technologies not yet paying out (genomics, …)
  - longer development timelines
- increasing time to market. For instance, a delay in the launch of a drug can cost a company up to US$ 23 million per day in terms of lost sales in the USA alone and almost US$ 37,000 per day in terms of additional development costs.
- impending patent expirations of blockbuster molecules. For example, a large lump of the Big Pharma revenues are at risk as drugs worth $ 47 billion are expected to go off – patent in the US alone over the next 3 years
- pricing pressure in US and Europe (by governmental pressure reducing health care cost)
- increased penetration of generics
- considerable reduction in the numbers of new product approvals (in 2007 FDA approved just 19 new drugs, the lowest in 24 years)
- low public opinion
- challenges to intellectual property by increasingly aggressive generic companies

- re-importation pressures

All this means MNC's have to radically rethink their strategic options and business model: how to defend revenue, how to increase productivity, how to lower unit cost?

One way out is to look out towards Asia for solutions - not only with respect to manufacturing or support services but R&D. Offshoring R&D has already proven beneficial and even essential in comparable high-skill industries as software industry. Global sourcing of R&D can help pharma companies to unlock significant productivity gains.

In addition, now, more than ever, pharmaceutical companies must outsource R&D to their biotechnology counterparts - and they are doing so in record numbers to fill their pipelines with potential blockbusters. The fact that currently five major MNC's have no billion-US-dollar blockbusters in late-stage development underscores the growing importance of these collaborations.

It's reported that nearly one third of innovative pharmaceutical products are developed through such alliances. But Big Pharma companies are not the only ones gaining from these partnerships, the smaller biotech firms take benefit from it as well. They are lacking the marketing muscles to launch their new products and to boost peak annual sales although their assets are scientific minds and proprietary technology. On the other hand MNC's bring to these partnerships the ability to navigate regulations minefield and marketing expertise and marketing power.

To exploit the benefit of such alliances and partnerships, biopharmaceutical companies need to:

- streamline the exchange of information about partner resources, drugs, clinical trial processes, synthesis processes to improve time-to-market
- avoid drug discovery dead-ends by keeping partners abreast of developments while safeguarding their own intellectual property
- improve quality and reliability of clinical trials
- speed up regulatory approval

7.2. THE SITUATION IN PHARMA

7.2.1. Costs, Competitive Advantages and Opportunities for Pharmaceutical **MNC's** in Asia

The huge English speaking talent pool (second to US in size & availability of skilled English speaking manpower; annual number of trained chemists six times higher than US) and an independent judiciary are besides the cost aspect (a biogeneric manufacturing or a research facility costs one-third of Europe or one-fifth of the US) competitive advantages of India as the leading pharma hub in Asia. Labour costs in India are amongst the lowest in the world – in pharmaceutical manufacturing the ratio USA: Singapore: India: China is about 100: 40: 17: 11.

Dr. Swati Piramal (Director Strategic Alliances and Communications at Nicholas Piramal) claims that India could reduce the costs to develop a NME (New Molecular Entities) based product to less than US$ 100 million.

Based on experience it's almost impossible to make uniform statements concerning labour costs or cost savings, because all highly depends on location (megacities like Mumbai vs second and third tier cities and nearby countryside), kind of activity (R&D vs manufacturing), type of R&D activity (clinical trials vs pharmaceutical / analytical type of work vs discovery etc), background of scientists (with or without Western experience), business model (Contract Research Organization CRO / Contract Manufacturing Organization CMO, Western MNC Indian affiliate, Indian company), and productivity differences. Extra costs for bringing Expatriates to India (e.g. QA experts), and initial internal coordination needed in the West for the start-up phase, come into any cost saving equation as well. Nevertheless, it seems to be close to reality to assume savings up to 50 percent for manufacturing of solids or about 40 percent of parenterals, biologics or complex API's compared with US or Western Europe. According to a McKinsey Quarterly report, R&D costs for Indian pharmaceutical firms are 75 percent less than those of a multinational firm.

Besides low direct labour costs, low building cost and low cost to buy land are contributing to the overall favourable cost structure. But again, it can't be overemphasized, that the ultimate cost differentials West vs Asia or India highly depend on all the influencing factors above and are subsequently extremely variable.

The Indian government has emphasized the importance of a strong pharmaceutical sector and has created incentives as higher or no limits for foreign direct investments, tax relief, increased R&D funding and public encouragement of MNC participation in domestic market. In that context Indian government plans at least 10 so called Biotech Parks by 2010 to foster additional growth in this sector. On top, several state governments as Karnataka, Tamil Nadu, Andhra Pradesh or Maharashtra have taken out their specific policies to boost the biopharmaceutical sectors in their areas by various incentives as simplified labour laws, tax exemptions, concessional electricity tariffs, special funding etc.

It's said that the current 545 Pharmacy colleges with an intake of 20,000 students/yr are expected to increase to 1,000,000 students by 2020.

Now that product patent era has been unleashed, many Indian companies believe they have to come up with NME's to survive long-term, i.e. most of the pharma companies now have a mission of becoming a discovery led global company.

Even though it is not obvious at this point, product patent acceptance by India is likely to catapult Indian pharma into a new era of NME development and approvals for not only India but also for the global market. In order to remain handsomely profitable Indian pharma is likely to get into NME discovery and development. This probably helps MNC's also to lower their cost of drug development and allows them to put a new drug into market by spending below half a billion dollar.

This change may not help the local pharma industry and the MNC's immediately, however this will not only create new opportunities for offshoring but also it may lead to creative ways of putting new drugs in the market at a cheaper cost and faster. Some of the NME's developed by Big Pharma never see the light of the day because their CTL (cost to launch) and cumulative return are not attractive. Growth of Asian NME development engine may provide a new life to these compounds. We are likely to see newer ways of co-developing these NME's in Asia, especially India.

7.2.2. **Pharmaceutical MNC's** Presence and Alliances in India

With an opportunity to now earn higher margins MNC's begin to introduce increasing number of patent products in India – but the enforcement and interpretation of the IPR law will affect the magnitude of the market opportunities for MNC's.

Company	International acquisitions	Foreign alliances, joint ventures and other tie-ins
Nicholas Piramal	Pfizer-Morpeth (UK), Avecia Pharmaceutical Dobutrex brand acquisition (US), Rhodia's inhalation business (UK), Biosyntech (NPIL Pharmaceutical) (Canada), Torcan Chemical (Canada), 51 percent of Boots Allergan (US), Bio Syntech (Switzerland	Ethypharm (France), Genzyme (US), Eli Lilly(US), Biogen Idec (US), Chiese Farmaceutici (Italy), Minrad (US), Pierre Fabre (France), Gilead Sciences (US), Allergan (US), Hoffmann-La Roche (Switzerland)
Ranbaxy	Terapia (Romania), Allen -GSK (Spain & Italy), Ethimed (Belgium), Betapharm (Germany), RPG Aventis (France), 40% stake in Nihom Pharmaceuticals (Japan), Brand-Veratide (Germany), Efarmes (Spain), Be-Tabs (S. Africa), Akrikhin (Russia), Basic (Germany), Ohm Labs (US)	GlaxoSmithKline (UK), Janssen-Ortho (Canada), IPCA Labs (US), Zenotech (India), Sonkel (S. Africa), Cephalon (US), Gilead Sciences (US), Schwarz (Germany)
Dr. Reddy's	Betapharm Group (Germany), Trigenesis (US), BMS Laboratories and Meridian Healthcare (UK), Roche's active ingredients business (Mexico), BMS Labs (UK)	Novo Nordisk, Bayer AG (Germany), Par (US), Novartis (Switzerland), Merck (Germany), Clin Tech, Pharmascience (Canada), ICICI (India)
Marksans	Nova Pharmaceuticals (Australia)	NA
Aurobindo	Milpharm (UK), Pharmacin (Netherlands)	Gilead Science (US), Citadel (India)
Sun Pharmaceutical	Able Lab (US), Caraco (US), Valeant Pharmaceuticals (US & Hungary), ICN (Hungary), MJ Pharmaceutical	Dyax
Dishman	Amcis (Switzerland), Solutia's Pharma (Switzerland)	Azzurro (Japan)
Orchid	Bexel Pharma (US)	Stada, Alpharma, Par, Apotex
Biocon	Nobex (US)	Centre of Molecular Immunology (Cuba)
Wockhardt	Wallis Labs (UK), CP Pharmaceutical (UK), Esparma (Germany), Pinewood Laboratories (Ireland), Dumex (India)	Pharmaceutical Dynamics (S. Africa)
Cadila	Alpharma (France-formulations), Dabur Pharma Redrock (UK)	Schering (Germany), Boehringer Ingelheim (Germany), Viatris (Germany), Novopharm (Canada), MCPC (SaudiArabia), Cipharm (Ivory Coast), Geneva(US), GSK (UK), Ranbaxy (India),Mallinckrodt (US), Mayne (Australia),Shinjuki (Japan), Zydus Atlantager
Jubilant Organosys	Target Research Associates (US), PSI (Belgium), Trinity Laboratories (US)	NA
Matrix Labs	22 percent controlling stake in Docpharma (Belgium), Explora Lab (Switzerland), MCHEM (China), Fine Chemicals (S. Africa), API (Belgium)	Aspen, Emchem, Doc Pharma, Explora Labs
Glenmark	Kinger Lab (Brazil), Uno-Ciclo (Brazil), Srvycal (Argentina), Medicamenta (Czechia), Bouwer Bartlett	Forest Labs (US), Lehigh Valley Technologies (US), Shasun (India), KV, Apotex (US)

Selected international acquisitions and foreign tie-ins by the Indian pharmaceutical industry Source: IBEF, Ernst & Young, The Economic Times, individual company web pages

Foreign direct investments in the pharmaceutical sector experienced the greatest year over year growth from 2003 to 2004, going up to US$ 340 million. More MNC's (72 percent) are conducting development activities in India today than in any other emerging country, and about 45 percent of midsized and smaller Western pharma companies have set up some sort of R&D. This happens partly by outsourcing of R&D and manufacturing to CRO's and CMO's but also by building up their own organizations for clinical trials, research and development. Much of this involves offshoring of API and intermediates (sheer sourcing but also chemistry process research and development) and clinical trials. Classical formulation and analytical development is still to come - Johnson & Johnson is an early mover setting up that specific capacity (2007/2008).

Here are some more recent examples:

The largest single investment by Sanofi-Aventis in India to date was inaugurated (Goa Development Centre, GDC) in 2007. Its capacity will be to develop 12 NME's per year. Bristol-Meyer Squibb outsourced safety monitoring to Chennai, India. The new centre will run in parallel to BMS' in-house pharmacovigilance centre.

AstraZeneca opened in Bangalore 2007 a US$ 15 million process research and development unit next to its already existing research centre for tuberculosis.

But also international generic companies have started acquiring and collaborating with Indian units to access low-cost manufacturing bases and establish their presence in India. For example, currently Ratiopharm (Germany), Ivax (USA), Baxter Healthcare (USA) and Sandoz (Switzerland) are about setting up or extending product development and manufacturing in India.

7.2.3. Indian Domestic Pharmaceutical Industry and the Contract Research and Manufacturing Services (CRAMS) Sector

The growth of the Indian pharmaceutical industry has outperformed the growth of the global pharmaceutical industry while rapidly integrating into the global industry. The Indian pharmaceutical industry is still highly fragmented (> 20,000 companies) with three local hubs: Mumbai, Hyderabad and Bangalore. It has come a long way and evolved multi fold over the last few decades. The industry has witnessed impressive growth and expansion across different segments. According to a new KPMG – CII (Confederation of Indian Industry) report India is poised to scale new heights and emerge as the pharmaceutical hub of the world. The report also states that India has emerged as the preferred destination for outsourcing of drug discovery, clinical research and manufacturing functions - but pharmaceutical development capacities will further enrich that variety.

So India's strong value proposition has compelled pharmaceutical MNC's to explore India as a strong back-end.

India is meanwhile the world's largest producer of pharmaceuticals by volume (20 percent of global production), still driven by supplying generics to the domestic market (market share in India control close to 40 percent of the domestic market) but increasingly to international markets. It also has a growing biopharmaceutical sector. Elimination of product patents in early 1970s created high skill levels for reverse engineering of formulation and low-cost manufacturing of API's, intermediates and finished products. These capabilities

helped some Indian companies to leverage their domestic success to become significant global competitors as exporters of API and/or generics as well as providers of CRO/CMO services.

Currently 35 percent of all Drug Master Files (DMF's) and 25 percent of all US FDA ANDA (Abbreviated New Drug Application) filings are from India (expected to exceed 50 percent by 2009).

Just to illustrate the magnitude of Indian domestic pharma:

- 105 US-FDA approved API & formulation plants are located in India, the highest number outside the US
- Highest number of DMF's and ANDA's filed in USA
- API's from India are expected to reach US$ 10 billion by 2010…overtaking Italy as the world's second largest API manufacturer behind China
- India's API export rates are the highest in the world, including exports to highly regulated markets like the US

Company	Revenues
Ranbaxy Labs	1,156
Cipla	518
Dr. Reddy's	433
GSK India	343
Nicholas Piramal	308
Wockhardt Ltd	276
Lupin Ltd	270
Aurobindo Pharma	258
Zydus Cadila	250
Sun Pharmaceutical Industries	232
Orchid Chemicals 6 Pharmaceuticals	153
Biocon	152
Glenmark	140
Alembic	127

Top Indian Pharmas (based on 2005 sales -US $ million) – all of them but one domestic companies.

In terms of complex formulation technologies India's presence in injectible dosage forms, steroids/hormones, sustained or controlled release drugs, poor solubility drugs with difficult bioequivalence, dermatologicals, ophthalmologicals etc., is still almost negligible. But India, with significant lower costs of innovation and testing, is well-placed to capture these opportunities in the future.

India's CRAMS segment results from India's ability to position itself as a low cost manufacturer and supplier of high quality products and services. Over time, many companies have shifted their focus from pure generics towards CRAMS, to establish themselves as full-fledged service providers spanning the entire drug development and manufacturing value chain. The Indian contract manufacturing industry typically comprises:

- old generics and old molecules
- specialized generics
- patented drugs
- custom synthesis and scale ups

Meanwhile Indian companies have made some impressive deals in the contract manufacturing space. These deals, typically between US$ 15 and 50 million, validate India's potential to achieve a large share of the global manufacturing outsourcing market. They also prove that Indian companies have been able to win the trust and confidence of MNC's.

In the years to come, Indian CRAMS providers are likely to consistently move up the pharma value chain. They are expected to progress from their traditional experience in manufacturing API's and intermediates, solid and liquid dosage forms and vaccines to developing expertise in the manufacturing of high-complexity segments such as injectables, biologics and other niche areas. More and more generic players are likely to explore this segment as a lucrative business opportunity.

Indian company	Experience since	Clients
Dishman Pharma	1999	Solvay, Merck, Astra, Zeneca, GSK, KRKA
Jubilant Organosys	1992	Syngenta, 15 of top 20 MNC's
Piramal Healthcare	2003	Pfizer, AMO, Boots, Wyeth, Allergan
Dr. Reddy's Labs	2001	> 5 MNC's and over 25 emerging pharma companies
Divi's Labs	1990	20 of top 25 MNC's
Shasun Pharma	2006	Merck, Novartis, GSK
Suven Life Sciences	1994	Eli Lilly
Cadilla Health Care	2004	Nycomed, Hospira, Madaus,Altana
Hikal	2001	Pfizer, Alpharma

Major CRAMS players in India (all of them holding approvals by FDA and various European, Japanese and Australian Health authorities)

Next to demonstrating its competencies in manufacturing India is now rapidly emerging as strong global player in R&D. The pre-clinical drug research services is expected to take – off over the next few years. The number of early phase research and pre-clinical facilities is rapidly growing. The overall market size of that type of services will reach US$ 820 million by 2013.

Indian players have strengthened their positions in CRAMS segment by actively pursuing some synergetic acquisitions, enabling Indian companies to get closer to their global customer base. Besides, these acquisitions have boosted their capabilities in terms of newer technologies, expanded service portfolios, global manufacturing and research sites with international regulatory approvals and a ready client network.

7.2.4. The Changing Environment and New Challenge for Indian Pharma

But the reintroduction of product patent laws in 2005 now limits the growth potential from new product introductions to the domestic market of generic versions of products patented in the West. So the Indian industry has realized the need to shift from process innovation to building strong capabilities in discovery research that can India drive to a leadership position in the years to come.

As a result, the industry is in a state of transition as companies adapt their business models, likewise industry consolidation and active merger & acquisition is expected. India is developing its New Molecular Entity (NME) baskets and gearing up to launch its own patented molecules globally in the near future.

Responses to the changing competitive environment are

- R&D spending has risen to 6 – 10 percent of sales for larger companies
- many companies have expanded into CRO / CMO to bring Indian advantages to Western pharmas
- strategic and tactical collaborations with MNC's through licensing and joint development agreements in order to cope with the high costs and risks associated with NME development
- most of the companies are investing to grab a larger stake in the global generics, API and bulk markets

Given limitations in financial resources, capabilities, and experience with NME development, Indian R&D is not yet ready for a start-to-finish model. Therefore Indian companies are now increasingly pursuing R&D licensing and development deals and many other types of general collaborations with Western organizations. Co-development agreements, licensing deals and other kind of alliances between Ranbaxy and GSK, Dr. Reddy's and Novo Nordisk, Torrent and Novartis, Glenmark and Tejin Pharma (Japan) or Merck KGaA (Germany), Nicholas Piramal (now known as Piramal Health Pharmaceutical Solutions) and Eli Lilly but also Merck (cancer drugs) are just a very few examples.

Ranbaxy and Dr. Reddy's belong already to the top 10 in the global generic market. They as other big players are increasingly focused on establishing a still bolder position in the global generics market e.g. by acquisitions as part of their strategy. Amongst many examples, Dr. Reddy's acquisition of Betapharm (Germany) in 2006, or the acquisition of Docpharma (Belgium) by Matrix Laboratories in 2005, are just some of the recent ones, but there are many more.

Even that today it's still more a dream, Indian pharma is heading to provide end-to-end solutions, i.e. to make the vision "India as One-stop-Pharma-shop" reality. To achieve that vision more of the basic requirements (e.g. capital, trained personnel, strong IP infrastructure, IT with access to public domain infrastructure, regulatory structure) need to be fulfilled and a change in mind set and attitude is needed. A few companies like e.g. Dr. Reddy's, Ranbaxy, Torent, Glenmark, Piramal and Biocon are already pritty progressed.

7.2.5. Selected Recent Developments and Acquisitions in the Indian Pharmaceutical Landscape

In a dramatic announcement, the promoters of Ranbaxy labs, India's largest pharmaceutical company, announced in 2008 that they were selling out to Japan's Daiichi Sankyo in a deal that valued Ranbaxy at US$ 8.5 billion. Ranbaxy takeover appears to be a "perfect fit" at the firm level. Ranbaxy needed huge doses of capital, to meet high costs of patent challenges, R&D and high entry costs in foreign markets; Daiichi on the other hand required a large network of markets and proven capacities and know-how both in research and manufacturing. Some other companies at the top end of Indian pharmaceutical industry have also been vulnerable, lately.

Independently, Ranbaxy and Merck have signed a collaboration agreement for drug discovery and clinical development of products in the anti-infective field. Besides, Ranbaxy

and Orchid have entered into a business alliance agreement involving multiple geographies and therapies for both finished dosage forms and API's. Ranbaxy is also the first Indian company establishing a major presence in 11 countries of Middle East comprising 160 approvals till date in the region - most recently commencing its operations in Yemen.

Dr. Reddy's Labs has signed an agreement to acquire Dowpharma's small molecules business as associated with Dow's UK sites. In addition Dr. Reddy's will acquire BASF's CRO business and facilities in USA.

Jubilant Organosys is acquiring 100 percent stake of Canada - based Draxis Health Inc, worth about US$ 225 million. With this acquisition Jubilant will become one of the leading providers of contract research manufacturing of small volume parenterals to large pharmaceutical and biotech companies in North America. It is also offering Jubilant entry into the attractive, regulated, high growth and high-margin radiopharmaceutical business. At the same time, Jubilant has acquired Specialty Molecules, an Indian niche manufacturer in specialty intermediates.

Jubilant Biosys (subsidiary of Jubilant Organosys) and Amgen have entered into a drug discovery partnership under which Amgen and Jubilant will collaborate to develop novel drugs across multiple therapeutic areas.

Lupin has acquired a stake in Australian drug – maker Generic Health. The Australian market is a significant global market with sales over US$ 10 billion and witnessing rapid genericisation. In addition Lupin has acquired Hormosan Pharma in Germany, a sales and marketing generics company specialized in CNS medicines. Lupin is also planning to evolve its overseas operations in USA and emerging markets by acquisitions, capacity expansion and a foray in biologicals.

Zydus Cadila has acquired 70 percent of Simayla Pharmaceuticals of South Africa. Over the next few years Zydus plans to launch 50 products in African markets.

Very recently Orchid has announced the formation of its wholly-owned subsidiary in Japan, headquartered in Tokyo. This will drive Orchid's entry into the high potential and growing Japanese generics market.

As a last example, indicative for the interest in India's drug development and manufacturing capabilities, in July 2009 Sanofi Aventis announced to buy the Hyderabad-based vaccine firm Shanta Biotechnics, an almost US$ 1 billion deal.

Importantly enough, US FDA announced to set up offices in different parts of India and collaborating with its Indian counterpart, Drugs Controller General of India.

7.2.6. Indian Companies as Alliance Partner and Focal Point

An overall summary about India as partner and focal point for Western pharmaceutical companies can be formulated as below:

- India has a highly developed and pretty mature bold domestic pharmaceutical industry which is still mainly geared towards generics
- Although most advanced Indian companies keep further strengthening their generic franchises and are on their way to become truly global player they have set off to change business models and strategy towards NME development

- The severe interest of Indian pharmaceutical companies in collaborations and alliances with Western MNC's offers many opportunities to create "win – win" situations for both sides. Substantial cost advantages for Western pharmaceutical companies by doing business in India are only one benefit for MNC's
- Indian companies aren't just offering world-class manufacturing service, both in finished product and in particular in API sector, but in R&D as well
- Within the R&D sector so far medicinal chemistry type of work, chemistry process research and clinical testing were the strongest areas – but chemical and pharmaceutical development including comprehensive analytical services is about emerging
- Up to now Indian companies have focused on developing drugs "faster and cheaper" and deploying their capabilities in chemistry research, clinical trials and manufacturing of oral solids. The second lap, expected over the next five years will extend capabilities to include complex manufacturing of injectables, cutting edge clinical trials including proof of concept trials, and more sophisticated biology-based research platforms. The third lap will likely occur 2013-2015, when Indian companies are expected to start manufacturing of biologics and offer cutting-edge R&D platforms such as cheminformatics
- All this (including achieving the respective cost advantages) can be accomplished by various operating models: sheer collaboration with CRO / CMO's, joint ventures between Indian pharma companies and Western MNC's and MNC's setting up their own capacities
- Better IPR protection as e.g. in China, English speaking manpower, relatively small time difference vs Europe and the political democratic system are extra supportive factors for MNC's setting up their own offshoring R&D capabilities in India or collaborating with Indian companies
- Given the focus of this article, i.e. chemical & pharmaceutical development activities in full GMP up to pilot scale, India is by far the preferred Asian destination for that type of development
- all these pros have to be seen in balance with some deficiencies, which are …
  - lack of attractiveness for Expatriates
  - still weak infrastructure
  - generic mindset
  - sometimes lack of certain skill sets (QA, maintenance) in the country
- any more theoretical tremendous cost benefits derived from sheer cost differentials West vs India are often unrealistic – reality gets more reflected by taking into account factors as Expatriates costs, coordination efforts to be made and efficiency differences

7.2.7. The Chinese Pharmaceutical Industry and its Environment

China has three major areas of concentration of (pharma) R&D centres: Beijing, Shanghai, and Guangzhou. The Chinese domestic pharmaceutical industry itself is highly fragmented, a large number of smaller local players account for about 70 percent of the countries overall drug market. But a process of consolidation has started. The rising number

of middle-class families with increased access to healthcare and negative healthcare effects due to changing life styles are triggering interest from global investors.

More and more the use of Traditional Chinese Medicine is complemented by Western products. Increased governmental standards and controls, stronger IPR protection and return of Western educated Chinese with technical and management skills are additional factors. 98 percentof China's drug products are still generic copies. There are increasing DMF filings (~ 75 in 2005) with an effort to follow the Indian model (approx. 1-5 years away from ANDA filings).

Sinopharm has, under the control of central government, 10 wholly owned subsidiaries or shareholding companies. Sales in 2004 were $ 2.3 billion with import/export volume of $ 500 million. Sinopharm chairs many pharmaceutical associations in China.

Zhejiang Hisun (one of the largest bulk manufacturer for antibiotics, anti-tumor and statins API) exports more than 80 percent of API production to EU / USA and otherwise focus' on domestic market. Other bigger players are Zhejiang Huahai, Shanghai Fosun, Harbin Pharma, SJZ Pharma Group, Hisun Pharma SPG, Hengdian Group, Neptunus, Shandong LuNan, Yangzijiang and Founders Group.

The most significant challenge of domestic Chinese pharmaceutical industry is its ongoing emphasis on GMP compliance. China is committed to building and expanding the pharmaceutical industry, i.e. there is strong encouragement from the government to invest in the pharmaceuticals sector.

In contrast, there are the foreign MNC's operating in China with expansive R&D budgets and global resources. For example, the government is building science parks, like the Zhangjiang science park ("Drug Valley") in Pudong, Shanghai area. Eli Lilly and Roche have R&D facilities in the latter science park. Another development zone is TEDA, Tianin Economic Technology Development Area, in the Beijing area.

Efforts have been made to attract talent back from the West. Comparable to India, the reverse "brain drain" is fuelling up the Chinese talent build up. For example, the number of overseas educated students returning grew from year 2000 (9,000) to year 2004 (25,000) by almost 30 percent. There are signs, that two third of the 320,000 Chinese graduates that have studied and stayed abroad are returning.

As an example, the newly established Guangzhou Institute of Biomedicine and Health, is actively recruiting scientists, with a strong preference for people with an international experience.

Further, since 2004, foreign – invested Shanghai – based firms, are eligible for receiving subsidies for new patented technologies and / or methodologies used in new products. Previously, only domestic firms could apply for these subsidies. These funds can represent up to 75 percent of the R&D costs, if performed in Shanghai.

China allowed a beneficial tax environment for foreign companies (20 percent tax vs 33 percent for domestic companies), but this is about being uniformed to 24- 28 percent. However, favourable tax incentives will still apply for R&D collaborations with Chinese research institutes and for those R&D companies that are registered in the so called High-Tech Development Zones (HTDZ). Incentives seem to be more attractive in Shanghai vs Beijing HTDZ's.

Along with Beijing, Shanghai is a popular location for foreign-owned pharma R&D centres, due to its growing variety of any other business providing service to pharmaceutical industry.

Tax concessions and access to capital for favourable rates are in addition to direct savings on facilities, overhead and salaries.

Interestingly, the Chinese domestic rapidly growing biotechnology industry has become one of the largest and most prolific one in Asia (e.g. the world's first licensed gene therapy medication by Shenzhen-based SiBiono GeneTech Co. Ltd. in 2003).

CRO's are becoming an increasingly important component of the drug development industry. Chinese CRO growth is outpacing that of the industry. So a growing number of foreign and domestic CRO's have established operations in China.

Amongst China's emerging CRO's is number 1 WuxiPharmatech. It was founded in 2001 and has grown to over 900 staff. It claims current customers include 18 of the top 20 pharmaceutical companies and 8 of the top 10 biopharmaceutical companies in the world. The number 2 ChemPartner was founded in 2003 and has grown to 400 staff. Its customers include Eli Lilly, Merck, and many of the top 20 global pharmas.

Two key trends are driving the growth: lower costs and the continuing return of Western-trained scientists.

7.2.8. The Attractiveness of China for Pharmaceutical R&D

Amongst those Asian countries who are alternatives to India for conducting pharmaceutical R&D, China and Singapore are the most interesting ones. But for different reasons – whilst China is of strategic importance as a market and offers low labour costs, Singapore mainly attracts by tax incentives and infrastructure.

China is a somewhat challenging country in which to conduct business due to its varied culture and business environment.

Asking the question "why drug R&D in China" there are several aspects:

- Supportive government policies
  - Building infrastructure to support biopharmaceutical R&D (industrial parks)
  - Tax incentives
- Large talent pool and well-educated workforce
  - 4,5 Million university graduates annually
  - Bench scientists with few major knowledge gaps
- Academic research
  - High individual quality
  - Productive collaborations possible with proper guidance
- Low cost structure. In particular low cost of conducting clinical trials, due to low labor costs and speed clinical trial recruiting. But cheap labor cost won't stay for ever …so come for cost and stay for quality, market share and talent pool.
- Quick entry to the huge potential of the fast growing China market
- Huge naive patient population
- Abundant preclinical animal resources
- Rich TMC (Traditional Chinese Medicine) / natural medicine knowledge

But there are challenges too as e.g. …

- SFDA (State Food & Drug Administration) approval process lengthy in time, lack of transparency
- Still language barrier …delaying communication and compromising cost advantages (e.g. by use of interpreters)
- Import tax for instruments and reagents
- Weak IPR (trade secret, patent protection, confidential agreement etc)
- Lack of experienced R&D personnel
- War for talent in focal areas as Shanghai
- Lack of "smart capital"
- Limited GMP experience related to GMP sensitive areas as full development (e.g. analytical and formulation)
- Cooperation with authorities difficult and bureaucratic

Of course, all that hasn't to be seen black – and – white and it might apply to India as to Asia in general up to some extent or occasionally as well. But the aspects above are according to the broad experience including the authors own one more specific for China than e.g. for India.

India is in fact a complement and less an alternative to conduct R&D in China. So evaluating pros/cons for executing R&D between China and India is basically useless – all depends on strategic intent, the type of R&D activity, business model and so on as outlined previously. Most aspects are specific as shown in a study from Boston Consulting. In other words, the issue is not China vs India but China and India. Where to offshore or to invest depends on importance of several factors:

- Strategic intent
  - Cost savings?
  - Market access/ potential?
  - Access to talent?
- Type of R&D activity
  - Clinical?
  - Medicinal chemistry?
  - Chemical & pharmaceutical development?
- Risk tolerance
  - Exposure to IPR risk?
  - Operational risk?
  - Investment risk?
- Payback time
  - Short term returns?
  - Long-term investments?

More than in India localization in China is a MUST. A local presence definitely helps to initiate and / or expand faster. Likewise relationship matters in every part of the business and dealing with the right partner is the key.

According to an Economist Intelligence Unit (EIU) survey in 2004 China and India are emerging by far as the top favourable destinations outside of their home country for spending on R&D over the next 3 years.

A strong driver in China is, besides the general high economic growth rate, the national reimbursement list whilst in India the focus is on public procurement of generics.

7.2.9. **Recent MNC's** Activities in China And Potential Chinese Business Partners

In 1985, Janssen Pharmaceutica (Johnson & Johnson) was the first Western pharmaceutical company to set up a factory in China (Xian). But already in 1983, Janssen had signed a cooperation contract to modernize products in an existing, but old, chemical factory in Hanzhong. Today Xian Janssen is China's top joint venture with a turnover in 2006 of about $ 400 million and more than 1,500 employees.

Novo Nordisk inaugurated the first international R&D centre in China in 2002. Over the past several years, the pace of expansion into China has accelerated, with 38 foreign pharmaceutical companies now operating in the country. Of these, AstraZeneca, Eli Lilly, Novo Nordisk, Pfizer and Roche run their own clinical trial centres in China, with much of this activity centered around Shanghai.

The decision to locate in Shanghai reflects the city's growing reputation as a technology hub. Aside from what has been called the best physical infrastructure in China and an expanding base of several hundred biotechnology and medical enterprises, many foreign chemical and pharmaceutical companies have set up operations in Shanghai including Degussa, Dow Chemical, DuPont, Honeywell, Pfizer, Roche and Toray Industries.

The Roche centre was inaugurated in 2004 and now employs 80 people including 56 scientists. Of these, about one third are Western-trained scientists of Chinese origin returning home to work. Roche has said that the facility may eventually employ as many as 250 drug discovery scientists.

Recently Roche announced to build a second R&D site in China, spending $ 100 million to create the first fully functional China clinical drug R&D centre owned by a pharmaceutical MNC.

Pfizer invested US$ 500 million in China, amongst plants in Dalian, Suzhou, and WuXi also in a clinical trial centre, opened in 2003. It forms a key part of the company's global R&D network and joins just a handful of similarly sized facilities for Pfizer.

In November 2006, Novartis announced the construction of a 400-person, 38,000 square meter Shanghai R&D centre (Zhangjiang Hi-Tech- park, close to Roche's centre), reflecting a $100 million investment while at the same time building a new API plant in Jiangsu province. Prior to the establishment of the centre, the company had been bringing European experts into China to establish centres in hospitals with good clinical practice to allow it to conduct clinical trials in China in collaboration with Chinese partners such as the Shanghai Institute of Materia Medica, WuXi PharmaTech, Chinese University of Hong Kong National Institutes of Biological Sciences, and Kunming Institute of Botany.

Similarly, Wyeth unveiled its first R&D facility in China in 2006. The Shanghai-based centre will act as Wyeth's regional clinical development centre in Asia. To augment the centre's in-house capabilities, Wyeth has established a joint early clinical development centre with Peking Union Medical College Hospital in Beijing.

Eli Lilly's China presence is one of the most impressive ones with offices and facilities in Shanghai, Beijing and Guangzhou, headquartered in Shanghai. The company established a joint venture in Suzhou and wholly owned it in 2002.

Eli Lilly's Suzhou manufacturing plant and Shanghai research centre together employ about 1,000 people. Its 250 Chinese chemists, which represent the largest of its non-US drug development teams and about 20 percent of its overall scientific strength, are working in all stages of drug development. At the same time, however, Lilly intends to reduce its global R&D budget from about US$ 3 billion in 2006 to US$ 800 milion by 2010. The company aims to do this through joint research with Chinese and Indian organizations. In China, Lilly has been working with ChemExplorer in Shanghai since 2003 on molecule selection and now outsources 20 percent of its discovery work to ChemExplorer. Recently, i.e. in 2007 Eli Lilly also entered into a new strategic partnership with Hutchison MediPharma (HPML)

GSK is planning to establish and invest US$ 40 million in a large stand-alone R&D centre in China, devoted entirely to discovering innovative drugs and healthcare solutions. GSK, which established its first production plant in China 22 years ago, has small R&D units in Beijing, Shanghai and Tianjin and spends 17 percent of its sales on international R&D every year. While GSK already uses China as a manufacturing hub to produce medicine, its new centre will allow for development of new products end-to-end.

Merck is also active in Shanghai, although its presence is largely through R&D collaborations rather than its own in-country staff. In 2006, the company announced an agreement with the Shanghai Biochip Co. Ltd. on genetic and biotechnology research for cancer treatment. Under the agreement, the companies will collaborate on an oncology research program.

In 2006 AstraZeneca set aside US$ 100 million for a new R&D centre, called Innovation Centre China ICC, to start operations in 2009, while also heavily investing into their manufacturing site in WuXi.

Begin of 2009, Bayer Schering AG, the pharmaceutical division of Bayer HealthCare, announced that it will be strengthening its global R&D capabilities through the foundation of a global R&D centre in Beijing. The company will invest some 100 million Euro over the next five years to establish the centre. With the establishment of the centre in China, especially Asian patients will benefit from considering the clinical profile and medical needs early-on.

Servier, the largest independent French pharmaceutical company, has set up a joint venture with Tianjin Huajin Pharmaceutical in Tianjin after already establishing a R&D company in Beijing in 2001.

Some drug developers are seeking to expand their activities to include traditional Chinese medicines. In 2006, for example, German Merck KGaA entered into an agreement with Chi-Med's large Shanghai research centre giving Merck access to Chi-Med's library of botanical compounds.

One of the earliest European pharmaceutical companies to expand into China, Novo Nordisk, is steadily building upon it's presence in China as many of its competitors. Headquartered in Beijing, Novo Nordisk reached about 1,000 employees in China and has become the leader in diabetes products in the country with fully integrated R&D, production, sales and distribution. Recently another US$ 10 million investment in Beijing for a Biotech Development Centre was announced by the company.

The companies below could serve as potential partners or act as CRO's for Western MNC's:

Mainly for discovery chemistry

- WuXi Pharmatech
- Sundia Meditech
- Bridge (Bejing)
- Shanghai Chempartner (preferred supplier of Merck)
- Albany Molecular
- Yangtse River Pharma
- Sinochem
- Zhejiang Hisun

Some of the best positioned chemical development suppliers are

- Harbin Pharmaceutical Group
- North China Pharmaceutical Group
- Jiangsu Yangtze River Pharmaceutical Group
- Shijiazhuang Pharma Group
- Tianjin Pharma Group Corp
- Northeast Pharmaceutical Group Co. Ltd
- Shandong Xinhua Pharmaceutical Co. Ltd

7.2.10. Singapore

Some years ago Singapore's government has formulated the strategic objective to make the country a centre of pharmaceutical, biotechnological and medical-technical industry. Besides tax incentives,aworld-class infrastructure, political stability and the countries IPR protection record, Singapore offers highly professional authorities, amongst them the Singapore Economic Development Board (EDB) who supports investors and companies considering to set up presence in Singapore.

Many pharmaceutical MNC's, amongst them GSK,Sanofi-Aventis, Merck, Pfizer, Schering – Plough, Johnson & Johnson and Wyeth have invested in Singapore into their own R&D centres, manufacturing facilities, marketing and distribution hubs or support functions as IT or Finance.

Only a few examples: the companies now part of GSK, have invested since the 1970s US$ 1 billion in Singapore. Part of it is a US$ 68 million investment for an R&D centre.

In recent years Pfizer and Schering – Plough initiated API plants in which they invested several hundred million dollars each. Merck moved it's Asian regional headquarter from Hong Kong to Singapore in 2007 because of its favourable business environment. Eli Lilly announced in 2007 to triple the size of its existing Research Centre in Singapore by investing US$ 150 million.

In total all MNCs probably employ more than 3,000 people in Singapore. One deficiency of the country is (besides absence of a domestic market) the fierce competition for experts and scientists, subsequently currently still low labour costs will further go up, because the

surrounding countries can hardly provide the growing need for qualified manpower whilst more and more MNC's are coming into the country or expanding their presence. But the attractiveness of Singapore for Expatriates from the West and the influx of foreign experts still compensates up to some extent for that problem.

Singapore is in particular attractive for MNC's, because the saving potential for their pricy products is higher due to the offered tax incentives. Just to mention is that Pfizer will spend US$ 300 million on R&D in South Korea, the largest such investment by a foreign entity ever in South Korea.

7.2.11. Comparison India, China and Singapore

India, China and Singapore are in direct competition with pharmaceutical MNC's well-established locations in Europe, USA and Japan. As discussed before, the question where to settle or invest or to collaborate for a Western company is often difficult to answer and highly depends on many factors. But it's fair to say that often the answer will be, at least for big MNC's, to become active in all 3 countries An attempt has been made by *Floether* to compare pros and cons of China, India and Singapore in general. But it can't be overemphasized that his SWOT analysis of course, needs to simplify matters – which automatically means to falsify aspects to a certain extent. Nevertheless, it could serve as a guidance for those who want to become familiar with the subject of Pharma R&D in Asia the first time.

Just zooming into India and China only, each country offers different advantages despite general similarities. In other words, India's and China's capabilities aren't uniformly world-class across R&D value chain.

But the picture may look rather different in a few years.

Activity	India	China
Biology research	few capabilities, evolving	some capabilities, rapidly evolving
Chemistry research	strong and proven capabilities	good capabilities in basic services
Chemical & pharmaceutical full development	bold experience in full GMP capabilities (chemical, formulation, analytical)	limited to API development; chemical, formulation / analytical in full GMP still immature
Preclinical trials	emerging capabilities, rapidly evolving	emerging capabilities, evolving
Clinical trials	fairly strong capabilities, fast growing	strong capabilities, fast growing

India's and China's capabilities still differ in certain R&D areas

The best opportunities in both countries still are chemistry – based activities and clinical trials. Although India, with regard to chemical activities, has by far more complete service in the CM&C (Chemistry, Manufacturing & Control) area, including formulation and analytical services up to full development for international filings.

Typically, many API companies in India have insignificant understanding of biology and managing of microorganisms.

Preclinical and biological capabilities are still more an opportunity in both countries with China outpacing India in innovative biology.

In general, China is stronger in biology and rapidly improving its skills. China has been the only country in the developing world to participate in the International Human Genome Project. Thanks to heavy investments, Chinese companies can now produce hepatitis vaccines, recombinant insulin, interferon and other generic therapeutic biologics. Even that India's biotechnology sector is growing rapidly, emphasis is still on vaccine production and bio-services.

Likewise China is a dominating force in fermentation technology. Large state investment has changed the landscape in China, thwarting Indian attempts to succeed in bio-generics. India has lost large volumes of fermentation business, such as Pen G, 7-ACA etc. to China, with its low cost in energy. China has gone for huge capacity expansion and captured global market with very aggressive pricing. Power interruptions, which are not so uncommon in India, are fatal for fermentation and therefore India is realizing that the skills in this segment should not be lost forever to competing nations as China.

Governmental support for pharmaceutical R&D in general is bolder and more committed in China.On the other hand, India has a much broader vendor base (which is also directly accessible, often not the case in China), a workforce fluent in English and less risky IPR protection.

There is another interesting contrast between domestic companies in China, India and Singapore. Indian companies have the strongest appetite for acquisitions (see below) and the least appetite for divestments. 48 percent of Indian companies are considering acquisitions compared to 31 percent in Singapore and just 17 percent of Chinese companies. In turn 46 percent of Chinese companies and 44 percent of Singaporean companies are open to foreign investment in their companies compared to just 20 percent in India.

Year	No. of Acquisitions
1995	1
1996	0
1997	1
1998	1
1999	0
2000	1
2001	1
2002	6
2003	7
2004	12
2005	20
2006	14
2007	14

Number of overseas acquisitions made by Indian pharmaceutical industry (1995-Oct.2007) Source : Exim Bank

7.3. FOCUS BIOTECHNOLOGY

7.3.1. Introduction

The first biotechnology-pharmaceutical couple of companies will earn the reputation of being an ideal alliance partner and will gain a huge competitive advantage, useful to bag the best deals. As long as still no clear leader has emerged re the "ideal alliance" Pfizer remains the partner-of-choice. It has leveraged its alliance expertise to become the leading MNC on the globe. Small to medium pharmaceutical companies seeking to commercialize their products knock on Pfizers door. Today the giant collaborates with almost 500 partner companies on various fronts - quite some in the biotechnology sector.

Another Big Pharma company, Eli Lilly, has overhauled its approach to alliances. In less than two years, it has reorganized the way alliances are managed. The company is in more than 300 alliances now, about 50 percent in R&D. Just the partnership with Takeda e.g. produces more than US$ 223 million in 2008. Lilly often selects alliances in key areas of R&D as neuroscience, endocrine, oncology, infectious disease, bone inflammation and nuclear receptors – biotech partner being amongst them.

7.3.2. Increasing Demand for Biogenerics

Biogenerics are the generic versions of pharmaceutical preparations involving a biologically active substance that has generally been created using modern biotech tools. These products are still in their infancy due to relatively recent patent expirations of the first biotech products. Biotech-engineered drugs are products based on large molecule proteins. On the other hand, generics generally refer to non-biological products, i.e. small molecules.

Biotech drugs and biogenerics offer great potential in particular to Indian pharmaceutical companies which have been traditionally relying on generics. The largest Indian firms have recently ramped up production of biogenerics and are already producing equivalents of patented drugs.

Biogenerics as well as generics are in a strong growth mode, however biogenerics are in a slightly earlier phase of their growth cycle than generics owing to the lack of clear regulatory processes, needed to approve drugs.

But there are specific challenges too. Lack of regulatory guidelines, potential shortage of bulk active biopharmaceuticals obtained through non-patent-infringing routes and, most critically, the belief that minor modifications of the bioprocess may lead to variation in product safety and quality, pose significant challenges. The regulatory bodies and industry need to work together to ensure that follow-on products will not risk patient safety.

During 2002-2004, as many as 20 biotech drugs have lost their patents in the US. Of the many drugs, the US patents of 13 biotech products will expire or have already expired. Similarly, many other blockbuster drugs are expected to lose patent protection over the next few years, paving the way for competitor products to legally manufacture biogeneric versions of the biotech products and market them. This represents tremendous potential for biogeneric manufacturers since there is no real need to invest into drug discovery and clinical

development, biogeneric manufacturers can sell these products at lower prices than the original drugs. This is particularly important for companies in developing countries like India.

The average annual cost savings from the use of generics and biogenerics varies significantly among the market segments, and varies further within segments that comprise different countries or regions. For example, Eastern Europe tends to use more generics than Western Europe, so proportional cost savings are greater in that part of the overall European market. Likewise, generics represent a lower portion of overall drug use in Japan compared to China and India.

7.3.3. Therapeutic Focus

There seems to be a tendency to specialize rather in therapeutic or disease areas than mechanism of action by companies. In other words companies are focussing on areas with a high degree of patient compliance.

For example, therapeutic areas as diabetes, cardiovascular and oncology are in focus. Another one is formed by inflammation-related diseases.

Originally, because of issues with immunogenicity, adverse side effects, costs and other problems, biologics were mostly thought of as acute treatment. But with current technology to produce fully human or humanised monoclonal antibodies, long-term clinical experience and success stories for biologics in rheumatoid arthritis, biologicals start to penetrate into chronic indications.

7.3.4. Example India: R&D Spending

The R&D expenditure of leading Indian pharmaceutical companies has crossed INR 15 billion in 2007. In value terms companies like Ranbaxy and Dr. Reddy's labs led the way in spending. The other leading R&D spenders include Biocon (INR 479 million), Cadila Healthcare (INR 505 million), Lupin (INR 1.421 million), Panacea Biotec (INR 505 million), Sun Pharmaceuticals (INR 1.536 million), Torrent Pharmaceuticals (INR 739 million) and Wockhardt (INR 1.278 million). In addition to these, several companies are spending about 5-6 percent of their total sales on R&D activities. Indian companies are strengthening their manufacturing capacities and R&D focus. The two leading players namely Serum Institute of India and Biocon have granted the Special Economic Zone (SEZ) status and are making huge investments upwards of INR 10 billion on developing the infrastructure for the same in Pune and Bangalore respectively. Other players like Biological E and Jubilant Organosys have submitted proposals for setting up biotech SEZs and are waiting for approval.

Contrary to the pharmaceutical companies, most of the biotechnological companies are still engaged in R&D activities depending on government support for funds.

7.3.5. Biotech R&D Productivity

An emerging distinction between biotech and BigPharma is the productivity of R&D. According to the CEO of Genentech R&D spending by large pharmaceutical companies has

been steadily increasing over time, while the number of new drug approvals coming out of these companies has been decreasing. In 2006, the R&D expenditure of the industry rose to $ 27.7 billion compared to $ 23.3 billion in 2005 with growth of 19 percent annually. This is mainly attributed to many acquisitions of R&D related companies made by Big Pharma companies and as a result the cost of R&D increased.

7.4. Intellectual Property Rights (IPR)

7.4.1. General

Why is sufficient patent protection in India and China important? Shortcomings in adequate patent protection can discourage MNC's, especially from USA. These companies stand to lose about $ 450 million every year due to piracy.

Firms in India and China are important suppliers of low – priced API's and increasingly finished products domestically, to developing countries and to the West (India). So there has been a fear that the introduction of product patents will destroy these industries and lead to increased drug prices in the importing countries. But the impact of the changed patent regime is much broader: besides access to new medicines in India and China, changing IPR is influencing the business strategies of Indian and Chinese firms and their incentive to invest in R&D in order to move up the product / market hierarchy. Furthermore Western MNC's operating in those countries (may that be by selling their products as well as by investing in a local presence in either R&D or manufacturing operations) are highly affected.

The IPR situation in China is still perceived as "tricky". MNC's are further establishing or expanding their presence in China allowing them also to test the conditions of the market and establish relationships for the future. Many of the local engagements will remain focussed on discovery research activities, avoiding projects that are from IPR standpoint considered "sensitive". Quite some companies are still reluctant to bring those projects to China.

India API manufacturers provide evidence that confidence is building that pharma companies are now bringing more sensitive projects to India. However, India still has a reputation of relatively weak IPR protection.

While perceived as an issue, IPR protection is a decreasing barrier to ally with Asian companies. In particular R&D like e. g. chemical and pharmaceutical development, are generally less affected. To make it illustrative: upscaling and optimizing an API manufacturing process for a NME, formulation development, analytical method development and validation as well as running analytical stability studies are all activities which typically happen in a late stage of the R&D process long after completed patent protection of a new molecule. Furthermore, generally they are less related to IP origination.

Based on the information available in public domain up to now, there haven't been any IPR issues or violations occurred across industry. With proper contractual agreements in place and careful selection of a vendor (reputed), this danger may be effectively managed. One may have to understand that for major pharmaceutical firms (especially in India), who are putting lot of efforts for establishing themselves as significant players in international

pharma market, infringing on the intellectual properties of the customer is not in the best interest of the service provider.

7.4.2. India vs China

All in all there is no doubt that India has a more mature legal system for IPR protection than China. But significant practical issues exist still in both countries.

Whilst the risk for legal aspects as patent registration process, patent law coverage / protection and information disclosure requirements by customs / government in India is considered low, it's at least medium in China.

The risk for practical aspects as law enforcement / legal system efficacy and support of overall environment (IPR track record, governmental policy, business environment and culture) is medium in India but rather high in China.

The Boston Consulting Group has summarized its findings in a study executed in 2006:

Subject	India	Rating	China	Rating
Patent registration process	• Filing requirements at par with US / EU	++++	• Long and complex process	
Law protection	• same strength and application as UK • Both process and product protection under WTO agreement	++++	• Significant differences "first to file" vs " first to use" • Laws are not always equal for domestic and foreign companies	++
Law enforcement	• Litigations can be settled in courts in EU	+++	• China's court system still struggles to handle IPR issues • Established patent training institutes for IPR administrations	++
Culture / Government	• Historically lacks IPR protection environment • Significant improvements in recent years	++	• Traditional view of IPR as a common good • Government invests in public education	+

None + = least favourable → ++++ = most favourable

Specific Comparison between India and China with regard to IPR Concerns

7.5. CLINICAL TRIALS IN KEY ASIAN COUNTRIES

Globally, the clinical research outsourcing market was estimated at US$12.3 billion in 2007. This market is expected to reach US$ 23.1 billion by 2011. The Indian clinical research market was estimated at US$ 200 million in 2007 as against US$ 140 million in 2006 and a mere US$ 70-80 million in 2001-02.

As of 2007, about 100,000 clinical trials were underway around the world, involving at least as many physician investigators and more than 2 million participants. This is a substantial increase from a decade ago, when the number of trials was less than two third of that level. That increase can be attributed to several factors, for example rising data requirements from regulators, greater use of lifecycle management such as indication expansion (requiring clinical tests) and the ongoing development utilization of data collection and management technologies that enable larger scale testing. As the number of trials increases, their size is also growing. According to the FDA patient volumes have risen by about 25 percent from the early 1990s to about 4,500 volunteers per NDA in 2006. This increased size and volume translates directly into a greater need for patients.

At the same time however, rising levels of consumer medication are making it more difficult to identify potential study subjects who are not taking medicines that could interfere with the action of the drug under investigation. The result is that clinical trial recruitment in the West now consumes about 30 percent of overall clinical trial time and up to 40 percent of clinical trial costs - more than any other activity associated with clinical testing.

So MNC's are worrying about the steadily escalating new drug development costs. Clinical trials now cost as much as US$ 5,000, $ 6,500 and $ 7,600 per patient for phase I, II and III respectively.

The situation above has led to the expectation that within the next two to three years up to 65 percent of the studies regulated by FDA and sponsored by MNC's will be done outside US, Asia being a key destination.

Many researchers and pharmaceutical companies are beginning to look at China's and India's massive population as an asset for clinical trials. Emerging diseases such as Severe Acute Respiratory Syndrome (SARS), and diseases that are particularly prevalent in China - such as diabetes and hepatitis - present an opportunity to make rapid advances in clinical research. Further, still relatively few Chinese and Indians have access to medicines ("drug – naive patients"), which makes it more straightforward to test drugs without worrying about interactions with other compounds. Meanwhile widely introduced GCP/GLP guidelines and other Western regulations in most of the Asian countries are another supportive aspect.

As to the cost of clinical studies, testing in China is reported to cost only one third of trials in the Western world. On the negative side there is still an Achilles' heal, i.e. Chinese regulators typically take as long as a year to grant companies permission to conduct clinical trials (compared with just two months in Singapore). With regard to the clinical trial capacity, as of 2006 there were 205 institutions accredited in China to conduct clinical studies. The fact that the number of SFDA approved multinational clinical studies in China has gone up from zero in 2002 to 53 in 2007 is illustrative.

But there are also some limiting factors e.g., in China, which are good to know before approaching any decision. Drugs, which aren't already commercialized in any other country have to pass clinical tests from phase I to phase III in China. Besides, without a phase I in any

other country there won't be approval for clinical trials in China. Drugs which are already marketed in a different country can skip phase I/II in China – but only if phase I/II were carried out in East Asia (e.g. Korea or Japan) – otherwise a retesting in China might be required. As bad as this situation sounds, a well thought strategy may convert this into an opportunity. Looking at the high cost of clinical trials, the innovative company may enter into co-development rights in Chinese market. This may allow Chinese pharmaceutical companies to gain some quality pharmaceutical development experience, much needed credibility, and also establish them as serious partners.

What about India? McKinsey estimates that by 2010, global pharma majors would spend around US$ 1-1.5 billion just for drug trials in India. So by today all big global pharma names like Novo Nordisk, Aventis, Novartis, GlaxoSmithKline, Eisai, Eli Lilly and Pfizer as well as international CRO's Quintiles, Covance, PPD, Parexel, Icon, Omnicare, and Clintec have begun clinical drug trials across various Indian cities.

CRO's, which compete with each other to provide clinical trial services for pharmaceutical companies, are mushrooming across India. US companies are acquiring Indian CRO's and turning them into hubs of their clinical research activities. India currently participates in about 1 percent of worldwide biopharmaceutical clinical trials, involving 757 sites, according to a recently published article in Nature Reviews Drug Discovery. But its average relative annual growth rate is nearly 20 percent.

The high incidence in lifestyle diseases (Diabetes, Heart Disease, etc.) and adiverse population (all three general racial classifications - caucasoid, mongoloid and negroid - adequately represented by the Indian population) are supporting factors for clinical trials in India.

Of course, there are hurdles too. At the federal level, the central ethics committee at the Indian Council of Medical Research issues guidelines but has no policing power. There are plans under way to convert the current ethical guidelines into law. Likewise the potential for GCP violations still exists.

In 2005, the government of India enacted a new rule that allows foreign pharmaceutical companies to conduct trials of new drugs in India at the same time that trials of the same phase are being conducted in other countries. This new rule supersedes a directive of India's Drugs and Cosmetics Rules that required a "phase lag" between India and the rest of the world. According to the old rule, if a phase III study had been completed elsewhere, only a phase II study was permitted in India. Even under the new laws, only those drugs that have already passed phase I safety trials in the country of their origin can be tested on Indians.

7.6. Operating Models for Big Pharma In Asia

One of the key decisions to be made by any company aiming to establish a presence in Asia is choosing the optimal business model. Each model will perform differently under different conditions. It's obvious that any given project or R&D area might lend itself to a certain model. So the choice will be determined mainly by the nature of the activity. For example, clinical trials might safely be outsourced to a reliable vendor, whereas full scale GMP chemical and formulation development requiresa captiveinvestment equipped, staffed and operated to Western GMP standards. But the decision about the model is likewise

determined by the country (China vs India vs Singapore), by the nature of the company, its objectives and long-term goals, the degree of flexibility needed, IPR aspects as well as by it's risk tolerance, available budgets, and already existing engagement in the respective country.

MNC's have tried a number of different approaches. Five business models have emerged as the main options:

1. Captive R&D Centre

Key features:

- MNC operates at a fully owned site
- large investments and limited flexibility
- full control over IPR, talent and know-how

This model stands for the most serious and committed presence in any offshoring destination. But it's vulnerable to problems with planning and construction permissions, red tape issues in general and limits flexibility with regard to many aspects. One mitigation might be to start with a joint venture in order to get assistance by a local partner how to operate in the country. After ending the joint venture contract and ending the relationship the MNC takes over or alternatively, buys out the partner before.

2. Partnership

Key features:

- partnering with a local provider who acts on behalf of the MNC and returns the project to the MNC after the respective work is done
- moderate investment and higher flexibility
- easy access to local talent
- limited IPR control

This model can help to ease capacity constraints and leverages on the partner's experience in managing local red tape - but intellectual property protection might get compromised.

3. BOT (Build-Operate-Transfer) model

Key features:

- after forming an alliance with a local company the local provider hands over facilities and workforce at an appropriate time point
- investments spread over time
- fast access to local talent and managing red tape via local ally

There is good track record of that model in other industries. It allows the MNC to test local ways of doing things before taking the risk of setting up its own full-fledged centre.

4. Third party outsourcing / vendor – based outsourcing

Key features:

- outsourcing of selected activities to third party providers
- almost none investments
- high degree of flexibility
- know-how transfer and IPR risk limited

It's the least risky and most careful approach to "Go East", particularly useful for well-defined, less complex concrete activities (e.g. stability testing), but also limited in insights regarding the respective country and limited in creating a strategic presence.

As obvious, in practical terms there are also all kinds of hybrid models. An MNC might migrate in two stages e.g. from a vendor-based to a captive business model.

Almost needless to mention, the location and city selection is an important aspect as well. Key factors are e.g. the ability to attract talent, cost aspects (land, workforce), clustering effect, proximityto MNC'sheadquarter, proximity to authorities, PR impact etc.

In China Shanghai area is the city of choice for R&D centres, followed by Beijing (largest number of institutes and universities), Guangzhou, Tianjin and Hangzhou.

In India the focus is on the Mumbai / Pune area, Hyderabad and Bangalore. Zooming into China and India again as the two core destinations for pharmaceutical offshoring it can be stated, that generally China might demand a different business model than India. Of course, this shouldn't be seen black-and-white – but certain specifics of the country translate into certain preferences regarding the operating model a MNC might choose.

In China the preferred business model seems to be the captive centre. The existence of a captive site is signalling the MNC's commitment to China. This is more than just symbolic because it's about visibility, establishing the brand name with patients, doctors and authorities eventually translating into sales. China officials like to see country's technological advancement – which is best served by a captive centre. It's seen as the best way to assist Chinese R&D institutions and vendors to move along their learning curve by demonstrating international best practices and inspiring local R&D providers. It helps to ingratiate with Chinese officials and might be instrumental in influencing regulatory and pricing policies as well as tighter IPR protection.

7.7. Conclusions and Outlook

The biopharmaceutical industry came late into Asia. But pharma stands to benefit at least as much as other industries from the opportunities that Asian alliances and expansion present, since its real value lies not just in simple cost savings but also in the faster development of new compounds and in penetrating huge new markets.

Now the global pharmaceutical industry is seriously embracing the advantage of offshoring and general expansion towards Asia, i.e. to huge potential markets and low-wage powerhouses as India and China. The reality of shrinking profit margins, drying pipelines, patent expirations, intense generic proliferation and increased R&D costs has made partnership and offshoring an attractive strategy.

In particular R&D activities come into focus of MNC's. Next to conducting clinical trials (which are 60 to 80 percent of a NME's development costs) and API related activities as chemical process research, increasingly full end-to-end R&D activities are about being set up by MNC's in Asia. The business models applied are manifold, mostly by acquiring local companies, strategic partnerships and increasingly by setting up wholly owned R&D subsidiaries.

But MNC's are also correct to be wary of sensitive and vital operations. There is low tolerance for error industry-wide; simple mistakes can compromise results, or even harm patients, resulting in massive and expensive liability.

On top, the cost of an unsuccessful partnership is more than just a financial issue, since the company loses crucial time and opportunity that it could have done elsewhere. By outsourcing to a third party there is also a loss of partial control as it passes from client to provider. Poor communication can lead to problems with quality and delays. Concerns about intellectual property have been already addressed. Last but not least, working across multiple languages and time zones is introducing extra complexity.

Nevertheless, given the objective constraints in pharmaceutical industry, the globalizing world and the importance of newly emerging markets, forming alliances and expansion towards Asia is simply unavoidable, regardless by which means and business model.

Delivery of benefits for Western companies require beside sustained investments and development of management experience in particular endurance and adaptability to cross-cultural differences – this all in line with the pace of capability development in individual geographic Asian environments.

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Chapter 8

STRATEGIC ALLIANCES: POST-ANALYSIS AND PROJECTION

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ABSTRACT

This section summarizes, reviews, and previews major observations, trends and fundamentals of pharma-biotech alliance formation.

The network economics dimension of alliance formation among biotech and pharma companies have been at the core of our understanding of industry change. Alliance formation with a particular focus on the R&D dimension is likely to produce competitive advantage through collaboration though in general quite a significant part of them have failed [1]. In view of pharma-biotech alliances, as results in Section 4 appear to indicate, the more successful biotech firms are more likely to be engaged in collaborative ventures though the converse that more collaborative firms are more likely to be successful in the marketplace does not necessarily hold.

As suggested in Section 3, a small biotech and a large pharma firm might have the same objective (e.g. to successfully develop a new drug) while having somewhat different motivations. They are both motivated by the creation of new knowledge, represented by the competencies dimension, but the small biotech firm allies as well to have access to the pharma firm's sales and distribution network, combining market structure and competencies. A large pharma firm allies in order to fill its new drug pipeline, and hopefully leverage its sales and distribution capability. So, each firm pursues the alliance for related but somewhat different motivations. This is at the very essence of a networked increasing returns economy. Though this fundamental trend remains intact, it could be accelerated by downward cycles, as

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evidenced by the current global financial crisis with recent M&As of Pfizer and Wyeth, Merck and ScheringPlough, Eli Lilly and ImClone, GSK and Stiefel.

A critical distinction suggested by the taxonomy involves the orientation of various network strategies. Firm constellations primarily allied under network economic conditions are often characterized by horizontal relationships, in that alliances are more likely to be characterized by alliances between firms providing similar offerings to the market than those in other categories. The nature of standards based industries encourages firms to establish a baseline of compatibility, a purpose for which firm networks can be quite effective. Often, this purpose manifests itself as alliances between firms in the same industry, providing similar products or services. Constellations formed for competencies objectives tend toward vertical relationships. Normally, firms that ally to leverage complementary competencies address different parts of the value chain in their industries. Competency networks of firms can even arise across industries, outsourcing non-core functions providing the most obvious example. Outsourcing information technology or human resources services can require significant, long-term arrangements between firms. This is not a hard and fast distinction between horizontal and vertical firm networks. Horizontal competency alliances can arise between firms in the same industry with very similar product and service lines. Such alliances often occur in the form of cooperative research ventures, particularly in the case of expensive, long-term basic and applied research efforts. New automobile or jet engines and pharmaceuticals offer examples. Nonetheless, the vast majority of competency-based alliances involve firms in vertical relationships to each other. Serious competency alliances often require sharing firm specific knowledge that might provide a competitive advantage against direct competitors, either at present or in the future. This level of trust and openness mitigates the creation of competency alliances between direct competitors.

Market structure constellations tend toward either orientation, depending on the type of structural issues involved. For instance, in situations where anti-trust regulations restrict mergers and acquisitions that might otherwise make strategic sense from the individual firm level, alliances can develop in a horizontal fashion, in order to achieve some economies of scale without violating anti-trust regulations.

During the last ten years, the pharmaceutical industry began a significant evolution in the platform technologies, that is, ‘economies of scope in R&D’, necessary to develop new drugs or recombinant vaccines (e.g. using genomics, systems biology, combinatorial chemistry). Alliances offered a successful strategy for incorporating these emerging capabilities into pharma firms' R&D portfolios. As evidenced by dramatic productivity increases in the software industry [2] analogously this R&D tool promises further great potentials in the pharma-biotech industry, however, conditional on the specific R&D process of drug discovery to be successful runs through various forms of stochastic processes.

The search for new drugs requires a substantial degree of seminal innovation. In contrast to incremental innovation, large firms find seminal innovation to be much more difficult to accomplish internally. The challenges presented by seminal innovation, including a high degree of unpredictability, encourage large pharma firms to pursue collaborative relationships.

Given the unpredictability of seminal innovation, an effective alliance strategy provides firms with a broader portfolio of options on R&D efforts than that which internal R&D alone can accomplish. The expanded options provided by collaborative relationships appear to have

translated into superior market valuation performance for large US. pharma firms during the period under consideration..

An alternative explanation for the correlation between collaborativeness and market valuation could be that firms seeking partners tend to ally with more successful firms. Further research could address this alternative hypothesis by examining the increase or decrease in alliance activity of pharmaceutical firms following and during periods of both positive and negative market performance. Nonetheless, this hypothesis, if it turned out to be valid, would not invalidate the assertion that a high rate of collaboration positively impacts market valuation performance of pharma firms. It is quite likely that performance and collaboration rates are mutually reinforcing. Firms exhibiting superior performance might experience higher demand as a potential partner, leading to access to more, higher quality deals. Here quality deals would presumably lead to superior performance of collaborative projects, improving the performance of the firm's overall R&D portfolio. Superior performance of the R&D portfolio likewise reinforces superior performance in terms of market valuation. The co-evolution of the biotechnology and pharmaceutical industries underscores the importance of understanding the impact of critical events and trends. These events not only impacted the nature of the relationships between firms, but also transformed the structure and direction of each industry. Industry consolidation as a result of the FDA's regulatory changes following the Thalidomide Crisis, a market structure influence resulted in very few small firms pursuing cutting edge research. It would be interesting to explore whether industry consolidation during this period resulted in a decreased diversity and variety of research efforts in the private sector. Life sciences research continued at the academic level, eventually leading to the founding of the early biotech firms; however, small firms could no longer independently navigate the drug trials process. The agreement between Genentech and Eli Lilly represented the nascence of successful alliances between biotech and pharma firms, and remains representative of many practices to this day. Throughout the 1980s and 1990s, pharma and biotech firms evolved in varied forms of inter-firm relationships in order to combine the innovativeness of smaller firms with the resources of their mammoth counterparts. Finally, the introduction of genomics, proteomics and bioinformatics during the late 1990s began to transform the industry into one dominated by information. As access to broad, diverse information became increasingly important for pharma and biotech firms, network economics began to play a role in defining the competitive and cooperative relationships between firms and, as such, the competitive dynamics of both industries.

In view of big pharma’s persistent problems of ‘drying up the drug pipeline’, this suggests a change in the strategic course along the network economics, competency and market structure dimensions:

i.) a platform drug discovery on a broad scope, to generate multiple ‘blockbuster’ potentials utilizing novel genetic-based targeting procedures combined with complementary delivery mechanisms (e.g., through nanotechnology/nanomedicine) with emphasis on systems biology. The best platform technologies are not only those that enable drug discovery to proceed, but are new classes of molecules that themselves act as drugs. Monoclonal antibodies (Mabs) are in this category. For example, Genentech has Mabs like Herceptin for breast cancer, Avastin for colorectal/breast cancer and Rituxan for non-Hodgkin’s lymphoma.

ii.) a drastic shift toward building a biologics portfolio since it is less threatened by generics as biosimilars that otherwise would more easily and speedily erode competitive strength, profitability and productivity,
iii.) to streamline and shorten the product development process would take selective outsourcing in the value chain, notably in R&D and clinical trials,
iv.) a major facilitating factor of drug development is a balanced approach to bringing innovative drugs timely to the market and having an effective risk assessment in drug approval. In this regulatory process the US FDA has long been the leader but is now increasingly challenged by rivals such as the European Medicines Evaluation Agency (EMEA) that will decide independently and possibly more expeditiously for an even larger market. It has recently come to light that major European pharma companies such as GSK, Sanofi-Aventis and Novartis, are or have been contemplating to skip the FDA process altogether in favour of going through the EMEA first.[3]

The recapitulation of the industry history, as traced in Section 3, reflects the evolutionary nature of firm networks. Different types of events and trends impact firm networks in varied manners. The placement of these events can help better understand the entrepreneurial past, as well as extrapolate to the future. Critical events can have substantial implications for firms attempting to pursue network strategies- or, for that matter, firms choosing to avoid employing a network strategy. How could we go about validating the applicability? For example, how do critical events impact the evolution of firm networks in other industries? It should be possible to identify consistency in the application across industries, given its general construction. Further, our discussion suggests insights regarding the importance of firm networks for firms pursuing innovation competencies under varied conditions. For instance, firms competing in very mature industries tend to pursue incremental innovations (whether or not this is the optimal strategy). Firms in fast changing industries where new knowledge drives value creation must pursue more significant, even seminal, innovations. Firms pursuing patentable therapeutics offer a compelling example. Still open questions remain whether industries requiring more seminal as opposed to incremental innovation are indeed more likely to exhibit a stronger correlation between collaborativeness and market success than those industries more concerned with incremental innovation.

TECHNOLOGY AND INDUSTRY EVOLUTION

The history of the biotech and pharma industries also further validates the application of the evolutionary change to technological and economic development. In an evolutionary framework, the preponderance of evolutionary change also occurs during periods of event-based ‘disruptive’ change, where the introduction of substantial mutations, environmental changes or a confluence of factors encourages significant change within a relatively brief period of time. These periods account for the preponderance of evolutionary transformations.[4,5] Evolution typically occurs incrementally, with living systems attempting to achieve some form of equilibrium, though not necessarily reaching it. Evolutionary change pertains to the relationship between technological change and economic development. Economic development within a particular society and time period relates to the

institutional environment, the innovativeness of the population, and, by corollary, the introduction of substantially new technologies to the marketplace as in a 'history-friendly' model of the industries. [6]

Relative to the biotech and pharma industries, changes in the institutional environment represented by regulatory events, and the introduction of dramatically new technologies to market initiated periods of significant change, followed by periods of adjustment. The distinctions between regulatory events (market structure), the introduction of new therapeutic technologies (competencies), and the introduction of functional genomics, proteomics and bioinformatics (competencies and network economics) to the industry underscores varied implications for inter-firm alliances and competitive dynamics. In view of a critical event analysis of the pharma industry, competitive selection preferred large, integrated firms. As substantially new therapeutic technologies arose from basic biotech research, competitive selection between firms favoured the adaptation created by alliances between innovative small firms and resource-rich established pharma companies. Each of the critical events examined exerted impacts strong enough to introduce inconsistencies in the otherwise incremental evolution of inter-firm relationships, industry structure and competitive dynamics. The empirical analysis of Section 4 appears to support the assertion that a period of punctuated change occurred during the final half decade of the twentieth century, given the dramatic increase in correlation between collaboration and firm performance, although this assertion requires further validation. The taxonomy emphasizes the distinctions between these critical events and their differential influence on relationships between firms.

Related to discrete evolutionary change, Clayton Christensen's notion of disruptive technologies describes situations in which technologies present a disruptive challenge to existing products provided by established competitors. [7] Firms introducing disruptive technologies to market are typically new competitors, and are often new firms. Their original products normally target a market space unserved or underserved by existing offerings. If successful, these new products often define a new market space, entering into competition with established competitors" Clearly, the biotech industry has offered a number of potentially disruptive challenges to traditional approaches to drug development. Genentech's first two products, insulin and human growth hormone, both introduced substantially new technologies that replaced prior products. The insulin product proved disruptive for Novo's and Lilly's traditional insulin products, despite both firms' active pursuit of alternative production methods. Novo did not ignore the need to innovate, it simply chose the wrong direction for research. By contrast, Eli Lilly sought to lock-in three research teams pursuing rDNA produced insulin, resulting in its access to Genentech's successful version. While the new product obsolesced Lilly's existing animalderived product, increased sales and supply far outweighed the loss.

Many other disruptive technologies have arisen in the pharma industry, such as Prilosec and Prevacid's replacement of histamine H2 blockers such as Tagamet and Zantac. The pharma industry, however, has used alliances as a useful mechanism to deal with an ever-expanding universe of new drug technologies. Beginning with Lilly's successful leveraging of multiple relationships to acquire the insulin product, the industry has evolved extensive inter-firm networks. Nonetheless, it took large pharma firms a while to recognize the potential of their biotech competitors. In this sense, the entire field of biotech that emerged during the late 1970s and 1980s can be viewed as disruptive.

Due in part to denial and skepticism, the pharma industry succumbed to the myopia that enables new competitors to thrive from disruption. If pharma firms had pursued the technologies of the biotech firms on their own, there might not have been an opportunity for the upstart to develop. This assumes that large pharma companies could have succeeded in developing the relevant emerging technologies primarily through in-house research. This is probably an erroneous assumption.

Let's take a counter-factual approach to this discussion. Assume that the large pharma firms had devoted substantial resources to the emerging DNA-based technologies early on, prior to the development of successful biotech firms. It is most likely that the large corporations would not have succeeded in eliminating the threat from start-ups. There were too many scientific and technological directions in which to go, as well as too many radically new technology platforms, for even large firms to accomplish sufficient in-house R&D to replace start-ups. Moreover, the risk to even the largest firms would have been too great to undertake all of this emerging research in-house. In retrospect, it is clear which technologies and products succeed. Prospectively, outcomes are never so clear. It was not at all apparent which technologies would succeed in the marketplace, so a single firm's portfolio of research would have needed to have been much too broad. No one would argue as we enter the early 21st century that big pharma companies do not recognize the promise of biotechnology, yet, biotech firms still exist in abundance. Alliances between massive drug companies and small innovative firms continue to represent the industry model of best practice, and will likely do so for many years to come.

Even after the biotech-pharma alliance culture began to expand following the success of Genentech's insulin product, the industry required many years to adjust. Alliance competencies do not occur over night, particularly alliance “mindsets”. Further research should examine the development of the alliance culture in the life sciences industries, particularly during the 1980s and 1990s. During these years, the industry evolved highly successful network strategies that fulfilled the needs of large and small firms alike. Understanding developments in this sector could provide useful insights for other industries undergoing substantial disruptive technological change largely driven by smaller, emerging firms. The large pharmaceutical producers could provide a model for other companies facing disruption. Moreover, it is important to take action against disruption before recognition of a specific threat. By the time a competing product reaches a critical mass in the marketplace, it is probably too late. Firms in any industry can monitor the technological and market horizons and construct a portfolio of access to new technologies through alliances with new firms pursuing potentially relevant technologies. Such outsourcing of R&D can provide insurance against being caught unaware, and help produce a successful product pipeline.

FIRM NETWORK LIFE CYCLES

Similar to the established notion of life cycles of individual firms, further research should uncover that firm networks exhibit strong consistencies in their life cycle evolution. The manifestation of these life cycles will appear more complex than those of single firms, given the increased complexity introduced by multiple firm actors, looser central control and hybrid organizational forms. The motivations taxonomy should be helpful in parsing out issues in

such a way as to allow researchers to identify consistencies in the life cycles of different types of firm networks. Network life cycles should appear more consistent within similar motivation spaces than between different motivation spaces. For instance, an alliance between two firms can increase the likelihood that they might consider a merger or acquisition with each other in the future. Alliances offer firms the opportunity to decrease information asymmetries and understand how they might best work together as an integrated firm. Employing the taxonomy, one might reasonably hypothesize that alliances within the competencies space are more likely to result in M&A activity than those characterized by purely network economic influences. Competency-based alliances tend to demand greater information sharing and trust building than alliances formed primarily as a result of network economic factors. Identifying such contrasts between inter-firm relationships differentiated by the taxonomy could provide useful insight into network life cycles. Ultimately, the creation of network specific value motivates the creation, development and maintenance of any inter-firm relationship. As alternatives to firm or market organization, hybrid organizational forms must produce real or at least perceived value for their participants in order to persist. This value could arise from many factors, such as the creation of real collaborative value, the dominant position of a particular firm in the network (e.g.automakers and their suppliers), or regulatory regimes. This is not to assert that managers make optimal choices of organizational forms; rather, managers make optimal choices based on a boundedly rational view of the world, constrained by the real world factors in which they act.

REVISITING THE STRATEGIST'S DILEMMA

While network strategies can afford firms access to broader and deeper information than markets, and greater internal focus than integration, developing and maintaining firm networks generates additional complexity. Network strategies demand corporate and managerial capabilities somewhat different than typical firm strategy. As interorganizational forms proliferate and evolve, the fields of corporate strategy, organizational economics and organization behavior should assist in the elucidation and maturation of network strategy competencies. Practitioners will lead, through ingenuity, trial and error, encouraged by the prospect of superior returns and the ever-elusive competitive advantage.Whither sustainable competitive advantage? While academic and applied approaches to corporate strategy continue to evolve in response to accelerating technology and marketplace change, the resultant increasing uncertainty of dynamic markets ensures that the Strategist's Dilemma of commitment in the midst of uncertainty will continue to confound. The ultimate dilemma of the strategist occurs as a result of the competitive marketplace that has brought us so much general prosperity. The more effective the strategies employed by marketplace participants in general, the more elusive becomes sustainable competitive advantage. As strategy becomes more sophisticated and managers better informed, overall competitiveness should increase, ever-thwarting the pursuit of advantage. In the manner of Schumpeter, market competition should “creatively destruct” strategic advantages, providing expanding value for consumers while increasingly challenging competitors to innovate in the quest for supernormal profits.

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Supplement

STRATEGIC ALLIANCES, MERGERS AND ACQUISITIONS

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ABSTRACT

This supplement reviews the various industry-specific, structural and regulatory conditions that promote or inhibit strategic alliance/joint venture formation across industries with special regard to network industries, in particular those that have beneficial effects on innovation incentives.

S.1. INTRODUCTION

nStrategic alliances or joint ventures combine the resources of partners, integrate their operations and share profits. If the partners were competitors, they would stop competing with each other. From the viewpoint of competition, the effect can be the same as merger. Even more so in network industries that thrive on demand and supply side economies of scale, spawn off in complementary activities, as in the context of biotech- pharma industries, it is logical to view strategic alliances like mergers. Merger-based analysis has been taken out from traditional industrial economics. It focuses on underlying structural conditions of the market in the belief that market structure substantially influences market consequences. In a fragmented market, firms are unable to make profits by raising their prices or reducing their output because otherwise customers would easily shift to other producers. The principal anti-competitive concerns, such as price increases and output reductions, largely depend on the current production concentration in the relevant market. The anti-competitive risks of strategic alliances, as those of mergers, are closely related to competition within a highly concentrated industry or market. Given the market concentration, the relevant structural

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factors include the number of firms participating in the market, the participants' actual or potential share of those markets, the transaction's effects on concentration, the likelihood of entry and the ability of potential entrants to deter supra-competitive pricing. If a firm or a few firms occupy large shares of the market, which means higher level of concentration, the collusion risk and supra-competitive pricing through coordinated behaviour will occur and might last over time in a certain market [1].

Merger-based analysis is also adopted by anti-trust agencies. The 1992 US Dept. of Justice and Federal Trade Commission Antitrust Guidelines for the Licensing of Intellectual Property [2] set forth a merger-based plus efficiency analysis. Under the guidelines, the agencies define the relevant market and identify the entities that have the incentive and capability to undertake R&D closely substitutable for that to be undertaken by the venture. The agencies ordinarily will not challenge a research venture whenever there are four or more other independently controlled firms with comparable research capabilities and incentives. If there are fewer than four such firms, the agencies will consider whether the venture is likely to give the parties an incentive or ability collectively to retard the pace or scope of the R&D efforts. They will also consider the potential efficiency justifications for the venture, such as combining complementary R&D assets in a synergistic way that makes successful innovation more likely, more rapid, or less costly.

Although a merger-based market structural analysis might be a pervasive approach widely adopted by the judiciary, it collapses following the emergence of modern industrial economic analysis. First and foremost, this approach neglects the importance of economic efficiency that joint ventures are able to bring in. This is particularly substantial when the transactions engage in a concentrated market or the participants own a certain market share. For example, under the merger-based approach, joint ventures would not pass the test if the participants already have high market shares in their home markets [3].

Also, the merger-based approach requires a complicated assessment of the relevant product and geographic markets, each of the partners' share of those markets, their competitors' market shares, and any increase in market concentration resulting from the transaction. Those determinations are in fact intensive and time consuming, and their outcome is difficult to predict.

This is particularly difficult in network industries. Network industry strategic alliances may make it more difficult to define the 'market' at an early stage. This is because here joint ventures may be formed to create new products that may not exist in any current product market. Furthermore, the characteristics of various forms of dynamic, non-price competition, the changing features of products over time and short product life cycles increase the difficulties of applying conventional market definition methods, which are based primarily on price responsiveness. As a result, market definition in network industries is a very difficult process, and more easily subject to error than in conventional industries. Network economics deal with economic activities that provide more value combined than the sum of their separate activities. They are able to give rise to increasing returns that contribute to the growth of industries and economies. Both biotechnology and large pharmaceutical firms compete in an industry characterized by rapid technology change, in particular, these firms depend on the creation of new knowledge.

A large part of network industry strategic alliances are concentrated in the research and development area. The analysis of research joint ventures, or production joint ventures that begin production only after a considerable period of research and development will be

difficult. It requires consideration of the effects of the transaction both on research competition and on competition in product markets in which venture participants are present competitors. Nevertheless, the market structural approach is backward looking. The assessment of relevant market and the market shares of the partners to a joint venture basically rely on present and past market records. Research joint ventures often promote long-term efficiencies and their specific impact on the relevant market will not be measurable until some time in the future. Additional complexities may arise because market delineation for research and development may often be a more uncertain exercise than in the case of output markets, and competitors in R&D markets must be evaluated on the basis of qualitative evidence of their likely future competitive significance. In a market in which innovation is emphasized the market position of incumbents changes rapidly, new entrants will appear and sometimes totally displace the incumbents. When technologies change, appropriate antitrust market conditions may change over time as well. Also, standards may quickly become obsolete, or, alternatively, the technological capital that might provide some members of the industry with a competitive advantage will turn out to afford only a short-term advantage. Attempts to employ the standard for a longer-term advantage will suffer from the general uncertainty and unpredictability of the future.

In fact, many of the analytical and evidentiary tools that are used in the delineation of output markets will have only limited use in describing research markets. Concepts such as cross elasticity of demand may be difficult to apply when the contours of the output market in which the research may come to fruition may not be clear. Evidentiary tools such as customer perceptions of the market, may lack value when customers themselves are ignorant of the likely impact of product development on their business.

S.2. INTEGRATION

The most significant economic characteristic of strategic alliances or joint ventures is the integration of separate resources to achieve the efficiencies the individual firm could not reach otherwise. Efficiency values whether an alliance is worthy of support even if it creates market power. Efficiency, however, is difficult to quantify, and even more difficult to 'trade off' against anti-competitive effects. Nevertheless, levels of integration can be proxies for efficiency. For example, a high level of integration associated with joint construction of new productive assets or substantial reorganization of existing assets generally indicates substantially more efficient operation than would occur in the absence of any joint arrangement. Also, if a joint venture can be quickly formed and quickly abandoned, the level of integration is lower. The more complicated the structure of joint ventures, the higher the level of integration of the joint venture. The more easily formed or abandoned a joint venture is, the more it is like a cartel [4]. Some proposals have been made for an analysis of strategic alliances based on the degree of integration. They assert that integration-based analysis provides a clear picture and easy way to evaluate the joint venture. They also contend that the integration-based analysis can explain some cases denying the contentions of joint ventures. For example, labeling joint ventures with no real integration of any resource, which means if no economic efficiency can be achieved to balance the restriction of competition caused by such arrangements it should be condemned automatically from an antitrust perspective [5].

In addition, different business stages of arrangements usually represent different possibilities of anti-competitive risks. If a transaction engages in an upper stage of business, for instance, a joint research and development venture, which represents only a very small proportion of the input of a final product, anti-competitive risks will be very unlikely. In contrast, a downstream stage of business such as joint marketing arrangement produces likely anti-competitive risks.

Other analysts, nevertheless, argue that there is no economic basis for using the degree of integration to sort anti-competitive practices from pro-competitive ones. Moreover, using the degree of integration to characterize an entity as a joint venture or a single firm for antitrust purposes would provide incentives for joint ventures to become more integrated, especially joint ventures that are interested in pursuing policies that would be subject, reasonably or not, to antitrust scrutiny. Instead, it is more sensible to develop a policy that focuses on the effects of a joint venture on competition and welfare than to try to devise a rule for determining when some joint ventures will be treated as if they were unitary firms.

S.3. NETWORK VERSUS FIRM SPECIFICITY

Although the notion of firm specificity converts well conceptually to network cases, some of the insights change when considering inter-organizational relationships. Firms' flexible investments tend to provide less strategic impact, as well as requiring less commitment from a firm. By definition, a firm's flexible investment can usually be sold if needs change without a substantial loss of value (i.e.-the firm makes a lower "commitment" to the investment). The downside is that, since value can easily be transferred and garnered by other firms, the strategic value should be less, in the sense of providing a competitive advantage. If competing firms can easily acquire and benefit from the same capability (technology, service, etc.) for similar return, then the investment offers little strategic value, beyond staying in the game. Firm-flexible resources are at best a ticket to the ballpark, unless firms combine such investments with other capabilities and resources that create a unique competitive advantage. Such combinations can convert a firm-flexible resource into a firm-specific resource. This neat distinction between firm-specific (generally strategic) and firm-flexible (generally non-strategic) investments from the resource-based perspective changes when we consider network investments. Network specific investments in any case must be considered as commitments, similar to firm-specific investments, as these resources tend to be difficult or impossible to transfer should strategic direction change. Unlike firm-flexible resources or capabilities, there are cases where network-flexible investments could provide a substantial strategic impact for firms. For example, in the mid 1990s, Merck Pharmaceuticals invested $50 million in a joint venture with the University of Washington, Seattle, to create a publicly available database of SNPs (single nucleotide polymorphisms). While on surface the investment appeared to be intended to further the cause of science, in fact it was a strategic move aimed at thwarting Celera Genomics, Human Genome Sciences and other emerging biotech firms from acquiring proprietary rights to the profitable use of the knowledge. Merck invested a substantial sum of money in an avowedly network flexible resource (in that it was to be publicly available), and yet the firm made the investment toward a substantial strategic objective.

What explains the contrasting implications of the flexibility dimension at the firm level as opposed to the network level? The most general answer reflects the impact of network economics. In such cases, giving it away might be the most strategic solution. With the Merck/UW case, we begin to observe the fact that network strategic can differ, and sometimes conflict, with strategies considered solely from a firm perspective. Merck could have decided to invest the $50 million in building a proprietary SNP database, competing directly with Celera. Certainly, Merck could have motivated the resources. Merck decided to create a database in the public domain. Why? Laying aside motivations beyond the purview of economic interests (e.g.- altruism, public good, quest for knowledge), the answer exists in considering how Merck makes it money. While drug discovery presents a core competency of the large pharma companies, big pharma makes the preponderance of its profits from the sales of new therapeutics. Moreover, most big pharma companies source a substantial portion of their new drug pipelines from other firms or research organizations, such as biotech firms, university research centers and even other phanna companies. From Merck's perspective, a widely available SNP database (a network flexible resource) provides more researchers with tools necessary to discover a much higher and more diverse set of new drug candidates than a database owned by a single firm. Moreover, once all of the important SNPs have been catalogued, a supply of new forms will only arise very slowly (theoretically, only as mutations or new interpretations of the genome occur. Merck's access to the breadth of the biotech field suggests that the firm would benefit more from encouraging public availability of SNPs. Certainly, a SNP database controlled by Celera Genomics presents an interesting competitive threat to firms like Merck. Merck could have decided to build its own proprietary database. By nature of basic scientific research such as this, researchers not funded or employed by Merck would have almost assuredly not provided Merck access to their discoveries, except insofar as other initiatives were in the public domain. In fact, there were many private initiatives, which threatened to fragment access to a complete database. Ultimately, the most value can only be derived from the complete database. From a research perspective, investigating the implications of a subset of SNPs would neglect situations involving cross or multiple causation. Incomplete access could stall a researcher, or even lead to erroneous or incorrect conclusion. From a commercial perspective, simply having access to the information describing SNPs, falls short of providing a viable target for drug development, if another entity holds the rights to commercialize the knowledge. Moreover, intellectual property law is still evolving as a result of the substantial transformations in the life sciences fields over the past few decades, which added another level of complexity and uncertainty to Merck's decision. In any case, Merck's investment in the SNP database represents a network flexible investment with substantial strategic and competitive implications.

Inter-organizational relationships offer firms the opportunity to focus on core competencies, while coordinating activities across a wider portion of the value chain. These collaborative relationships can alleviate the risk of a firm becoming too narrowly focused, providing deeper information and feedback from a broader realm of the market. Thus, alliances enable focus, while helping to avoid myopia. In this context, focus refers to an effective division of labor between allied firms.

Not only must firms effectively define their competencies, they must also take care not to diffuse efforts across too broad a network of firms or varied activities. As discussed in the examination of the biotech industry in Section 3, many early biotech firms suffered from a

desire to accomplish too many diverse objectives. As a result, many early biotechs allied with numerous partners over diverse initiatives. While Genentech and Amgen refocused early in their history, Cetus failed to do so and ran out of the funding necessary to maintain independence. Although Genzyme Corporation's diversity provides a successful exception, most early-stage biotech firms have found that focusing on a limited set of objectives, based on a core platform technology, provides the model for successful growth. In addition to directing firm energy toward a more limited set of objectives, focus in the context of network strategy also includes limiting a fir's coordination costs. It can be costly and time-consuming to manage inter-organizational relationships.

Understanding the implications of focus in the context of network strategy varies depending on the motivation-space in question. The competencies dimension space suggests the use of alliances as a mechanism to focus or expand a firm's competencies. Many integrated firms in mature industries divest themselves of upstream or downstream capabilities, then ally withh the acquirer. For example, most tier-one suppliers to the auto industry have divested themselves of metals forming operations, such as forge shops and foundries, providing a long-term supply contract to the new owner. Conversely, firms can leverage competency-based alliances to expand the breadth of an industry's value chain in which they compete. During their early stages, many large biotechs leveraged their alliances with pharma firms to expand their participation in the complete drug discovery, development, manufacture and sales process. Such was the case with Genentech and Amgen. Focus relative to the Competencies dimension can reflect more specific focus, or a broadening of focus.The Market Structure dimension underscores the external, institutional and competitive factors that impact the foci of firms within alliances. Regulatory regimes can restrict firms from integrating operations, such as the prevention in 2001 of the General Electric acquisition of Honeywell by European Union regulators. Focus in this context requires an understanding of institutional and marketplace contexts within which firms must decide where and how to direct their efforts, and when and how to ally. Within the Network Economics dimension focus most dearly manifests in situations where standards are in flux. Determining around which standard to construct a new product line can make or break a new firm, and remains a critical decision for established firms. Overall, network strategies can help drive or dilute a firm's focus, the motivations underlying relationships between firms modify focus issues, and the decisions can have substantial consequences.

S.4. Screening of Market Power

Notwithstanding the different approaches analysts adopted to assess strategic alliances or joint ventures they almost all agree that a market power screen is very helpful to screen out most joint ventures with no anti-competitive risk. The screen economizes on judicial resources, reduces the uncertainty of the outcome, and increases the predictability that firms face in doing business. The market power screen is based on the theory that firms without significant market power could not raise prices or reduce outputs from a competitive level without losing profits. The parties to a transaction combining no significant power could not restrain competition unreasonably in the relevant market because the consumers would suffer no harm. Similarly, strategic alliances or joint ventures of which the combined market power

of participants is insignificant should have no anti-competitive risk. If the parties to a joint venture do not have substantial market power, the efficiencies the arrangements can bring in may outweigh the anti-competitive effects of the venture. In network industries, particularly given the rapidity of technological change, it is unlikely that firms forming strategic alliances without significant market power have any anti-competitive risk. Their business arrangements should not be handicapped by antitrust concerns.

Traditional estimates of market power are based on three measurements. The first one is the Lerner Index. Technically, market power is a firm's ability to deviate profitably from marginal cost pricing. Hence, the Lerner Index measures the market power by ratio of market price above the marginal cost. The larger the ratio, the larger the market power.

At first sight, the Lerner Index offers an easy way to measure market power [6]. However, marginal cost and the elasticity of demand facing the firm are extraordinarily difficult to measure [7]. Further, a price largely above cost may come from a firm's superior ability to control costs on the lower level. Depending on the Lerner Index this may lead the antitrust authority to condemn an efficient practice. At the same time they realize the fact that there is a positive correlation between market share and market power. This correlation of market power and market share has permitted courts to use market share as a qualified proxy for market power in antitrust cases. For a long time, the US Supreme Court had defined market power exclusively by reference to market share. Market share has long served as a surrogate for market power [8]. The standard method of proving market share is relatively simple. It first defines a relevant product and geographic market in which to compute the defendant's market share, next computes that share, and then decides whether it is enough to support an inference of the required degree of market power. To be sure there is a bright line between those market shares that constitute monopoly power and those that do not.

While market shares greater than 65 percent typically support a finding of market power, shares below 50 percent generally will not. In summary, to jeopardize market performance, collusion must embrace suppliers who, in aggregate, have substantial market shares, of 60% at least. Nonetheless, it is often very difficult to define the product market accurately. Most importantly, differences in supply and demand elasticity can allow two firms with totally different market shares to set prices at the same ratio above marginal costs. As a result, the market share is not an accurate proxy of market power. A Herfindahl-Hirschman Index (HHI) is used to measure horizontal mergers defined as the sums of squares of the firms' market shares [9]. Since this calculation will give greater weight to market shares of larger firms, it may more accurately reflect the likelihood of oligopolistic coordination in the post-merger market. Hence, a market share index of less than (HHI) 1800 or the presence of five or more firms in the market, is conclusive proof of the absence of market power.

Under this traditional market power screen, a strategic alliance or joint venture should be upheld when the parties' combined market shares fall below a particular percentage. When the parties to the joint ventures having market shares that are above the safe harbour threshold but below the point at which substantial market power can be inferred the regulators should balance the efficiencies of the venture against its potential anti-competitive effects. Besides the market share and concentration calculation other relevant factors should be taken into account. These factors include barriers to entry, the production stage of the strategic alliances, the relative size of competitors, the homogeneity of products, the extent of competition, and the stability of market share over time. The theory underlying antitrust in markets is that policy makers should be skeptical of concentrated markets because they can be easily

cartelized. However, in network industries the probability of cartelization may not be a function of concentration. The economies of collusion are so very different in network industries, a market power determination based exclusively on numerical measures of market share ignores the indeterminacy of markets for research and future technology. In product markets, past market shares are unmeasurable and determining the number of firms in research and technology markets requires identification of potential innovators, which can be highly speculative.

S.5. EXCLUSION OF ACCESS TO ALLIANCE

Another issue involving the structure and management of strategic alliances is the exclusion of outsider access to the alliance. Basically, the participants in alliances freely choose their partners, negotiate their terms, and set up the structure for the alliances only subject to the antitrust laws limiting their scope and accumulated market power. On the contrary, very few laws will force a firm or a group of firms to share property rights with others or accept other parties [10]. The refusal of a member of an alliance to give the outsider access to the alliance may be based on management considerations such as inability of providing the necessary contribution, divergent goals or insurmountable transaction obstacles. Participants in an alliance have a legitimate interest in enduring that their partners provide valuable contributions to the alliance. Taking away the freedom of participants to exclude outsiders may force the alliance to accept incompetent partners. Mandatory access also increases the difficulty of coordinating members with different economic interests. Most importantly, the exclusionary access rules prevent free riding, thereby maintaining investment incentives. If mandatory access is required, potential partners may decide not to enter into an alliance at the outset, particularly a high risk one, and instead opt to join the alliance when it succeeds later. The participants, however, will be required to bear the losses alone if the alliance fails. This free rider effect creates a risk that efficiency-enhancing projects would be delayed or altogether deterred. At the same time, mandatory access may discourage excluded competitors from setting up competing ventures. As a result, mandatory access decreases the inter-venture competition.

The exclusionary access rule, on the other hand, may harm consumers by disadvantaging rivals so much that competition is adversely affected. For example, if the alliances control a major input that competitors can use to provide a better product, these competitors can be driven out of the market unless they can access the alliances, or, at least the input of alliances. Keeping competitors from the alliance excludes better products from the market or at least keeps market prices higher or prevents market prices from being factually lower than they would otherwise be. Alternatively, the exclusion rule may be used as a method to keep the monopoly profit in the alliance. It may slow innovation within a dominant system [11].

The mandatory access theory fundamentally results from the assumption that when joint ventures possess unique facilities, competitors could not compete with the members of joint ventures without them. Antitrust regulators so far did not provide clear guidance to identify in what kind of circumstance the joint venture could not refuse access to competitors [12].

Some views rely on the structure of the market to see if there is enough room to set up alliances besides the incumbent venture. They contend that if the 'outsiders' can reasonably

put together a joint venture of their own with comparable advantages, the original joint venture is justifiable in refusing to take in unwanted additional members. In practice, it means that if the joint venture itself includes parents accounting for no more than 30 to 40 percent of a market, the outsiders usually can organize a comparable joint venture. Even where the original joint venture includes parents representing a higher proportion of the market, access may not be required if the minimum efficient scale of the joint venture is low enough that comparable advantages can be achieved by a smaller undertaking. Conversely, if participation in a joint venture confers a 'significant competitive advantage' and the venture itself holds a substantial market position, the law may require that competitors be allowed to participate in the joint venture or obtain the advantages of membership on reasonable and non-discriminatory terms.

Other views present a more rigid approach toward membership restriction. They claim that the efficiency justification for the existence of a strategic alliance is one thing while the efficiency justification for the exclusionary access to the alliance is another. For a justification of exclusion to be valid, the efficiency benefits must result from the access restraints, not simply from the existence of the joint venture. The fact that it is efficient to permit a joint venture does not imply that every possible access restraint also is efficient. In short, there must be a reasonable connection between the exclusionary conduct and the claimed efficiency benefits.

Problems can be further complicated when involving network industries. We observe that network joint ventures are fundamentally different from non-network joint ventures. Even though the exclusionary access rule should be allowed in non-network ventures, particularly in research and development joint ventures, it needs to receive more scrutiny in network joint ventures. Note that network joint ventures generate more efficiency as more and more members join, exclusion of competitors might actually diminish the network's value by restricting the ability of the network to generate network efficiencies. Alternatively, network externalities exacerbate disadvantages of exclusion and tend to undermine intersystem competition. For example, the first mover advantage usually confers the incumbent a larger installed base, later comers will find it very difficult to enter the market occupied by the incumbent if the new entrant could not access the existing system. Therefore, demand-side scale economies associated with networks may warrant a heightened degree of scrutiny in assessing denials of access to joint ventures. Others, however, argued that while new members increase network efficiencies, they might also reduce the returns to earlier members through competition. Further, prospective network joint venture can free ride on the investments and risk taking of existing joint venture members in exactly the same way as occurs in non-network joint ventures. Particularly, when network externalities have fallen to near zero, free riding effects have exactly the same importance as they do for non-network joint ventures. As a result, given the existence of free riding there does not appear to be any reason to distinguish between network joint ventures and non-network joint ventures [13].

The arguments basically come out from whether competition among different systems is more important than competition inside the same system. In other words, is intersystem competition promoting initial innovation more critical to society, or is intrasystem competition promoting incremental innovation more critical? Those who propose that competition rely on different systems, argue that the need to invent around other's proprietary standards stimulates innovation, so that mandating access to other's standard may reduce the development of alternative technologies and goods. Also allowing the proprietary system

preserves incentives for developing resources to build an incumbent system in the first place and rewards sponsorship once the system is developed.

This may be important in network industries where marginal costs are close to zero, but the substantial fixed costs incurred in initial development must somehow be recovered. Because competition tends to drive prices down to marginal costs, admitting new rivals after the initial investment has been borne by the incumbent may not permit recovery of the fixed costs incurred in establishing the network. Moreover, it may be difficult to compensate the incumbent for the risk initially assumed alone. On the contrary, those concerned with network externalities and switching costs argue that the incumbent's potentially significant advantages from demand -side economies of scale or network externalities may make competition in different systems impossible.

If competition is to be ensured, it must come from entrants with access to the interface standards necessary to make their product readily substitutable for that of the incumbent. Such compatibility reduces consumers' costs of switching to rival primary products and thus facilitates entry and competition in the primary market by promoting intrasystem competition.

Whether intersystem or intrasystem competition holds priority for the consumer in any given situation depends crucially on whether the relevant market can support more than one network, and how to ultimately weigh the value of intersystem versus intrasystem competition in the particular scenario at hand. If the market has enough room to build up two or more systems the exclusion of access to the alliance system will be allowed in order to promote competition between different systems which often results in initial innovation. When there is not enough space in the market to set up a new system the exclusion rule deserves more scrutiny to prevent the deterrence of incremental innovation.

The 'essential facilities' doctrine is a better framework for bringing rationality and order to the network joint venture compulsory access issue. It has also been suggested that the essential facilities doctrine is best applied in situations where it would be impracticable or undesirable to increase competition in a given primary market, the essential facilities doctrine provides that a regulator may require a monopolist to provide access to 'essential' resources to firms in complementary markets. This remedy maximizes efficiency by leaving the natural monopoly in place while ensuring efficiency and competition in related, complementary markets. As a result, the antitrust policy toward the exclusion of access to the alliance should depend on the facts at hand.

It won't actually matter whether the essential facilities or other theories are adopted. The question is where the line is drawn: from the most strict policy towards the exclusion access rule to the most relaxed policy, which allow the alliance to decide accepting the new member or not unless there is no room in the market for setting up a new alliance.

The confusion of drawing a distinct line for the exclusionary access rule obviously results from the fact that excluded participants can be customers of the alliance on the one hand, and competitors in output market on the other. For example, the input the alliance provides is necessary to the outsider in an output market where outsiders compete with the participants in the alliance. For input the outsider is the customer of the input the alliance produces, for output the outsider is the competitor of the member of venture. Therefore, if we can distinguish customers from real competitors the problem will be easier. After all, a refusal of an efficiency-enhancing joint venture to admit new members is economically quite distinct from a refusal by a group of non integrated but colluding competitors to deal with a prospective customer.

To be sure, distinguishing customers from competitors is sometimes not easy. One way that can be used is to see if there is a market for the input. In other words, if there is no market for the input, but only the members of the venture and the prospective entrants, then the entrants are really the competitors and not customers. The only need of the input for the outsider is to compete with members of the alliance. The alliance should have the liberty to limit the ability of competitors to access the input unless the input constitutes a natural monopoly. That is what some commentators allege that the essential facility is the market as such.

On the contrary, if there is a market for the input and another market for the output then the "outsider" is the customer of input in the first market even though it is the competitor of the members of alliance in other markets. The exclusionary access to the alliance should be put into severe scrutiny.

To simplify the analysis a quick look may help to review the exclusion rules. If rivals access the alliance, aggregated benefits will increase and the alliance partners will be better off, then denial should be prohibited.

If the alliance partner will be worse off, the denial should be allowed even though the benefits to the rival outweigh the losses of the alliance partners, otherwise the incentive of formation of strategic alliances will decrease. When the alliance partners and rivals are better off even if the rivals get the most of the benefit and the alliance partners get less a benefit the denial should not be allowed because economic efficiency is improved and the social welfare are increased in this situation.

Discussion

In forming strategic alliances the objectives of participants in the alliance may not be totally parallel. The interests of an individual participant in the alliance may conflict with the interests of the alliance. Further, even if the goals of participants can be inconsistent, different corporate cultures and management philosophies can lead to different ways of solving problems. Finally, free riding and opportunistic behaviours can destroy the alliance. Therefore, in order to operate strategic alliances or joint ventures successfully, the participants inevitably impose 'ancillary restraints' on the alliances or the participants in the alliances. These restraints may restrict participants from competing with the alliance or competing with each other in order to prevent free riding and opportunistic behaviour.

Participants may be requested to exchange certain information to cover the risks of sharing information and to prevent one firm from dumping obsolete technology into the alliance for obtaining their partner's advanced knowledge. A secrecy agreement may be imposed on the research and development of alliance to protect the technology dissemination. This is particularly important when entering strategic alliances in high technology network markets. On the other hand, since restraints can constrain the competitors they are likely to generate concerns of deterring competition. In particular, these constraints may give not merited advantage to incumbent powerful firms over new, small entrants. From the viewpoint of competition, the importance of the ancillary restraints is no less than the alliance as such. In fact, the assessment of strategic alliances usually falls with the assessment of ancillary restraints.

Ancillary restraints can be a valve for the competitive concerns of strategic alliances. That means when the alliance in itself has great anticompetitive concern ancillary constraints can be imposed to eliminate competitive risk.

Conversely when the alliance poses little or no anticompetitive concern ancillary restraints used to regulate or protect the interest of the alliance can be allowed. For example, presuming there are two companies with the ability to develop a new technology. The two companies now enter into strategic alliance to develop the technology jointly, which means they can save a lot of expenses and most importantly accelerate research and development. Because the two companies are the most likely to succeed, the alliance has great market power in the relevant market. However, the efficiency the alliance may reach is also great. Hence, the restraints the agency may impose such as prohibiting joint production and marketing when the technology is developed, or nonexclusive license to other competitors of the alliance will mitigate the anticompetitive concerns of the alliance. Similarly, if the alliance has little market power, the ancillary restraints barring participants from disseminating to competitors or allocate the market may be allowed. Restraints are reasonably necessary to protect the interest of the alliance or the participants who provide the technology in the first place.

The exclusion of access to the alliance should be allowed when the exclusion only harms competitors rather than consumers or retards innovation. To be sure, the exclusion may be essential to facilitating collusion among the participants in an alliance. The main concern resulting from exclusion is, however, deterring innovation or harming the consumer. Also the exclusion rules may be necessary to maintain an efficient alliance after all. As a result, the mandatory rule of accessing should be imposed only when the access can improve innovation efficiency or consumer welfare and without harming the participants to the alliance.

Although most literature discussing strategic alliances concentrate on the arrangements integrating horizontal partners, many more strategic alliances are entered into by vertical partners, in fact.

Discussions focusing on the horizontal strategic alliances only reflect traditional antitrust concerns of collusion effects and the re-acknowledgement of the efficiencies of strategic alliances particularly in dynamic markets, meaning primarily network industries. On the other hand, more strategic alliances are formed by firms originally in vertical production or complementary stages. In those alliances the participants provide the complementary resources such as technologies, capital, production or marketing capabilities to integrate partners' resources vertically. At the same time participants may employ exclusionary practices to facilitate the operation of alliances or assure their profits in the transactions. These exclusionary practices include exclusive dealing arrangements, tying arrangements, and vertical integration. On the other hand, these exclusionary practices can be used to engage monopolisation, or exclude a rival without merits such as lower costs, better quality, new products or lower prices.

S.6. TYING IN STRATEGIC ALLIANCES

Many strategic alliances are created in order to transfer technologies from one party to the other from the research ventures jointly set by alliance partners to individual partner.

Accordingly, in network industries firms are most commonly seen to enter into patent or technology license agreements with their strategic partners or the joint venture firm to transfer the technologies.

On the other hand, in a patent licensing agreement the licensor often imposes a tying or bundling arrangement. In a tying arrangement the patentee grants its patent (tying product) on the condition that the licensee purchases or leases a separate product or service (tied product). With regard to bundling arrangements, the licensee is required to take a license under a group of patents. As we can see today, tying arrangements have become a strategic tool in network alliances.

Tying or bundling arrangements are so common in patent licensing practice that the earliest cases of tying all involve patents licensing. A patentee or a supplier of complicated components covered by intellectual property rights might require its licensee manufacturer to obtain other related inputs from it in order to enable the licensor to control the quality of the manufacturer's product. In this case, tying is necessary for a licensor to ensure the licensing technology functions as anticipated when the quality or quantity of tied product is important to the licensing technology. Particularly, when components of a product or process are covered by different patents, the bundling licensing of a group of patents is often required. Further, when a product needs a particular technology for its effective use, ties of the technology to the product sometimes provides innovation efficiency. To be sure, a licensee may in some occasions be sophisticated enough to find the best quality of input for the efficient use of licensing technology. Where market failures preclude the licensee from choosing appropriate substitutes through the market, however, tying may eliminate the problem of imperfect information and reduce search costs.

Most commonly, proponents of tying arrangements present it as the most important tool of price discrimination. A seller or licensor can charge lower price for tying product and charge higher price for tied product. Thus the higher intensity of consuming the tying product pays more whereas the lower pays less if higher consumption of tied goods signals higher valuation for the tying goods [14]. As a result, tying not only produces one market into the other market and foreclosing the second market. Particularly, where market failures exist, a monopolistic firm, which produces competitive complementary products simultaneously, can exclude competitors in the market for the complementary product through tying arrangements. Market failures usually can be economies of scale or imperfect information.

Another view rejects the leverage theory based on the assumption that the tied market has a competitive, constant-to-scale structure. However, if economies of scale exist in the production process for the tied good, tying may be an effective means for a dominant firm to foreclose the market by making continued operations unprofitable for tied good rivals [15].

In other words, by tying, the monopolist reduces the sales of its tied good competitor, thereby lowering the output of the competitor below the level that vindicates minimum economies of scale. As a result, the competitor of tied products will exit the market because of the higher costs that result from the deficiency in scale of output. Particularly, if the sale of a tied product has cost advantage due to the effect of learning by doing and competitive producers of the tied product understand this, then no one will enter the market for the tied good.

Information imperfection will also cause foreclosure in tied good markets. The licensee may ignore the tying arrangement because the tying goods are unique or the tied goods are of no material importance to him, so that he would not object to tying arrangement even if he

were knowledgeable about it. For example, when the licensee can easily shift the costs of tied products to third party, he would not reject a tying arrangement even if he knows the higher cost of tied product. Information imperfection also makes leveraging increase the aggregate return from monopoly.

Tying can also be a practice that forecloses competition in network markets. Suppose, for example, that a dominant firm has a product with a current technology that is supposedly legal by its intellectual property rights. Suppose further that the firm offers to license its technology only to those firms that agree also to license that firm's complementary product, and suppose that the complementary product builds on the firm's next generation technology. Such a tying arrangement could allow the dominant firm to create a new installed base of users of its next generation technology in a manner that would effectively foreclose the opportunities of competing firms to offer their products in the battle for the next generation technology. When tying does lead to exclusion of rivals, the welfare effects both for consumers and for aggregate efficiency are in general ambiguous. The loss for consumers arises because, when tied market rivals exit, price may rise and the level of variety available in the market necessarily falls making consumers worse off [16].

An injury to dynamic efficiency occurs if the tying seller can foreclose a substantial percentage of the tied product market, competing sellers of the tied product may face increased costs and be driven from the market. Barriers to entry or market penetration may also be raised. The effects on dynamic efficiency may slow the pace of welfare enhancing innovation.

S.7. Cross Licensing

The licensing of industrial property rights or know-how is the most common way of transferring technology between strategic partners. Entering into licensing agreements, partners may impose grant back provisions in the form of cross licensing. Usually, grant backs are couched in the form of a cross license wherein each partner grants the other a nonexclusive license. Grant back provisions oblige a licensee to transfer to the licensor any improvements in the technology represented by the licensed industrial property rights. These provisions will premise the license upon the licensee agreeing either to assign to the licensor any improvement derived from the licensed technology or to license the subsequently developed technology to the licensor. Cross licensing involves a mutual exchange between parties, for the parties' mutual advantage, which often helps local technological firms to form strategic alliances with foreign technological giants.

Grant back provisions may promote the dissemination of new technology, reduce bargaining costs, share risks, and reward the licensor for facilitating innovations. Also they may be advantageous to have or at least to encourage license transaction in the first place by ensuring that the licensor is not prevented from effectively competing because it is denied access to improvements developed with the aid of its own technology.

Cross licensing is particularly important in patent intensive industries, such as pharmaceuticals, semiconductor and network equipment industries because,for example, the production process of chips usually involve so many patents that not any single firm can own all of them. Also most of these patents granted on technologies are incremental or entangled.

Without cross licensing a semiconductor company would be unable to produce its chip without infringing others' patents. Cross licensing grants recipients with an opportunity to use technologies that it otherwise could not use. Cross licensing can be a highly effective way of resolving 'blocking patents'(which are essentially patents that cannot be used without the licensing of other patents). When firms engage in similar research or manufacturing areas, they often become involved in patent conflicts, including mutual patent infringement claims or conflict claims in patent interference. The costs associated with resolving these conflicts through litigation often can be high. Cross licensing patents in dispute provides a cost-saving, efficient way to implement their patents. Furthermore, in some industries, the pace of research and development and the market interdependencies between inventions are so high that advantages of being the first to the market make those firms cross license with their competitors.

From the standpoint of regulatory agencies, most cross licenses are, on balance, pro-competitive when licensing firms with no market power, or with complementary abilities are cooperating. In addition, agencies recognize that grant back provisions may be necessary to ensure the licensors' incentives to innovate in the first place. The pro-competitive effects of grant back arrangements usually outweigh the risks of reducing incentives to the licensee to improve the licensed technology. Nonexclusive grant backs are less likely to raise antitrust issues than exclusive grant backs, as they will allow the licensee to license any improvements in the technology to others. Although agencies acknowledge anticompetitive effects of cross licensing and grant backs in certain circumstances, they focus on collusion concerns only. Nevertheless, these arrangements may reduce the licensee's incentive to innovate and invest in research and development by reducing the possible gains. Exclusion effects that these arrangements can bring up shall not be ignored. Cross licensing between dominant firms is very likely to suppress the competition, to deteriorate consumers' purchasing power and to develop monopoly. Cross licensing can be used to protect the oligopoly rents by limiting the third parties' innovation. Likewise, grantback clauses when combined with other restrictions can be anticompetitive or improperly extend market power beyond that of the patent itself. Most importantly, these arrangements can provide to sustain the initial inventor's dominance and stifle sequential innovation.

S.8. VERTICAL INTEGRATION

Firms bring about vertical integration primarily by reducing transaction costs. That is to say a firm can achieve economies by avoiding the costs of using the marketplace. Using the market can be very expensive: negotiating contract costs money, dealing with other persons involves risk because of incomplete information about each other. Consequently, if a firm can produce the product or service as cheaply as an independent producer can, then it will produce them by itself because any imperfection in the market for that product or service will make it more expensive to buy than to produce [17,18].

Alternatively, vertical integration may coordinate design, production and even marketing (including feedback from customers). This coordination is not only cost-saving but also improves quality and leads to process innovation. Asset specificity also creates a motive for vertical integration. When products are unique the use of the market will be more costly.

From the viewpoint of competition policy, one may intuitively be against vertical integration that result primarily from that upstream monopolists integrating downstream competitive firms using upstream products as input, together with others, to produce a final good. Such forward extension of monopoly power increases the monopolist's profits, which means computer prices increase. However, the relationship between vertical integration and monopoly is more complex. Vertical integration is probably used as much to reduce monopoly as to facilitate it, because the monopolist has the same strong incentive as the competitive firm does to reduce transaction costs.

For many years, the conventional belief among economists was that an input monopolist had no incentive to integrate forward into a competitive final goods industry. In the market of imperfection, firms know little about the costs of those with whom they deal. This is particularly true if the other firm produces or sells a variety of products. A firm just cannot know if the price other firms charge is the lowest one. When a competitive firm integrates with a monopolist, the result is higher profits for the integrating firm and a lower price for consumers if the integrating firm can produce the product as efficiently as the monopolist did. Alternatively, when the integrating firm itself is a monopolist, vertical integration can remove the downstream monopolist and make more profit, which means a lower profit-maximising price [19].

However, conventional wisdom is only correct under conditions of fixed proportions in production at the downstream stage. Under conditions of variable proportions, when a certain input monopolist attempts to maximise its profit, the resulting price of monopoly input will lead the final good producers to use other input as a substitute for monopoly input. The high input price has adverse effects when firms are not vertically integrated. At first, the downstream firms will use less the input instead of using substitute beyond the optimal level. The substitution to other inputs maximises costs for the downstream firm, but is efficient when compared to the technology. With vertical integration, the firm can set transfer prices of the inputs that reflect their true costs. This will correct technical inefficiency and encourage more output. This behaviour creates an incentive for the monopolist to vertically integrate forward. In this case, vertical integration will tend to improve efficiency and enhance consumer welfare. Conversely, the relative size of the monopolized market is thus enlarged. As a result, allocative efficiency is likely to be reduced [20].

To be sure, vertical integration may lead to monopoly in a downstream product market, which was previously competitive. Thus, prices of final goods may increase as a result of monopolisation of that market and a new wedge can be erected between price and marginal cost. That is to say, downstream producers may charge a higher price than marginal cost. On the other hand, integration may eliminate the wedge between the monopoly price of the input and its marginal cost, because the merged firm would not charge itself higher than the marginal cost. The effect of this is to reduce unit cost and as a result, prices of final goods. Therefore, whether the price will be lower or higher depend on which of the two effects on product price is dominant. When the elasticity of substitution for the input is greater than the elasticity of demand for the product, vertical integration would increase the product price. Conversely, vertical integration would lead to a reduction of product price.

Vertical integration may enable the monopolist to increase its returns in either static or dynamic circumstances.At first, it enables the monopolist to price discriminatorily. Nonetheless, whether or not vertical integration which achieves price discrimination should be condemned under antitrust law is questionable. On the one hand, price discrimination often

results in higher output than a monopolist's non-discriminatory pricing. Perfect price discrimination provides both forms of efficiencies since price discrimination gives a monopolist incentive to increase output to the level of a competitive market, that is to say when the price equals marginal cost, the output is greatest. The increased production allows the large-scale producer to take better advantage of economies of scale, that is, to produce more efficiently. Price discrimination also enables the monopolist to match his price to the item's value, its marginal utility, to each buyer. In that way, a price-discriminating monopolist can approach allocative efficiency more closely than a single-price monopolist can do. Moreover, when a seller already has market power in a product, discriminatory pricing of the product, which permits the seller to make all sales above marginal cost, may be more efficient than forcing the seller to offer its product as its non-discriminatory, profit-maximising price. The latter situation would restrict output, however. On the other hand, any imperfect price discrimination scheme produces a certain amount of inefficiency both from less-than-competitive output and from the cost of operating the price discrimination scheme itself.

Yet we observe some serious anti-competitive effects that come from vertical integration. One anti-competitive effect comes from the fact that vertical integration enables the monopolist to evade public regulation of prices at the monopolized level. When a natural monopoly, of which price is regulated, integrated vertically with an input firm or an output firm that is in a competitive market, the regulated firm may have an opportunity to hide profits in competitive products. At the same time, with the integration of a competitive market the price-regulated firm can cross-subsidize its competitive affiliate with returns obtained in the monopoly market. As a result, the monopolist can leverage its power into the competitive market and deter potential entrants.

The most debatable issue of vertical integration is the foreclosure effect. It is used to believe that if a monopolist takes over all or most of the downstream market, it thereafter confronts potential entrants with the need to enter at two levels rather than one. The conventional view of anti-trust law condemned vertical integration primarily based on foreclosure arguments.

Either upstream or downstream foreclosure raises rivals' costs, forces rivals to increase prices and enables the newly integrated firm to enjoy increased prices. An integrated firm can place downstream rivals at a cost disadvantage in a downstream market. Other input suppliers may not take up the gap because, for example, the ability to expand is limited. The downstream price increase may harm consumers and cause the dead weight loss because the consumers reduce purchase below the competitive level. Also the unintegrated downstream firm engages the inefficient substitution of input.

Extending the integration to the monopoly downstream market also reduces competitive pressure of innovation [21].

Summary

Exclusionary practices are prevailing in network industries transactions, particularly embodied in strategic alliances. They are primarily used to enlarge the property rights of involving technologies. Consequently, they are likely to increase the incentives of initial innovation [22]. However, the market power of initial innovation can be inappropriately increased. By too broadly expanding the property rights of initial innovations not only offers

initial innovators a windfall but also harms the sequential or complementary innovation. Especially, when the market failures are significant in network industries, exclusionary practices can exacerbate market imperfection and deter the sequential innovation. The antitrust policy towards exclusionary practices should therefore take into account of the exclusion effect on the follow-on and complementary innovations.

S.9. INTERNATIONAL CONFLICTS

International conflicts of antitrust laws are resulting from the overlapping of different jurisdictions, they are also partly resulting from different economic and policy concepts. In many advanced industrial countries and regions the urge of protection of intellectual property is raising to the historical height in this decade. By combing the strong market power and strengthening intellectual property protection, the dominant firms in those countries seek to make it harder for firms in developing countries to gain access to the most valuable technologies or otherwise to catch up with the global high technology leaders. Of course, if there were no intellectual property protection the risk of suboptimal investment in technology innovation could be very high.

However, strong intellectual property tends to protect initial innovations. Over-protection of initial innovations could create legal barriers to entry. On the contrary, the small and medium sized firms whose incremental or complementary innovations often being the real engines of economic growth can be deterred. As a result, how to reach equilibrium of initial innovation and sequential innovation is probably an essential prerequisite of the solution of international conflicts in national antitrust laws.

International strategic alliances can lower prices and promote competition in the long term. They increase the potential economies of scale for both partners and eventually allow feedback from technology importing countries' markets to affect their foreign allies' own investments in new applications and improvements at home. On the other hand, the exclusionary practices embedding in strategic alliances may inappropriately expand the market power of initial innovation in transaction. As a result, the incentives of the partner's sequential innovation are very likely retarded. The antitrust policies of technology exporting countries tend to enlarge the market power of the initial innovation to the utmost, while technology-importing countries' policies usually favour the follow-on innovation. The policy conflicts thus cause the difficulty of international harmonization.

S.10. CONCLUSIONS

The uniform emergence of strategic alliances in network industries explains the need to form a new organizational alternative to overcome market failures in these industries. The market failures mainly stem from the characteristics in these industries: enormous sunk costs, economies of scale, network externalities, and compatible and complementary technologies and products. Market failures in network industries reflect two dimensions of competitive concerns. On the one hand, the requirement of collaboration of competitive or complementary producers in order to master market imperfections make us rethink antitrust policies.

Traditional antitrust risks towards collaborative arrangements such as price fixing, output reduction, or market allocation seem unlikely in network industries or at least not so urgently as in traditional industries. If any, risks often come from the ancillary restrictions imposed on strategic alliances to decrease incentives of innovation between partners. The administrative agencies or courts can adequately correct this concern by eliminating unnecessary restraints or imposing firewalls without harming the efficiencies the alliances may bring in. On the other hand, exclusionary practices incorporated in strategic alliances are very likely to be used in exploiting market imperfections in those industries. Strategic alliances are primarily formed in order to pursue innovations. They are more likely used to expand the property rights of these innovations to another or future markets. Exclusionary practices sometimes play a necessary kick-off function to facilitate the initial innovation though they more often deter follow-on improved or complementary innovation. Accordingly, the prevailing antitrust theory aiming at collusion concerns and ignoring exclusion risks apparently may need to be adjusted.

When exploiting market failures, such as economies of scale, externality effects, and interdependent technologies, exclusionary practices including exclusive dealing, tying, grantbacks as well as cross licensing, and vertical integration may strengthen their exclusion effect. As a result, carefully distinguishing anti-competitive exclusionary practice from those really promoting efficiency and balancing benefits to initial innovation against incentives to improve innovation are primary tasks. These tasks need fact oriented analysis and a deeper anatomy of market structure. Fortunately, modern industrial organization in combination with game theory provide advanced tools to understand the market structure of network industries. The more realistic models of competitive behaviour are ascertained, the more precise competition policy can be predicted.

In addition, most strategic alliances involve technology companies in different national territories. Overlapping jurisdictions inevitably increase costs and uncertainties of transactions for strategic alliances. Consequently, a coordination of antitrust laws becomes the task of an international legal and economic community in the next generation after successes in international trade. Greater international cooperation or harmonization will force the business community to compete on more equal terms. To attain the goal one must keep in mind that sequential and complementary innovations are not less important than initial innovations. Only when follow-on innovations have been equally weighed with initial innovations, the international harmonization can be reached. Hence, a more delicate, economic underlying antitrust policy in international community should be accepted if high technology industries need to develop more effectively.

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SUBJECT INDEX