Strategic Alliances in Global Biotech Pharma Industries

Hans-Werner Gottinger[*,1] and Celia L. Umali[2]

[1]*STRATEC, Germany*[1]

[2]*Faculty of Economics, Nagasaki University, Japan*

Abstract: This paper presents an application of network economics to the formation of alliances in the biotechnology-pharmaceutical 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 participants and change as additional dimensions. 'Change' introduces a dynamic, evolutionary aspect. 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 framweork, including a historical tracing, and an empirical examination of the relationship between collaboration rate (CR) 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.

Keywords: Strategic alliances, network economies, biotechnology-pharmaceutical industries, event anlaysis, pharmaco-economics.

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 biotechnology 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. All Goldman Sachs analyst reports on biotechnology firms devote time to exploring alliances, and Goldman Sachs publishes a comprehensive listing of biotechnology alliances [2]. In a study of the Canadian biotechnology industry, Baum *et al*. [3] 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 biotechnology industry in Europe [4]. 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 [5]. 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. Alliance competencies should be prevalent in any market characterized by fast changing intangible assets, given the difficulties 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.

2. THE 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 [6]. In order to narrow this analysis, we will 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). 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

*Address correspondence to this author at the STRATEC, Germany; Tel/Fax: 49-841-975117; E-mail:info@stratec-con.com

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technology-focused firms. Analysts and industry participants 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, analysts and industry participants define the biotechnology industry as including firms that apply technologies to the life sciences. Usually, there is an aspect of newly emerging or 'cutting-edge' to the technologies represented within the industry. Some firms characterized as biotechnology firms in the past have increasingly been categorized with pharmaceutical companies.(It used to be a joke to say that 'biotechnology companies are pharmaceutical

companies without sales' [7]) As a few once-biotechnology firms have matured their activities have expanded to resemble more integrated pharmaceutical companies or 'biopharmaceuticals'.. Some notable examples include Millenium Pharmaceuticals, Genentech, Genzyme, MedImmune and Amgen. 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, others of which do not.

One industry observer breaks the biotechnology industry into tiers based on market capitalization [8]. Tier-1 firms include the largest publicly traded firms, with market capitalizations above approximately US$800 million. 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 capitalization from approximately US$125-US$800 million. 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 US$20 and US$125 million. 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 biotechnology shares, firms migrate between tiers based on general biotechnology 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 [9]. 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 million in a stock for stock deal in order to accelerate its transformation from a genomics firm to an integrated pharmaceutical company.

As evidenced by the discussion of definitions, the distinctions between biotechnology and pharmaceutical firms are rather blurred. In large part this characteristic can be explained by the fact that the biotechnology "industry" is not an industry in the sense of a set of firms defined by their creation of end value products or services, such as "petrochemicals" or "metals and mining". Rather, analysts define the industry as the totality of firms or units of firms engaged in the application of technology to the life sciences, a wide, diverse range of firms. We will limit the discussion to firms involved in the pharmaceutical value chain. Within this subcategory (albeit a sub-category representing a majority of biotechnology firms) we can create a useful categorization of the industry by distinguishing between firms based on the capabilities they offer the marketplace: 1. Drug discovery and development, 2. Tools and enabling technologies, 3. Hybrid firms, offering a combination of both (1 and 2).

3. NETWORK FORMATION DIMENSION IN BIOTECHNOLOGY/PHARMACEUTICAL INDUSTRIES

Three network formation dimension factors-- network economics, competency and market structure--influence the biotechnology/pharmaceutical industries, but they do so in differing ways, depending on the sub-segment of the industry. The preponderance of biotechnology 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 pharmaceutical company's trials competency. Most of these biotechnology/pharmaceutical alliances fall into the interface category between competencies and market structure, due to the additional value provided by major pharmaceutical 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 biotechnology value chain where information plays a central role, such as in bio-informatics, genomics and proteomics, network economics factors help incentivize a network strategy. To illustrate how each incentive space might impact the evolution of firm networks within an industry, we only need to trace the history of the American biotechnology/pharmaceutical industries [10].

4. GENOMICS AND NETWORK ECONOMICS TO BIOTECHNOLOGY

The Competencies and Market Structure dimensions have played the predominant role in explaining the transformation of the pharmaceutical and biotechnology industries' network structure and behavior. Network economics has not yet been involved. On the contrary, 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. 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. 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, 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 refects the paradigm shift toward biopharmaceuticals [11]. 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. Our discussion will focus on the implications of the HGP for the alliance culture and structure of the pharmaceutical and biotechnology 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 ferment 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. Another likely critical event which began to define how firms might gain proprietary advantage from genetic knowledge occurred in 1980, with the US Supreme Court's decision in *Diamond v Chakrabarty*. The high court ruled that a patent could be granted for a genetically engineered bacterium. Before this ruling, living matter was generally assumed to be unpatentable. John Doll, the US Patent and Trademark Office's director of biotechnology, asserts that without the ruling in *Diamond v Chakrabarty* "you wouldn't have the sequencing project. You wouldn't have the large genomics companies. You wouldn't have biotechnology thriving in the US like it is right now' [12].

As the HGP progressed, internal conflict arose between various researchers 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 "vilified" by the NIH establishment as a result of his unorthodox views [13]. 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 million grant from Steinberg, Venter was able to conduct research without interference from the venture fund. In Venter's words, "It's really remarkable.... It's every scientist's dream to have a benefactor invest in their ideas, dreams and capabilities" [13]. 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 (2004) it's roughly a tenth of it, and Haseltine is about to retire [9]. 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. In order to survive in the near to mid-term, Haseltine and Steinberg approached Pharmaceutical 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 Rohrer, but the (then) British firm Smithkline Beecham (now Glaxo SmithKline Beecham, GSK) accepted in 1993, providing US$125 million in exchange for 7 percent of HGS and exclusive commercial rights to the gene portfolio. This represented the largest alliance between a pharmaceutical and biotechnology firm up to that point in industrial history. The announcement encouraged a number of other deals, most notably a US$70 million agreement between Hoffman LaRoche and Millennium Pharmaceuticals.

For a number of reasons, including a huge clash of egos and conflicting motivations for sequencing the genome, Venter parted company with HGS in 1997, waiving US$38 million of the US$85 million 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. 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 pharmaceutical and biotechnology industries.

5. FROM CONFLICT TO COLLABORATION: 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 orders 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 behavior of the proteins they create. Mapping each human protein independently requires such a blindingly long time as to be impractical; however, local structures within proteins, known as domains, reflect consistent behavior 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. As 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'* [14].

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" [14]. 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 their 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" [15]. 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" [14].

Celera's strategy to leverage its position in genomics to create an integrated pharmaceutical company, evidenced by its acquisition of Axys Pharmaceuticals in mid-2001, partly reflects the fact that the majority of the value created by the pharmaceutical industry accrues to those firms that successfully develop and market new proprietary drugs. Celera's aspiration to become an integrated pharmaceutical 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 **1**). 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 1. 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, 2001-2006.

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$125 million deal with SmithKlineBeecham during. its first year of operation, Millennium Pharmaceuticals' US$ 70 million

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 million and US$465 million respectively. Over the life of the original US$125 million agreement between HGS and SmithKline, the HGS's R&D program produced more medically important genes than the pharmaceutical 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. "A lot of people outside SmithKline thought we had overspent. History has shown we got the bargain of the century," boasts George Poste, SmithKline's former research chief [16]. 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 billion between June, 1999 and December, 2000. This enabled 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 biotechnology 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 pharmaceutical companies, other biotechnology 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 **1**) 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.

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

'*pharmaceutical companies have begun to realize that matching the breadth and technological sophistication of genetic research ongoing at biotechnology 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 biotechnology*' [12].

By the late 1990s and early 2000s, biotechnology 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 pharmaceutical 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 pharmaceutical-biotechnology collaboration over genomics, in January, 2001, Bayer, the German pharmaceutical giant, allied with the U.S. genomics firm CuraGen in an effort to discover drugs targeting obesity and diabetes. Worth US$1.34 billion dollars, 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.

6. RECENT PHARMACEUTICAL AND BIOTECHNOLOGY ALLIANCES

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 biotechnology platform providers or biopharmaceuticals. Some equities analysts suggested consolidation might ensue in biotechnology, 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 [16]. 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 and licensing to strengthen its overall product porfolio around a defined set of its perceived core competencies [17]. Even the largest and best financed pharmaceutical companies cannot afford to pursue all, or even most, emerging technology platforms through in-house R&D. Moreover, large pharmaceutical 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 pharmaceutical 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 pharmaceutical 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 [18]. The renewed consolidation of the pharmaceutical industry during the 1990s and early 2000s has occurred to a great extent as a result of the need to expand drug development pipelines. Filling the pipeline through acquisitions of other pharmaceutical or biotechnology 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 Pharmaceutical needs a new Business Model' [19]. In fact, the acquisition of biotechnology firms by large pharmaceutical companies tended not to be very effective. As Robbins-Roth [8] explored in his book, acquisitions of biotechnology 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. An exception may be Genentech, acquired by Roche in two transactions between 1990 and 1999. Only recently has it been announced that Genentech is filling up Roche's drug pipeline with the most promising cancer drug Avastin. 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 is publicly traded.

The European biotechnology 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 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 [20]. Novartis claims to manage hundreds of alliances with diverse biotechnology and academic centers (for example, Morphosys, Myogen, Xenon, Cellzome AG). The 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 biotechnology companies. 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 biotechnology 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 pharmaceutical companies. Even as of today Japanese pharmaceutical companies remain small by global standards. So when two Japanese drug makers, Yamanouchi and Fujisawa, recently announced a merger they would rank globally in sales only 17th even when they were Number 2 (after Takeda Pharmaceuticals) in Japan [21].

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 pharmaceutical firms allying with other pharmaceuticals and, more prevalently, with biotechnology firms, reflects the need to keep pipelines full. Consequently, equities analysts pay close attention to the quality of pharmaceutical firms' alliances [22,2]. 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". The president of R&D for Pharmaceuticalcia Corporation (now Pfizer-Pharmaceuticalcia) 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" [23]. Sidney Taurel, the 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 [24]. 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 percent – 45 percent of typical firm revenues will derive from licensing arrangements by the year 2002. From the perspective of biotechnology firms, many of these partnerships are working. Recombinant Capital, an industry consulting firm, reports that earned revenues for 100 pre-commercialization biotechnology firms they track totaled US$5 billion between 1997 and 1999.

While all large pharmaceutical 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 of US$40 billion 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 drier pipeline. In early 2001, Merck hired Peter Kim from MIT to lead its research efforts, which includes 6,500 research professionals. Merck has avoided mergers with other large pharmaceutical, 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 came

off patent protection in 2001, probably eliminating between four and six billion dollars in annual revenues, 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'. Throughout the 1980s and 1990s, large pharmaceutical 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 pharmaceutical firms have structured their efforts around niches within which they could pursue these high margin, smaller market drugs. Allergan, the eleventh largest U.S. pharmaceutical firm by revenues in 2000 represents an example. Validating the severity of the situation, the massive European pharmaceutical 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 inhouse, but also to ally with related biotechnology 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 pharmaceutical firms to overcome the quandary. Allergan has leveraged its relatively small size (nearly US$2.0 billion ytd, June 30, 2001 revenues) by licensing drugs for niche markets that its larger pharmaceutical brethren cannot efficiently market. Johnson & Johnson 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 & 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.

7. COLLABORATION INTENSITY OF BIOTECHNOLOGY/ PHARMACEUTICAL COMPANIES: AN EMPIRICAL PERSPECTIVE

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 pharmaceutical firms' primary products, a firm's ability to build and execute an effective network strategy might reasonably correlate with that firm's marketplace success. When pharmaceutical and biotechnology firms create co-development, in-sourcing, marketing and/or licensing agreements, they are creating a form of intellectual property 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. Analysts and market participants 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 of new products. The expansion of collaborative relationships in the pharmaceutical industry over the past twenty years illustrates the recognition by pharmaceutical 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 pharmaceutical firms with respect to collaborative activity. While the simplest hypothesis would suggest that pharmaceutical firms with broader portfolios of interfirm relationships should exhibit superior performance, certainly other possible correlations exist. One could argue that pharmaceutical 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 pharmaceutical 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 pharmaceutical and biotechnology 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 big pharmaceutical, 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. Second, we will examine whether a statistically significant change occurred during the period from 2000 to 2005 with respect to the correlation between collaborative activity and P/E ratios. 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, 2001, taken from the Fortune 500 for 2001. The following table lists the firms with their ticker symbols and revenues for the period.

Table 2. The Nine Largest US Pharmaceutical Firms by Revenues, ytd, June 30, 2001

Merck	MRK	US$ 45.3 Bil
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

Source: Fortune 500, 2001.

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

8. COLLABORATION RATE

The proxy for the level of collaboration used in both tests as the independent variable was defined as follows:

"*Collaboration Rate*", *or CR, defined as the number of collaborative agreements into which a particular pharmaceutical company entered during the period commencing January 1, 2000, through the end each year considered by the study (2000 -2005).*

The CR for the first test of total return included the total number of collaborative relationships of each pharmaceutical 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 A. The CR was based on detailed information compiled from the ReCap database, managed and maintained by the consulting firm Recombinant Capital [25], perhaps the most complete repository of information on inter-firm agreements in the biotechnology and pharmaceuticals industries. 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 biotechnology industries. Agreements between pharmaceutical and biotechnology firms have become more sophisticated on one hand and on the other hand 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 due 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 dollar 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 employed the ReCap database with very satisfactory results [26,27]. For an article dated 1997, 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" [27]. 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 Pharmaceutical firms. At around US$9.8 billion in revenues as of year-end 2000, it is one quarter the

size of the largest firm in the industry, Merck, at US$ 40 billion.

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 billion of revenues in 1998*,* compared with the firm's total revenues of US$8 billion for the year. During the third quarter of 2001, Claritin posted revenues of US$828 million on firm revenues of US$2.4 billion [28]. 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 favorably 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 pharmaceutical 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 endeavor. 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 [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 pharmaceutical 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 [29]. 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. Should Clarinex prove successful, SGP should be able to protect some of its lucrative antihistamine therapeutics franchise. If not, the company could face a crisis. The fact that prospects of a major firm such as SGP hang in the balance of one product leads one to question the company's R&D model. Averting crises requires a strong pipeline, which can either be driven by internal R&D or external collaboration and sourcing. While management denies it might be a takeover target, it is difficult to see how the firm will recover from the loss of its Claritin patent franchise and maintain its independence without a successful introduction of Clarinex. A stronger collaborative effort might have afforded the firm more options at a critical juncture.

9. COLLABORATION RATE TO PRICE-TO-EARNINGS RATIOS, 2000 - 2005

Aside from SGP's performance, the firms in the sample exhibit a high correlation between CR and total return over the decade (Test A). In order to delve deeper, another test (TEST B) 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 B 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 December 31, 2000 - December, 2005, at year end for each year. Both the P/E ratios and CRs are normalized in order to enable comparisons across years.

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 A. 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 A, 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, and 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 2001, pharmaceuticals contributed over 83.5 percent of the company's revenues (American Home Products, 2000 - 2005). Test B 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 R^2 fit is somewhat weak. Firms engaged in more collaborative activity tended to be valued more highly by the market.

10. R&D AND M&A

Two factors were transforming the structure of the pharmaceutical industry from 2000 – 2005 that might account for this condition. 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 Pharmaceuticalcia Upjohn merger with Monsanto's life sciences operation to become Pharmaceuticalcia. 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 pharmaceutical 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 pharmaceutical firms' interest in- and eventually, requirement for converting their R&D efforts to include an ever-expanding set of new biotechnologynologies. In particular, by 2000-2005, firms were intensifying their alliance formation with genomics and bioinformatics firms 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 pharmaceutical/biotechnology alliances with a commitment of US$125 million. 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 [16]. As mentioned earlier, the biotechnology consulting firm Recombinant Capital (ReCap) reported that earned revenues for 100 of the pre-commercialization biotechnology firms they track totaled US$5 billion between 1997 and 1999.

Most arrangements from this period, however, have still to bear out in financial performance. Nonetheless, analysts pay close attention to these agreements, so they must enter into any picture of market valuations. At the most fundamental level, the change in correlation between the variables from 1996 – 2001 corresponds with the maturation of the pharmaceutical industry. Consolidation typically accompanies market maturation, as growth rates slow and competitors expand, merge or exit and market share becomes concentrated in fewer dominant firms [30]. In contrast to many other industries, maturation 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 to drug discovery and development; and,
2. The conversion from small molecule chemistry to DNA-based biopharmaceuticals.

The consequence of it is inducing moves toward a further industrialization of R&D, that is shifting away from ‘wet science’ toward ‘in silico science’ through computational tools such as high throughput screening (HTS), genomic computation and combinatorial chemistry [6].

The transition exhibited by the collaboration to P/E ratio data to some extent reflects the conversion of the pharmaceutical industry's traditional drug development processes to new development paradigms. Rather than accomplishing this transformation internally, pharmaceutical 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- 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 biotechnology, and Millennium Pharmaceuticals and Human Genome Sciences, the latter of which began their ascent to the ranks of large pharmaceutical in the past few years. Large pharmaceutical firms have 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 pharmaceutical 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 [31]. As these new development platforms mature and large pharmaceutical 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 pharmaceutical 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 pharmaceutical firms beyond their boundaries in search of new knowledge.

11. DISCUSSION OF RESULTS IN LIGHT OF THE NETWORK DIMENSION

This exploration of data most directly addresses the role of network specific investments within the Competencies incentive-space. However, as presented in our brief history of the pharmaceutical/biotechnology 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) spaces. 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 pharmaceutical's ability to develop and manage alliance-based drug discovery and development. Effectively, the large pharmaceutical and biotechnology 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. Further study should investigate the differential performance of firms in terms of their success at managing andgarnering 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 biotechnology, pharmaceutical and academic partners. As in mating games, higher quality opportunities target more attractive partners. Less attractive, or more risky, biotechnology 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 pharmaceutical partners might also be able to command more advantageous terms from their partners. Understanding network strategy from an operational tandpoint requires investigation into these and many other issues at the applied level of the manager and the enterprise.

12. COLLABORATIVENESS AND PERFORMANCE IN THE PHARMACEUTICAL INDUSTRY: SEMINAL VERSUS INCREMENTAL INNOVATION

Innovative capacity dearly plays a central role in the success of pharmaceutical and biotechnology 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 adroitly 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 [32].

Pharmaceutical 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 [33]. Nonetheless, successful incremental innovation alone cannot support the strong shareowner value growth required by the market over the long term, particularly as competitors continually pursue potentially disruptive technologies. Large pharmaceutical 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 reve-

nue 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. Cases where firms pursue seminal innovation through in-house capabilities have shown mixed results. The classic example of Bell Labs produced substantial success at seminal innovation; however, the parent, AT& T commercialized a minimal percentage of the Labs' prolific output Many other firms benefited, however, from such innovations as the transistor.

Bell Labs also differs from most other cases, given it's parent company's long-term monopoly position. Certainly, Xerox's Palo Alto Research Center (PARC) provides the classic example of success at driving seminal innovation, and failure at capitalizing on these successes in the marketplace. Again, numerous firms arose or otherwise benefited as a result of research conducted at PARC, such as 3COM, Apple Computer, Microsoft and Aldus, but Xerox capitalized on almost none of this activity throughout the 1970s and 1980s. In an unintended manner, the numerous firms that profited from the seminal research at PARC and Bell Labs represented the natural development of a network--- firms, individuals and organizations coalescing around technological opportunities in a commercial vacuum.

The distinction between the demands of seminal and incremental innovation offers an important dimension for understanding the role of alliances within the Competencies dimension. Further research should investigate the relationship between collaboration and success in other industries, differentiating between those industries characterized by high rates of seminal innovation and those under more mature conditions.

13. CONCLUSIONS

Based on a framework of network dimension, through a history of the biotechnology/pharmaceutical relationship and a simple empirical analysis we are able to summarize a number of observations and conclusions:

1. At identifiable points in the history of the pharmaceutical and biotechnology industries, critical events encouraged the transformation of firm networks within and between both industries.
2. 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.
3. A strong, statistically significant, positive correlation exists between the Collaboration Rate of large pharmaceutical 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 1996 to 2001, the pharmaceutical industry began a significant evolution in the platform technologies necessary to develop new drugs (e.g., genomics, combinatorial chemistry), combinatorial chemistry now being blamed for drier product pipelines.

Alliances offered a successful strategy for incorporating these emerging capabilities into pharmaceutical 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 [32]. The challenges presented by seminal innovation, including a high degree of unpredictability, encourage large pharmaceutical 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 pharmaceutical firms during the period under consideration.

APPENDIX

Appendix A. Test A: Collaboration Rate & Total Return Data, Major Pharmaceutical Companies 2000 – 2005

Company Collaboration Total Return Rate (% 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

Appendix B. 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.

Appendix C. 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.

2000 Company PIE		Normalized P/E	2001 Company P/E		Normalized P/E
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 Company P/E		**Normalized P/E**	**2003 Company P/E**		**Normalized P/E**
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 Company P/E		**Normalized P/E**	**2005 Company P/E**		**Normalized P/E**
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 32.56.

Appendix D. Test B: Collaboration Rate to P/E Ratio, Normalized Data by Year and Firm

	Company	Norm CR	Norm P/E		Company	Norm. CR	Norm P/E
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
				2004	MRK	0.91	0.71
2001	MRK	1.09	0.73		JNJ	1.13	0.83
	JNJ	1.19	0.84		PFE	1.70	1.74
	PFE	1.02	1.40		PHA	1.43	1.81
	PHA	1.19	1.78		**BMY**	0.69	0.80
	BMY	0.80	0.78		ABT	0.74	0.60
	ABT	0.70	0.64		LLY	0.92	0.74
	LLY	1.44	1.01		SGP	0.49	0.76
	SGP	0.57	0.82				
2002				**2005**	MRK	0.78	0.72
	MRK	1.01	0.74		JNJ	1.11	0.97
	JNJ	1.23	0.87		PFE	1.64	1.22
	PFE	1.03	1.78		PHA	1.39	1.17
	PHA	1.27	0.79		**BMY**	0.68	0.82
	BMY	0.81	1.07		ABT	1.01	1.49
	ABT	0.75	0.71		LLY	0.91	0.86
	LLY	1.31	1.03		SGP	0.47	0.74
	SGP	0.60	1.01				

Appendix E. Significance Tests for the Regressions

Two-tailed t-Tests

Test	Degrees of Freedom	Significant at Alpha =		
		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
CR to P/E, 2002 - 2003	14	0.52	No	No
CR to P/E, 2004 - 2005	14	4.53	**Yes**	Yes

REFERENCES

[1] Powell WW. *et al*. Interorganizational collaboration and the locus of innovation: networks of learning in biotechnology. Administrative Science Quarterly 1966; 41:116-145.

[2] Goldman Sachs. Strategic alliances in biotechnology. Goldman Sachs Global Equity Research, New York: Author, 2005.

[3] Baum JA. *et al.* Don't do it alone : Alliance network composition and startups' performance in Canadian biotechnology. Strategic Management Journal 2000; 21: 267-294.

[4] EU European Commission, Enterprise Directorate General. 2002 European innovation scoreborard (Tech. Paper No.7). Biotechnology Innovation Scoreboard, EU Comission, Brussels: Author, 2002.

[5] Gottinger HW. The economies of network industries. London, Routledge 2003.

[6] Nightingale P, Mahdi S. The Evolution of Pharmaceutical Innovation. In: Mazzucato M, Dosi G, Eds. Knowledge accumulation and industry evolution: the case of pharmaceutical-biotechnology, Cambridge Univ. Press: Cambridge 2006; pp. 73-111.

[7] The Economist. Climbing the helical staircase 29 March 2003; 8317:3-7.

[8] Robbins-Roth C. From alchemy to IPO: the business of biotechnology. Cambridge, Mass. Perseus Publishing 2000.

[9] Hensley S. Human genome's chief is to retire. Wall St J 2004 March 25 [Retrieved 2004 March 25]. Available from: http://www.wsj.com.
[10] Temin P. Taking your medicine, drug regulation in the United States. Cambridge, Ma. Harvard Univ. Press 1980.
[11] Lichtenberg FR. Pharmaceutical Innovation as a Process of Creative Destruction. In Mazzucato M, Dosi G, Eds. Knowledge accumulation and industry evolution: the case of pharmaceutical-biotechnology, Cambridge Univ. Press: Cambridge 2006; pp. 21-72.
[12] Couzin J. Biotechnology: desperate no more. The Industry Standard, 2001 June 27:1 [Retrieved 2007 December]. Available from: http://www.thestandard.com/biotech-desperate-no-more.
[13] Davies K. Cracking the genome: inside the race to unlock human DNA. New York. The Free Press, 2001.
[14] The Economist. Structural genomics: strategic thinking 9 June 2001; 8225:82-83.
[15] Vitrup D. *et al.* Completeness in structural genomics. Nat Struct Biol 2001; 8(6):559-563.
[16] Stipp D. He's brilliant. He's swaggering. And he may soon be genomics' first billionaire. Fortune 2001; 141: 100-112.
[17] Cullen A. Roche overhauls way of managing biotechnology partners. Wall St J 2004, March 23 [Retrieved 2004 March 23]. Available from: http://www.wsj.com.
[18] Raghavan A, Naik G. The big drug mergers can be hard to swallow. Wall St J 2004, April 2 [Retrieved 2004 April 2]. Available from: http://www.wsj.com.
[19] The Economist. Fixing the drugs pipeline. Technology Quarterly 13 March 2004; 8366:37-38.
[20] Ernst and Young. Global Biotechnology Report, Author, 2004;10.
[21] Shimamura K, Singer J. Japanese drug makers to combine. Wall St J 2004, Feb. 12 [Retrieved 2004 Feb. 12]. Available from: http://www.wsj.com.
[22] Goldman Sachs. Biotechnology industry overview. Goldman Sachs Investment Research, New York: Author, 1999.
[23] Van Brundt J. Pharmaceutical's new vision. Signals Magazine 2003, May 19 [Retrieved 2007 December 12]. Available from : http://www.signalsmag.com.
[24] Aiken M. *et al*. A license to cure. The McKinsey Quarterly 2000; 1: 80-89.
[25] Recombinant Capital [Online]. 2001-2006 [cited 2008]. Available from: http://www.rDNA.com.
[26] Lerner J, Merges RP. The control of technology alliances: an empirical analysis of the biotechnology industry. J Ind Econ 1998; 46: 125-156.
[27] Pisano GP. R&D performance, collaborative arrangements, and the market for know-how: a test of the 'lemons' hypothesis in biotechnology (Working Paper). Harvard Business School 1997.
[28] ScheringPlough. Annual Report 2001. Schering-Plough Corporation, Kenilworth, NJ, 2001.
[29] Tanouye E, Langreth R. Time's up: with patents expiring on big prescriptions, drug industry quakes. Wall St J August 1997; A1.
[30] Dunne T, Roberts MJ, Samuelson P. Patterns of firm entry and exit in US manufacturing industries. RAND J Econ 1988; 19: 495-515.
[31] The Economist. Beyond the blockbuster 30 June 2007; 8535:23-24.
[32] Christensen C. The innovator's dilemma. Boston, Mass. Harvard Business School Press 1997.
[33] Wolcott RC, Wong ED. Ground rules are not necessarily the rules of the game: exploring pharmaceutical franchise extension strategies, Englewood Cliffs, NJ. Prentice-Hall 2002.

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