Organizational Entrepreneurship: A Historical Overview on Industry Alliances in Biotech and Pharmaceuticals

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Abstract: This article 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.

Keywords: Biotechnology industry, pharmaceuticals, entrepreneurship, strategic alliances, network 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. Following some conceptual work of Pyka and Saviotti [1], as well as Gottinger *et al*. [2] we could conceive innovation networks between large diversified firms (LDFs as 'big pharma) and dedicated biotechnology firms (DBFs)as strategic alliances for technology driven market dominance. In this vein, Powell [3], 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 [4] updated most recently [5]. In a study of the Canadian biotech industry, Baum *et al.* [6] 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 [7]. 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 [8], and more specifically applied to the globally operating pharma-biotech industry [9].

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Although network economic effects commonly apply to information and communication technologies (ICTs), as in telecommunications [10], they could also appropriately adapted to the R&D based pharmaceutical industry since "big pharma" exhibits supply-sideas well as demand side economies of scale giving rise to network externalities with direct and indirect network effects through competing drug platforms.

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 [11]. 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.

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The purpose of this paper is to show empirically how the emergence of the medical biotech industry provided –with some time lag -- an important scientific-technological platform and a major source for drug discovery to fill product pipelines of large pharmaceutical firms. This is even an ongoing process as a recent WSJ report reveals [12].

2. BIOTECHNOLOGY 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 [13]. 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' [14]). Similarly, along this line, as Powell *et al.* [3] 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 [15]. 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 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 million in a stock swap in order to accelerate its transformation from a genomics firm to an integrated pharmaceutical company.

3. NETWORK FORMATION

Three network formation 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 [16]. 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 [17] --- 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 [18]. Also the link to innovations could be part of a network strategy as it will generate dynamic efficiencies in R&D intensive

industries [19], here giving rise to pharma-biotech increasing returns mechanisms [20].

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. Grove [21] 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 **1**.

Table 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 [22]. 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' [23].

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 [24] 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' [25]. 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 [26].

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 [27]. 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 $14 million 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" [15]. 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 [28]. 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' [28].

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' [28].

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 million. Europe and the rest of the world accounted for another US$200 million. Its closest competitor, Novo Industri, had only about 30% 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 million 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" [28]. 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 [29]. 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% 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 [30] 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 billion 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 [15], 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 phar ma 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% of Genentech to the public in July, 1999, illustrated Genentech's continued value independent of Roche. The IPO raised $1.94 billion 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 [31]. 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 [32].

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 [33,34] setting itself on an alternative path to mega-mergers in the industry [35].

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 behavior. 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 [36]. 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 [37]. 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 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 [38], 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 million in exchange for 7% 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$70million agreement between Hoffman LaRoche and Millennium Pharmaceuticals.

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 [39]. 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.

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 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 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., not the least to reduce the uncertainty on scale and dimension of drug discovery [22]. 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' [40].

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" [40]. 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" [41]. 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' [40]. 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 **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 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) [42].

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 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 billion 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 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' [43].

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 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.

7. RECENT PHARMA AND BIOTECH ALLIANCES

As the biotech industry expanded their product pipeline in the US [44], 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 [45]. 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 [4]. 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 [33]. 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 [35]. 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 [46]. 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' [47]. In fact, the acquisition of biotech firms by large pharma companies tended not to be very effective. As Robbins-Roth [15] 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 [30]. 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% 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 [48].

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 [49]. 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 [50].

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 [4, 51]. 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" [52]. 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" [53]. Sidney Taurel, the former CEO of Eli Lilly reported a similar figure of 20% 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 [54]. 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% in 1992 to 32% in 1998. This translates into a 15% compounded growth rate, compared with a 9% compounded growth rate for internally developed drugs. The study predicted that 35% - 45% 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 $5 billion 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 of $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 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 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 [55]. 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 billion 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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