

@cn:Chapter 10

@ct:A Framework for the Biotechnology Industry

@ics:T@ic:he biotechnology industry is in transition. In the past several years, it has moved from infancy into a stage of rapid growth. Success stories such as those of Amgen, Genentech, and Biogen have given validity to the industry, its technology and products, and its viability. The industry has received public attention for such accomplishments as mapping the human genome and developing cloning technology, feats previously only in the realm of science-fiction authors.

@\$: Tremendous opportunity has come from the success of early biotech firms and the promise of their technological breakthroughs. Many new companies entered the industry, hoping to strike it rich during the biotech gold rush. Having seen the high failure rate of early biotechs, many of these firms tried to reduce their exposure to risk either by specializing in a single aspect of product development, such as research, or by developing tools for product-development firms. Many firms that hoped to capitalize on the technology by selling services have found, however, that the returns they had envisioned are not materializing. They have learned that product development and commercialization, while risky, is the most profitable and highly valued activity of the biotech industry. As a result, many biotech firms are forward integrating in the hope of leveraging their current competencies and expanding into product development.

This chapter examines how biotech firms are repositioning themselves to better capitalize on the value they are creating. It begins with a historical overview of the pharmaceutical industry and the drug-discovery process. Then the evolution of the horizontal business model is described, along with the shortcomings of that approach. An analysis of the hybrid business model next provides a framework for biotechnology companies that are considering forward integration. Finally, there are predictions for the structure of the industry in its next stage, maturity.

@h1:History of the Pharmaceutical Industry

@\$:Many large pharmaceutical companies evolved from chemical companies. These companies had established core competencies in chemistry, manufacturing, marketing, and sales. Over time, they migrated their core competencies into pharmaceuticals and built additional capabilities in biological research, development, and clinical trials.

This vertically integrated structure was adopted not only by pharmaceutical and chemical companies, but also by companies in industries such as automobiles, steel, and even computers. However, unlike these other industries, large, vertically integrated pharmaceutical companies have continued to prosper as a result of the dynamics of drug discovery.

@bh:Case Study: Pfizer

@bt:As one of the largest and most successful pharmaceutical companies in the world, Pfizer illustrates many of the characteristics of large pharmaceutical firms. It was founded in New York City in 1849, as a specialty-chemical company. The first medicine that it marketed was an antiparasitic that could be swallowed. Pfizer expanded its product line to include many chemicals and medicines. Interestingly, Pfizer's first blockbuster product was citric acid, which is needed for industrial applications and food products. Using a fermentation process it developed in 1919, Pfizer was the first company to mass-produce citric acid.

In 1944, Pfizer's expertise in fermentation allowed it to become the first company to mass-produce penicillin, and it became the world's largest producer. In 1950, after a hundred years of business, Pfizer introduced the first pharmaceutical that it had discovered in its own laboratories—the antibiotic Terramycin. More than 30 years ago, in 1971, Pfizer formally established its Central Research Division to bring efficiency and organization to the development of pharmaceuticals.

@bfn:<I>Source:<I>|en|www.pfizer.com.

@h1:Traditional Drug Discovery

@\$: Having evolved from chemical companies, large pharmaceuticals had expertise in chemistry and thus developed their drugs using small-molecule methods. Most small-molecule drug-development efforts use a screening approach, a methodology that begins with samples of organic material, such as plants collected from the Amazon rain forest. These materials often contain unique chemical species of unknown efficacy. In the past, screening such materials for efficacy against specific targets was time-consuming and laborious, but the technique of combinatorial chemistry has greatly enhanced this drug-discovery process.

After researchers have identified a new chemical as being active against a target disease, further development leading to commercialization is a notoriously long, arduous, and expensive process. Typically, developing a drug requires 10 years, and an investment of \$500 million to \$750 million. Further, for every drug or treatment that gains Food and Drug Administration (FDA) approval, 5,000 to 10,000 compounds and combinations are tested. Of these, 250 make it to the clinical-test phase, and only 5 ever reach Phase 3. On average, only one of these gains approval, and this in turn is no guarantee of commercial success.

## @h2: Drug-Discovery Value Chain

@\$: The drug-development value chain can be broken down into five stages: target discovery, lead discovery, clinical trials, manufacturing, and marketing, sales, and distribution (Table 10.1). These stages are often categorized and discussed as research (R), development (D), and commercialization (C).

@m: R D C

@\$: Each step along the drug-development value chain has an inherent risk and return associated with performing those activities. The value of a product increases as it moves from one stage to the next. At each successive stage, the likelihood of success increases, but the loss associated with failure increases as well.

## @h2: Target Discovery

@\$:The first stage of the drug value chain is target discovery. The goal of this process is to identify a target, or a physiological phenomenon, implicated in a disease that a drug can neutralize. Historically, this process was a bottleneck in the drug-development value chain because the screening approach took so long to identify new targets. Since it was a bottleneck, pharmaceutical companies often created copycat drugs that used the same biological target. The result was a significant number of competing drugs developed for similar indications.

## @h2:Lead Discovery and Development

@\$:With a specific target in mind, researchers use several methods to develop a substance, or <I>lead,<I> that regulates the target's activity in causing disease. Before lead molecules can be moved into the next phase of clinical testing in humans, researchers typically conduct in vivo preclinical trials in which molecules are tested in animals for efficacy and safety at effective dosage.

## @h2:Clinical Trials and Regulatory Approval

@\$:The third stage is clinical trials, in which lead molecules are tested in human models for efficacy and safety. The ideal end result is FDA approval, which is required to commercialize a drug. This step accounts for a major portion of the time and expense involved in bringing a drug to market. Designing and completing clinical trials, together with the FDA review process, historically has required 5 to 10 years and has accounted for 80 percent of the total cost of developing a drug. To gain FDA approval, new drugs must successfully complete three phases of clinical trials, as shown in Table 10.2.

After Phase 2 trials, the drug has demonstrated safety and efficacy. Once the product passes through this stage, its value jumps significantly as the prospects for commercialization increase. This phase can be seen as the tipping point in the value chain. According to Mike Gallatin, Vice President and Scientific Director at ICOS, the Phase 2 clinical trial is the "sweet spot." At this point, a small company can partner with a

pharmaceutical company to avoid the hefty registration fees associated with Phase 3 trials. By bringing a product through Phase 2, a company can get full value for it because the likelihood of reaching the market is high. After clinical trials are complete, the company submits a New Drug Application to the FDA. Following its review, the FDA Advisory Panel submits a recommendation for or against approval, and the FDA renders its decision.

@bh:Current Trend: FDA and the Prescription Drug User Fee Act

@bt:Prior to 1992, it took an average of 30 months for the FDA to approve a new drug. During that year, the Prescription Drug User Fee Act (PDUFA) was enacted. PDUFA provided the FDA with increasing levels of resources for the review of human-drug applications. Fees that the FDA collected from drug and biologics firms from 1993 to 1997 were to be used to reduce the time required to evaluate certain human-drug applications without compromising review quality.

This legislation reduced the average time it takes for drug approval to 12 months, and to as few as 6 months for breakthrough drugs. Since then, the number of drugs approved per year has increased by 40 percent, and the total development time has been shortened by 20 percent. The original act expired September 30, 1997, but the FDA Modernization Act of 1997 amended and extended PDUFA through September 30, 2002. [[Au: Any update?]]

@bfn:<I>Source:<I>|en|www.fda.org.

@h2:Manufacturing

@\$:Manufacturing can be performed in house or outsourced to other companies. This step in the value chain is highly regulated, and companies are required to follow stringent guidelines to enforce quality and uniformity in the products. In the event that a company fails to meet FDA requirements, it can incur significant costs and lost revenue. Depending on the therapeutic product, manufacturing capacity can be a bottleneck.

@h2:Marketing, Sales, and Distribution

@\$:Commercializing a drug requires considerable infrastructure to educate, sell, and provide support to health care providers,

health insurers, and end users. The infrastructure generally takes a sizable investment and results in a significant fixed-cost base. This is the stage at which a firm decides whether to build a consumer brand name for its company. Deciding whether and how to invest in this stage of the value chain represents one of the foremost challenges for biotechnology firms in determining business strategy.

@h1:Emergence of the Biotechnology Industry

@\$:The advent of biotechnology stemmed from the belief that, with advanced understanding of biological processes, researchers could manufacture molecules that are highly specific to the targeted biological pathway. Such drugs would presumably be safer and cause fewer side effects.

When recombinant DNA technology was discovered in the 1970s, it became a disruptive force for the entire pharmaceutical industry. The technology allowed companies to mass-produce human proteins for the first time by growing the proteins in *E. coli* bacteria. Instead of screening compounds and then searching for the active targets of those compounds, biotechnology now identifies disease targets first and then searches for ways to manipulate those targets. Technologies developed to perform this include genomics, bioinformatics, and molecular genetics.

Recombinant DNA changed the philosophy for developing drugs from the traditional process of trial and error with small molecules to a process that begins with understanding the disease pathway and then finds the proteins to modify the disease biology. Targeted proteins held the promise of more specific drugs that had fewer side effects (see Table 10.3).

Many of the initial biotechnology companies (Amgen, Genentech, and Chiron) emulated the structure of the large, vertically integrated pharmaceutical companies. That strategy was driven by four main factors. First, it was the known and established business model of the drug-development industry. Second, this model allowed companies to retain control so that they could continue to develop drugs differently—from disease to

drug, rather than from compound to disease to drug. Third, no pharmaceutical company had the technology or manufacturing prowess to manufacture the proteins. The biotechnology companies had the most knowledge about the processes, so it made more sense for them to develop these capabilities. Finally, biotechnology products had not been proven efficacious or cost-effective. The market value of the products was uncertain, so the pharmaceutical and biotechnology companies had difficulty agreeing on appropriate partnering arrangements.

@bh:Case Study: Genentech

@bt:In 1976, 29-year-old Silicon Valley venture capitalist Robert Swanson approached Herbert Boyer, a professor of biochemistry and biophysics at the University of California-San Francisco, about forming a business for drug development. Boyer had been conducting groundbreaking research with recombinant DNA, and Swanson believed that his research could provide a new way to create commercially viable human therapeutics.

Initially, Boyer was reluctant to create Genentech because the academic research community saw working in industry as selling out. Swanson, however, convinced him that together they could create a company whose research was as good as that being conducted in university laboratories and that he would be proud to be a part of it. They called their company Genentech and chose to focus on creating pharmaceuticals that addressed significant unmet medical needs. In doing so, they launched the biotech industry.

The following year, Genentech produced the first human protein, and in 1982 the first recombinant DNA drug was introduced to the market in a joint venture between Genentech and Eli Lilly. Since then, Genentech has developed eight drugs to treat cancer, heart disease, and diseases requiring growth hormones.

@bfn:<I>Source:<I>|en|www.gene.com.

@h1:Evolution of Business Models in the Computer Industry

@\$:Biotechnology companies that started during the early 1980s primarily evolved into fully integrated biopharmaceutical

companies. That trend is similar to what happened in the computer industry, where vertically integrated companies like IBM and DEC dominated early on (Figure 10.1). According to David Yoffie, a Harvard Business School professor, "This model was viable in the era of the mainframe because proprietary, closed products created a one-stop shop for the customer, which in turn generated very high margins for the dominant players." [[Au: Source note?]] These margins could then be reinvested into the entire value chain, which allowed the company to remain competitive. To be successful, companies had to be large and have access to sufficient resources. To sustain this model, they had to establish and maintain a large market share.

As the computer industry evolved, it began to decouple. Specialized core competencies and economies of scale allowed companies to become dominant at horizontal layers such as microprocessors and operating systems. The horizontal model emerged in the computer industry as firms like Microsoft and Intel came to power (Figure 10.2).

@h1:Shifting Industry

@\$:In the early 1990s, the biotechnology industry reached a critical mass of product-development companies, and new companies began to implement horizontal business models. These companies specialized in a particular stage of the value chain and used economies of scale to create profit by selling their services. Companies following this strategy established platform technologies and services that could be used across multiple drug-technology silos (Figure 10.3).

This shift toward horizontal models occurred because of certain dynamics in the industry and the emergence of three disruptive technologies. Three key characteristics of the industry were the inefficiency of research, the difficulty of successfully commercializing drug products, and the strength of intellectual-property protection. The three disruptive technologies were computing power, genomics, and the Internet. The fundamental change resulting from these disruptive

technologies occurred as companies realized that the drug-development industry was not product driven, but information driven. In essence, companies recognized that those firms that control the information created in the early research and development stages can control the downstream products and therefore the downstream profits.

## @h2:Dynamic 1: Inefficient Research Programs

@\$:As discussed, drug-development companies were originally vertically integrated and developed products around in-house expertise. Before the appearance of computers and the Internet, several aspects of the industry made this organizational structure ideal. Information exchange between collaborators—other companies, government agencies, and academic institutions—was slow, uncertain, and costly. Thus, in accordance with ideas first expressed in Ronald Coase's 1937 article, "Nature of the Firm," companies organized vertically to optimize the sharing and transfer of knowledge (value) across different functional areas within the company. Maintaining excellence in vertical models, however, is often difficult. Human and capital resources are limited, and companies are forced to make tradeoffs in some value-chain activities. It is extremely difficult to maintain a core competency in research, development, and commercialization.

Tradeoffs lead to two problems. First, because of the diverse competencies required, firms tend to allocate inadequate capital or human resources to compete effectively in any one area. Thus, they spread their resources too thinly and fail to establish a competitive advantage in any area of the value chain. Second, tradeoffs leave the firm vulnerable to competitors who make fewer, different, or ultimately better choices. More focused companies could innovate more quickly and produce services and products more efficiently than larger diverse companies.

## @h2:Dynamic 2: Risk of Product-based Strategies

@\$:Motivated by the economic incentive of profits from potential blockbuster drugs, early biotech companies performed all the activities required to develop and sell biotherapeutics. On average, however, only 1 in 10 of these early biotech firms was

able to bring a product to market. During the 1970s and 1980s, investors focused only on the tremendous upside potential of biotechnology, but in the early 1990s investors became less willing to sink money into the black hole of drug discovery. This gave rise to a deconstruction of the industry and created the opportunity for more nimble, horizontally oriented platform companies to enter the arena. They could compete effectively by specializing in one aspect of the drug-discovery value chain.

Discovering targets for larger companies or specializing in one link on the value chain was less risky, required less capital, and generated more immediate results. [[Au: Cite for Table 10.4?]]

## @h2:Dynamic 3: Strong Intellectual-Property Laws

@\$:During the 1990s, there was a correlation between the emergence of horizontal business models and the sharp increase in patents issued in the biotech industry. Most likely, the availability of patent protection drove the emergence of these companies (Figure 10.4).

Biotech firms in the United States understand that protection of intellectual property through enforceable patent rights is critical to success. Biotechnology is an information-driven science, and the industry thrives when researchers share thoughts and data. Since developing biotherapeutics and platform technologies is capital intensive, however, companies may be reluctant to innovate or share information unless there is a law to protect their discoveries. Biotechnology companies create and protect value as a direct function of their intellectual property. The preceding dynamics coincided with the following three disruptive technologies to drive the emergence of horizontal business models.

## @h2:Technology 1: Genomics

@\$:Genomics-technology development also led to a quicker and more accurate method of identifying drug targets and drug leads. Advances in DNA-sequencing technology and the development of microarray technology have driven the emergence of genomics. To begin with, the commercialization of automated DNA sequencers significantly

enhanced the collection of raw DNA sequence information. Using instruments such as the ABI 377 sequencers (produced by Applied Biosystems), laboratories could easily collect sequence information within hours on 32, 68, and eventually 96 samples at a time. More recently, the advent of capillary-based automated sequencers has further improved the quality and throughput of sequencing. This technology, combined with advances in fluorescent chemistry, has encouraged the emergence of specialized, high-throughput-sequencing laboratories that now sequence hundreds of thousands of DNA samples a week. The level of sequencing throughput has created an explosion of DNA information and allowed the first draft of the human genome to be finished years ahead of expectations.

In addition to sequencing technology, microarray technology has also had a profound impact on genomics. Microarrays consist of pieces of DNA attached to a substrate such as glass. In the mid-1990s, commercialization of this technology began with companies such as Synteni (acquired by Incyte Genomics in 1997) and Affymetrix. The density of DNA strands on microarrays is on the order of tens of thousands per square centimeter and will soon reach hundreds of thousands. This technology allows scientists to collect data such as expression profiles on tens of thousands of genes in a single experiment, with tremendous savings of time and money. Companies like Zyomyx are now commercializing microarray technology for proteins, which will achieve a similar exponential increase in proteomic information.

The disruptive technologies in DNA sequencing and microarrays have altered the structure of the value network in drug development. Using these advances, companies can specialize in specific areas of the value chain, such as target discovery, and execute faster, better, and more cheaply than by focusing on the entire vertical drug-development process. This has led to a dramatic change in the landscape. A decade ago, the vertical companies were developing therapeutics from approximately 500 targets. Now the number of targets has grown to 5,000. This has shifted the focus of early research to target validation and

lead-molecule development. Some are claiming that therapeutic targets are now commodities, but patent protection is still allowing genomic companies like Celera and Incyte Genomics to capture the value of the targets they have identified.

@bh:Case Study: Incyte Genomics

@bt:Incyte Genomics, formed in 1991, was one of the first biotech companies to use high-throughput, computer-aided gene sequencing to identify genes and their corresponding proteins. Today, Incyte is one of the leading providers of genomic technologies designed for research in the molecular basis of disease. It sells subscriptions to its genomic databases, genomic data-management software, microarray-based gene-expression services, related reagents, and services to pharmaceutical and biotechnology companies. They use this information in all the phases of drug research and development, including gene discovery, disease pathways, new disease targets, and the discovery and correlation of gene-sequence variation to disease.

Unlike other platform companies, Incyte has not chosen to forward integrate and use its technology to develop drugs. Instead, Incyte negotiates royalty rights to the targets that are identified from its database and eventually used to develop drugs. Given the lengthy time of drug development, Incyte has yet to see any money from these royalties. However, Incyte believes that by concentrating on its core competency of gene sequencing and letting the pharmaceutical companies develop and sell drugs, it will maximize its risk-return ratio.

@bfn:<I>Source:<I>|en|[www.incyte.com](http://www.incyte.com).

@h2:Technology 2: Affordable Computing Power

@\$:The second disruptive force was the tremendous advance that occurred simultaneously in the high-tech industry. It enabled researchers to handle the vast raw-data collection that was now possible with the DNA sequencing and microarray technologies. At this convergence of computer technology and biotechnology, a whole new field of bioinformatics appeared. The exponential increase in raw genomic data created the need for sophisticated algorithms and computer software to make sense of the data.

Companies like Incyte Genomics soon had more software engineers on the payroll than traditional scientists. Again, bioinformatics promoted the rise of platform companies that used large computer systems to perform such functions as massive parallel assays and genomewide sequence analysis. These companies could focus and create expertise in bioinformatics much faster, better, and more cheaply than a fully integrated drug-development company. Thus, they created value that vertical companies would buy.

Furthermore, the exponential increase in computer-processing power had a significant impact on bioinformatics. In the formative days of the industry, researchers used very expensive supercomputers that were affordable only to a few companies. Although the necessary computing tools are still a significant investment, they are much more broadly available and affordable. In perhaps the most notable example, Celera has assembled the world's most powerful supercomputer outside the defense industry. The system consists of 1,200 interconnected Compaq Alpha processors that can perform more than 250 billion sequence comparisons per hour for more than 300,000 genomic fragments per day. It feeds Celera's database at a rate of 15 to 20 gigabytes per day. In addition, Incyte Genomics has assembled one of the five largest Linux farms in the world, and the largest outside the financial-services industry.

These technological innovations have altered the very nature of the biotech industry. According to Randy Scott, Chairman of Incyte Genomics, the industry has seen an application to biology of principles similar to Moore's law for the growing power and decreasing costs of electronic hardware and information processing. Whether it is DNA sequencing, microarray-expression analysis, or single-nucleotide polymorphism (SNP) analysis, the cost has come down dramatically.

@h2:Technology 3: Internet Communication

@\$:The biotechnology industry is organizing itself as a network of companies that create and exchange information. As an industry becomes information driven, the arguments for vertically integrating become less compelling. Information, compared with

products such as automobiles, can be easily manipulated, stored, and exchanged among companies. The emergence of the Internet has allowed information sharing to become more efficient and has made it possible for smaller, horizontal companies to thrive in the industry. Coase suggests that when market transactions become more efficient than the costs of maintaining a fully integrated firm, the industry will decouple. Large companies will no longer need to generate expertise at every level in the value chain. Rather, smaller and more specialized companies can add value within the network of the larger firms.

@bh:Case Study: The SNP Consortium

@bt:The SNP (Single Nucleotide Polymorphism) Consortium is an excellent example of individual companies leveraging the power of the networked economy and working together to accelerate the growth of their own industry. Eleven large life-sciences and technology companies, one bioinformatics company, four research centers, and one nonprofit foundation established the consortium. Its goal was to code the 300,000 SNPs in the human body and to create a publicly available database for drug discovery.

The purpose of the consortium was to provide a common road map for the human genome. This road map now serves as a research tool for every organization that conducts genomic research. According to consortium president Arthur Holden, the members viewed the map as a "precompetitive research tool." By collaborating, the members were able to create the map more quickly while sharing financial risk and reducing the duplication of effort.

This consortium illustrates both the power of shared information and the utility of networks. The organizations realized that a common backbone was necessary to advance their companies and the industry. Now that the infrastructure is established, each member can easily interact with other members of the consortium. Thus, the utility of the network for all members has increased exponentially.

@h1:Shortcomings of the Horizontal Model

@\$:Horizontal companies have been successful in generating immediate revenue; for several reasons, however, the profits have not been as large as anticipated.

## @h2:Stiff Competition and Rapid Technological Changes

@\$:Companies that seek to make extraordinary profits through advanced technology have difficulty maintaining their competitive advantage. First, new entrants emerge with similar products and steal customers. Second, existing technology improves, increasing competition and eroding margins. Third, with numerous companies and academic institutions pouring significant resources into research, technology in this industry advances extremely quickly. A firm's technological source of competitive advantage could easily become obsolete within a few years or even months.

To prevent the loss of market share, companies that sell technology must continually invest in research and development. This investment may ensure the sustainability of a company, but it does not ensure its profitability. For example, in FY2000, Incyte Genomics invested 105 percent of revenues in research and development. Although that has sustained Incyte's industry leadership, the level of expenditure prohibits its profitability [[Au: Any update?]].

## @h2:Long Product-Development Cycle

@\$:Horizontal companies sometimes anticipate compensation through royalties generated by sales of the drug. Since sales may not be recognized for 7 to 10 years, this places a large strain on their financial position. Further, as few drug candidates are actually brought to market, major potential revenue for horizontal companies may never be realized.

## @h2:Principal-Agent Problem

@\$:Another reason biotechnology companies have had difficulty negotiating for what they perceive as fair value from prospective buyers is that they disagree with their negotiator about the likelihood of the drug's success and therefore its value. Biotech companies systematically overestimate their products' likelihood of success. They do so largely because they have invested a tremendous amount of time, effort, and money into their

development. Similarly, biotech companies often underestimate the difficulty and importance of a sales force in making a drug successful, while large companies systematically overestimate the effectiveness of their sales force. Because an efficient capital market is lacking, the biotech companies often lose this argument about value. As a result, the bargaining zones between the seller and the buyer don't always overlap. This disagreement is a form of the "principal-agent problem."

What's more, biotech companies have more information than their negotiating partner does, and as the seller, they do not have the incentive to fully disclose all the risks associated with their product. Realizing that likelihood, the more risk-adverse pharmaceutical companies systematically underestimate the likelihood of success. This is the "lemon problem." The bidders knowingly bid low because there is a chance they will be stuck with a lemon--a product that has no value.

@h2:Inefficient Capital Markets

@\$:Perhaps the most significant reason that horizontal business strategy has not worked is the inefficient capital market within the drug-development industry. The efficient capital-market theory states that market prices are correct on average. In the market for biopharmaceutical products, however, that is seldom the case because there is limited competition for those products.

Globally, only about 20 pharmaceutical companies are in a position to buy biotechnology products. Within each therapeutic area, the competition may include only one or two companies. Thus, the pharmaceutical companies can underbid, knowing that the biotechs do not have other sources of capital, and the biotech companies are left with few choices. Further, large pharmaceutical companies require new drug candidates to have potential sales of at least \$700 million, which means that many drug candidates have no interested bidders.

@h1:Emergence of the Hybrid Model

@\$:The failure of the horizontal biotechnology model has led to a hybrid business model. A hybrid model results from a platform (horizontal) company attempting to forward integrate and develop

its own drug candidates. Platform-based companies are beginning to develop drugs to capture more of the value created by their technology. Forward-integration strategies include in-house product development, collaboration and licensing, and mergers and acquisitions.

Figure 10.5 provides a schematic representation of Millennium Pharmaceutical's migration from a platform strategy based on target discovery to a hybrid strategy that incorporates aspects of the vertical value chain.

@bh:Case Study: PPD, Inc.

@bt:PPD is another example of a platform company that has adopted a hybrid business model. PPD began as a contract research organization (CRO) that performed contract Phase 1 through Phase 3 clinical trials for drug-development companies. Today, it offers data-management tools and consulting services in addition to contract research. It has also forward integrated into contract sales and marketing services and has backward integrated into target- and lead-identification services.

By offering customers drug-development solutions, PPD believes that it can offer them more value. In effect, it lessens the extremely high fixed costs and risk associated with drug development. It also believes that this strategy will allow it to capture more value. Currently, PPD is working for, or partnering with, such firms as Affymetrix, Oracle, Bristol-Myers Squibb, Axys, and Eli Lilly.

@\$: Although the hybrid strategy may sound like a panacea, the approach has potential pitfalls. The first is that it is extremely expensive. Maintaining a technology lead alone is difficult and expensive; developing a drug at the same time significantly increases the expense and complexity of a company's operations.

The second pitfall is that this strategy stretches a company's focus. A hybrid company must be conscious of its core competency and expend its managerial, financial, and human resources to maintain it. To do that while attempting to forward integrate is very demanding. As hybrid models emerge, the key

challenge companies face is how to forward integrate (the same challenge that start-up product-development companies face). The following is a strategy for evaluating options of forward integration.

@h1:Strategy for Successful Forward Integration

@\$:Since many small biotechnology companies have their own products to develop, these companies all face issues of what to do when their initial products look promising enough to warrant further development. Many the firms must deal with this question in the near future, since the industry is maturing and more drug candidates are being developed.

The Strategic Decision Matrix (Table 10.5) is a conceptual framework to help executives and management teams of small biotech companies reach informed decisions about the strategic future of their company and its key products. The framework describes three major sets of variables directed at a company's internal capabilities that management should consider as the product passes through the drug-development value chain. These variables are related to the biotech company, its product and portfolio, and important external factors to which all companies are subject.

We have identified three basic options for the further development of the company's product. The executive team could consider licensing the product to another company, partnering with another company, or building in-house capabilities for bringing the product to market. By building in-house capabilities, a company can choose to develop these activities internally, including mergers and acquisitions, or control contractual arrangements with another organization. Thus, the ultimate decision involves a matrix matching these two broad areas: analysis of internal capabilities and options for the further development of the product. At the end of this process, the executives must weigh their decision in light of the added value to their company. Decisions may be different depending on the individual product or technology. A truly disruptive technology or blockbuster drug might drive the executive team to

develop pure in-house capabilities that will leverage its value rather than to pursue a licensing or partnership agreement. The ideal option will maximize the value of their company, leave it with the most independence, yet increase its attractiveness to both investors and potential acquirers.

A popular decision is for the company to license its product to a larger company for development. This creates an immediate revenue stream and credibility in the marketplace. Often a company must license its initial products at a lower value than perceived to raise capital for future development, validate its technology, and learn skills from its partner.

As the company grows and develops new candidates, it is more likely to forward integrate. According to Geron's CEO, Thomas Okarma, the way to build a company is to "vertically integrate by first renting activities (licensing) to create cash flow, and when you reach critical size, then make (build) in-house capabilities." [[Au: Source note?]]

On the other hand, when a company has a true disruptive technology or blockbuster drug, it may be wise to skip the licensing stage altogether, obtain financing, and build an independent sales and distribution network.

@bh:Case Study: Geron versus ICOS

@bt:Geron and ICOS are companies that have decided to forward integrate but have considered the variables in the Strategic Decision Matrix and have chosen differing business strategies.

Geron is a biotech company that has three proprietary platform technologies and has adopted the strategy of complete forward integration. As it develops its technologies and products, it is trying to do as little partnering as possible. According to Geron's CEO Thomas Okarma: "When you partner with pharmas, you are really selling assets. The only time you should partner is when you cannot access capital from the markets."

Geron has high risk tolerance in both its strategy and its technology. Geron is developing products based on its controversial stem-cell research and has also purchased the

rights to the cloning technology that developed DAHLi. Therefore, partnering is difficult because of the controversial, cutting-edge technology that they are developing.

George Rathman, an original founder of Amgen, created ICOS Corporation in 1989. ICOS is one of the few biotech companies established in the 1980s that have survived to launch their first product[[Au: Need to update]]. To stay alive the 13 years it took to bring its product to market, ICOS has chosen to colicense all the products it is developing. According to Mike Gallatin, the vice president and scientific director, this decision is based on the need to reduce risk. Because of the low probability of success but high financial return associated with drug development, he says, "I would rather have a 50 percent stake in two products than a 100 percent stake in one." [[Au: Source note?]]

@h1:Future of the Biotechnology Industry

@\$:Over the past 20 years, the biotechnology and pharmaceutical industries have evolved as a result of technology advances. This evolution resulted in changes in company strategy and structure. Initially, companies such as Amgen and Genentech sought to emulate the vertically integrated pharmaceutical companies. In the early 1990s, firms such as Incyte Genomics and Applied Biosystems sold tools and information to emulate the horizontal business model so successfully implemented by Intel and Microsoft in the PC industry. By the start of the 2000s, the poor profits in the horizontal models caused firms such as Millennium Pharmaceuticals to employ a hybrid strategy, in which they used the revenues from the technology to fuel their own drug-development programs.

It is likely that product companies will continue to capture the most value from the drug-development process. Although it is risky, such companies have the most sustainable business model once a drug is introduced. Opportunities will also probably continue to exist for horizontal business models as companies identify innovative approaches that create efficiencies and cost savings for drug-development companies. These companies, however,

will not be able to achieve extraordinary profits like Microsoft and Intel.

From these two views, the following trends appear.

@h2:Continued Forward Integration

@\$:Companies seeking to develop drug candidates, whether hybrid companies or product start-ups, are indicating that they will build in-house capabilities for all stages of the value chain. Companies that are active in research and development have a stated objective of commercializing their products because they gain increased value and profitability further down the value chain. The most value is created when a company demonstrates that a product shows safety and efficacy. Biotech companies typically start with a core capability in research and then acquire competencies in development. Thus, companies forward integrate to gain and control the rewards garnered downstream from commercialization. This trend toward forward integration will continue for three reasons:

@nls: 1. @nl:Many biotech companies have products in development. This suggests that these companies are looking to build their marketing and sales infrastructure. Many companies will do this.

@nls: 2. @nl2i:Since the critical inflection point for a drug's value is achieved after the drug passes Phase 2 clinical trials, most biotech companies will seek to bring their product to that point before seeking licensing or partnering arrangements. The forward integration to this stage will occur because inefficiencies in negotiating with large pharmaceuticals before this stage are likely to remain.

@nls: 3. @nlfi:Biotech companies have been validated by the investment community and are therefore able to obtain funding from the capital markets. These companies now have the resources to build infrastructure and bring products to market on their own.

@\$: Though the stated objective of the biotech companies is to bring products to market, most companies will not achieve this on their own. Once past Phase 2, they will license their drug

candidate or collaborate with other firms to bring the product to market. The stated objective of being able to bring a product to market simply increases the option value and improves a biotech company's position in negotiations with potential partners. George Rathman, the Chairman and former president and CEO of Hyseq, concurs: "You need to get a joint venture because the pay-off reduces thereafter." [[Au: Source note?]] The way to accomplish this is by having positive clinical data. Rathman further elaborated on this concept by saying that when negotiating a partnership, "you have to pose a credible threat of forward integration" to get fair value for a product.

## @h2:Increased Mergers between Biotechnology Companies

@\$:There will be more mergers and acquisitions in the industry. The M&A activity will continue between pharmaceutical and biotech companies but will be most prominent between biotech companies. This trend is predictable for two main reasons. First, the biotech companies that choose not to partner with pharmaceutical firms [[Au: Ref. as meant?]] will need to merge to achieve economies of scale in the value chain, particularly in clinical trials, manufacturing, and marketing and sales. Companies need to bring more than one product to market to achieve economies of scale. Second, by obtaining the acquired competencies, they will be able to make deals that they could not accomplish previously. These M&A activities will increase the option value for biotech companies and allow them to enter into negotiations and deals not possible or even considered earlier.

## @h2:Increased Global Partnerships

@\$:As biotechnology has been transformed into an information-driven industry, the boundaries for new companies have expanded. Regardless of location, companies can share the same information, such as genomic databases, to add value to the drug-development process.

The trend toward globalization of biotechnology will increase as opportunities for mergers and acquisitions are centered around coordinating activities on a global scale. For example, venture capital can be raised in Japan or Israel, while

managerial talent can be supplied from the United States and Germany. Target and lead development and pharmacology and toxicology tests can be outsourced and performed in India. The potential drug can then be licensed to a large pharmaceutical company that can shepherd it through clinical trials and market it around the world. Thus, each stage of the drug-discovery chain is optimized globally.

@bh:Case Study: Gilead-NextStar

@bt:The merger between Gilead Sciences and NextStar is an excellent example of both the value of embedded options in capital investments and the increasing trend toward globalization. In 1999, Gilead purchased NextStar, a biotechnology company based in Cambridge, England. The NextStar acquisition helped Gilead to round out its portfolio of infectious-disease and cancer products, as well as a new liposomal drug-delivery platform.

Because NextStar had a sales presence in Europe and Australia, embedded in the purchase was the option for Gilead to expand its products into these new markets. The value of this option was not lost on Gilead's CEO, John Martin: "We not only gain a new drug-delivery platform of proven liposomal technology, but the international resources to fully realize the commercial potential of future products in our combined pipeline." [[Au: Source note?]]

This international presence has led to further opportunities. In January 2001, Gilead entered into an exclusive partnership with Cubist Pharmaceuticals whereby Gilead will market Cubist's infectious-disease products in 16 European countries in exchange for licensing and royalty fees. [[Au: Update?]]

@bfn:<I>Source:<I>|en|www.gilead.com.

@h2:Continued Existence of Horizontal Models

@\$:There are compelling reasons for companies to continue competing in horizontal spaces on the value chain. First, product companies cannot effectively bring a product to market and be technology leaders. They will continue to outsource and buy

technology from horizontal companies, which will be the source of innovation within the industry.

Second, although platform companies have not generated sustainable profits, they generate immediate revenue and have the potential to provide an effective resource and financial base for becoming a hybrid company. Millennium Pharmaceuticals started as a target-validation platform company but now has adopted a hybrid strategy to bring drug candidates to market and achieve maximum value.

Finally, the shortcomings associated with the horizontal model are changing. More and more biopharmaceutical products are entering the market, and biotechnology companies are establishing themselves as successful organizations with solid business models. It follows that the market for their products and the likelihood of reaching an agreeable valuation with pharmaceutical companies will improve, as is seen in the valuations of such companies as Millennium and Amgen. The market is realizing the value they are creating and bidding their valuation up accordingly [[Au: Update?]].

@h2:Continued Evolution of Virtual Corporations

@\$:The existence of niche horizontal companies creates the potential for virtual vertical companies to evolve. Virtual corporations control the activities of many smaller firms and synthesize the information obtained in a central location. Evidence of this trend is seen in larger firms, such as Pfizer and Pharmacia, which may evolve into virtual corporations and organize networks of the best firms around them. The information network of the biotechnology industry will allow this scenario to happen because companies can combine, cooperate, and disassemble more easily and quickly than in the past.

A notable difference between the biotechnology industry and other industries is the ability of smaller companies to more easily sustain themselves. In the microelectronics, personal computer, and Internet industries, smaller companies are often swallowed or worked around by larger companies. However, smaller companies in the drug-development industries show more staying

power and can remain independent because of the regulated nature and complexity of the industry, as well as the protection of patents.

Because of the complexity of the landscape, the ability to synthesize information and orchestrate technologies to provide solutions will be an important source of value creation. Tremendous opportunity exists for virtual companies that are brokers in high-quality networks and can control a network hub. Large pharmaceutical companies may be the best candidates to pursue a virtual strategy. First, they have established consumer-brand equity. Second, the large pharmaceutical firms are maintaining their ability to shepherd products through clinical trials. Finally, they are developing the expertise to manage a large network of companies as they attempt to participate in "plug and play" with the best available companies for particular projects.

@h1:Conclusion

@\$:As the biotechnology industry has matured since its inception in the late 1970s, one fact has remained constant—the biology creates the profits. Those companies that create safe and effective drug therapies capture the most value and are the most successful. Throughout the past 20 years, firms have employed strategies for capturing profits. Some models, however, did not achieve a level of extraordinary profitability. This reaffirmation that the largest financial gains come from developing products will drive horizontal, platform companies to develop drug candidates.

@h1:References

@r:Arader, Harry. Northwestern University TechVenture Lecture (March 6, 2001).

Barron, David P. <I>Business and Its Environment.<I> 2d ed. Prentice Hall, 1996.

Bernstein, Karen. "The Deal-Maker." <I>BioCentury<I> (December 12, 1994).

\_3\_. "Post-Industrial." <I>BioCentury<I> (June 26, 2000).

Bernstein, Karen, et al. "Big Thinkers II." <I>BioCentury<I> (June 15, 1998).

Bernstein, Karen, and Michael Schuppenhauer. "Back to Fundamentals." <I>BioCentury<I> (January 8, 2001).

Calkins, Kathryn. "Millennium's Product Plays." <I>BioCentury<I> (October 15, 1999).

Coase, Ronald. "The Nature of the Firm." <I>Economica<I> (1937). Reprinted in Coase, Ronald. <I>The Firm, the Market, and the Law.<I> Chicago: University of Chicago Press, 1988.

Davidow, William H., and Michael S. Malone. <I>The Virtual Corporation.<I> HarperCollins Press, 1992.

Eisenberg, D.M. "Medical Malpractice Implications of Alternative Medicine." <I>JAMA<I> (November 11, 1998).

Feldbaum, Carl. "Primer: Genome and Genetic Research, Patent Protection and 21st Century Medicine." <I>BIO, Issues & Policies<I> (July 2000).

Garber, Ken. "Homestead 2000: The Genome." <I>Signals Magazine<I> (March 3, 2000).

Heron, Elaine, and David Greeting. Applied Biosystems Presentation (March 14, 2001).

Kelly, Kevin. <I>New Rules for the New Economy.<I> Viking Press, 1998.

National Bioethics Advisory Committee. "Research Involving Human Biological Materials: Ethical Issues and Policy." <I>Guidance,<I> Vol. I, <I>Report and Recommendations of the National Bioethics Advisory Commission,<I> August 1999.

Naude, Alice. "Focus Report: Pharmaceuticals/Drug Discovery 99: Contract Research Organizations Grow from the Core." <I>Chemical Market Reporter<I> (August 16, 1999).

Rogoski, Richard R. "Firms Meet Biotech, CRO Software Needs." <I>Business Journal<I> (March 24, 2000).

Rohde, Laura. "Smart Cards to Contain Biometric Data." (February 9, 2000).

<http://www.cnn.com/2000/TECH/computing/02/09/biometrics.card.idg>

Rosen, Ben. "Keynote Address at the 1999 Biotechnology Industry Organization Conference" (May 18, 1999).

Sawhney, Mohan. "Net Economy Boundaries: Use 'Em and Lose 'Em." *Business 2.0* (July 11, 2000).

\_3\_. "Seeing Ahead by Looking Back: Lessons from Network Evolution and Implications for the Internet." [[Au: Publication?]](February 2001).

Scott, Randy. "Incyte Genomics Chairman Predicts New Phase of Genomics-driven Discovery as Science Harnesses Knowledge of Gene Transcripts and Proteins." *Incyte Genomics Press Release* (2000).

\_3\_. "Testimony of Randall Scott." *Subcommittee on courts and Intellectual Property. Committee of the Judiciary, House of Representatives* (July 13, 2000).

SNP Consortium. <http://snp.cshl.org>.

U.S. Food and Drug Administration. *Prescription Drug User Fees* (February 13, 2001).

U.S. Patent and Trademark Office. *Technology Profile Report, Patent Examining Technology Center, Groups 1630-1650, Biotechnology 1/1977-1/1998*, April 1999.

U.S. Patent and Trademark Office. "Utility Examination Guidelines." *Federal Register* (January 5, 2001).

Van Brunt, J. "Pharma's New Vision." *Signals Magazine* (June 1, 2000).

Waxes, Stephan Beckert. "Poetic about Telematics." *Executive Insights: Strategis Group*. [[Au: Date?]]

Werth, B. *The Billion Dollar Molecule*. New York: Touchstone, 1994.

Wolk, Marianne, and Bryan Candace. "Wireless Data-The Next Internet Frontier." *Robertson Stephens Technology Research* (January 25, 2000).

Yoffie, David. "Chess and Competing in the Age of Digital Convergence." *Competing in the Age of Digital Convergence*. Harvard Business School Publishing, 1997.