Harvard Business School
Case Selections (Reprint)

哈佛商学案例精选集

（英文影印版）

实务系列
From the Field

# 生物制药业

# INSIDE Biotechnology & Pharmaceuticals



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From the Field

# *INSIDE* BIOTECHNOLOGY & PHARMACEUTICALS

Harvard Business School Publishing

# SERIES INTRODUCTION

Welcome to this entry in the *From the Field* series of case collections from HBS Publishing. We have three main objectives for this series:

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The Editors

# INTRODUCTION TO THIS COLLECTION

Each item in this collection has been chosen because it reveals important elements that shape today's biotechnology and pharmaceuticals industries. Each of the seven items is introduced with a summary and followed by a set of "Questions and Ideas to Consider" that we hope will drive you to the Internet for more research!

We open the collection with a rich overview that asks the compelling question: "The Pharma Giants: Ready for the 21st Century?" This piece looks at changing competitive dynamics in the industry and introduces key themes that appear in the subsequent case studies.

We've put "Eli Lilly: The Evista Project" first among the cases because it touches on several of those key themes – especially the time-to-market challenges facing the pharmaceutical industry – in a concrete and compelling way. A case on Merck's integration of Medco provides perspective on the critically important "pharmacy-benefit manager" sector of the industry. Through the next three cases – on Novartis, Biopure, and Millennium – we explore some of the changes being wrought by the new science of genomics.

We close with a brief but cogent piece from *Harvard Business Review* that argues that marketers need to have greater power in the modern pharmaceutical industry.

**Did You Know?**

**HBS Publishing has many other recent cases on biotechnology and pharmaceuticals. Here is just a small sampling of cases published since 1997:**

- The Upjohn Company: The Upjohn-Pharmacia Merger 197-034
- Genzyme Genetics 797-073
- Eli Lilly and Co.: Drug Development Strategy (A)&(B) 698-010; 698-026
- Ajinomoto Co., Inc. 900-016
- CVS: The Web Strategy 500-008
- Kendle International, Inc. 200-033

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# RESEARCHING COMPANIES ON THE WEB

As you read the cases in this collection we are sure you will want to conduct research using a variety of Internet sources. Obviously, it always makes sense to visit the Web sites of companies profiled in these cases, since that is often the handiest way to gather basic information about current lines of business, marketing campaigns, and recent financial performance. But there is a wealth of information available on other sites, too. Below we list a number of Web sites that provide information about public companies, much of which is available free of charge.

Business-information sites we've come to like:

- Hoovers.com for basic company profiles, including lists of key subsidiaries, executives, and competitors.

- The "News and Media" section of hotbot.com, a regularly updated archive of items from many news sources.

- Kompass.com for information on foreign companies.

- For information on and discussions of technology companies, magazines run some of the most useful sites, including redherring.com and thestandard.com.

- Quicken.com, Smartmoney.com, Dowjones.com, and the "Business and Finance" section of Yahoo.com, for clear, readable presentations of key financial performance data and access to useful screening tools.

- CBS Marketwatch.com or – by paid subscription – wsj.com, for breaking financial news.

A final note about currency: At certain points we will tell you what we found at particular Web sites while we were putting this collection together. We apologize for any out-of-date directions and "dead links" you may find, but such is the transitory nature of certain information on the Web.

# CONTENTS

# THE PHARMA GIANTS: READY FOR THE 21ST CENTURY?

(R.H. Hayes / #9-698-070 / 34 p)

## Summary

Presents the changing competitive dynamics in the global pharmaceutical industry and possible implications for large drug companies.

Harvard Business School

9-698-070
May 6, 1998

# The Pharma Giants: Ready for the 21st Century?

*The primary challenge facing the pharmaceutical industry is accepting the fact that superior economic performance in the new millennium will require a new way of thinking. Relying on blockbuster drugs is no longer enough. In the future, companies must develop a mindset and culture of cost consciousness as well as an understanding of the critical role of marketing and sales, the need to use technology to improve every aspect of the organization, and the fact that every individual can make a difference.*

—A.T. Kearney report[1]

*Over the past few years, the big-pharma companies have been playing . . . a giant game of pac-man—eat or be eaten. Firms have been swallowing one another in a search for economies of scale (and, all too frequently, a desire to purchase a pipeline with the profits of one or two blockbuster drugs, to compensate for internal research failures). . . . Meanwhile, the proliferation of small biotechnology firms suggests that those economies of scale count for less than they used to, and that barriers to entry are dropping.*

—*The Economist*[2]

As the end of the twentieth century drew near, the giant companies in the $222 billion[3] global pharmaceutical industry faced a potent dual threat to their hegemony. While governments and large institutional buyers continued to exert strong downward pressure on drug prices and company earnings, a scientific and technological revolution promised to change the way in which drugs were discovered, developed, and tested, and in the process to expose the industry to a wave of new competitors. These might look nothing like the pharma giants of old, the huge, vertically integrated centenarians that historically had done everything from basic research through development, manufacturing, marketing, and distribution. Instead these competitors could be small, fleet of foot, highly specialized, and free from tradition.

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[1] "Maximizing Pharmaceutical Health in the Next Millennium: A Prescription for Shareholder Value," A.T. Kearney, Inc., 1997, p. 27.

[2] Geoffrey Carr, "Survey of the Pharmaceutical Industry," *The Economist*, February 21, 1998, p. 16.

[3] Source: IMS Pharmaceutical World Review.

*Senior Research Associate Perry L. Fagan prepared this note from published sources under the supervision of Professor Robert H. Hayes. The authors wish to thank Professor David Collis of the Yale School of Management for his contributions to this note.*

## Turmoil in the Early 1990s

Traditionally, the global pharmaceutical industry was characterized by rapid growth, high profits, and competitive stability, even while showing dramatic innovation. The industry had been one of the most profitable in the world measured by standard accounting practice, although economic returns (i.e., returns adjusted to recognize R&D as an asset) were in line with the industry's cost of capital.[4] The industry was highly fragmented, with hundreds of pharmaceutical companies competing in more than 20 different therapeutic categories, and no one company controlling as much as 5% of industry sales.[5] (See **Exhibit 1** for worldwide market share data.) Nevertheless, a few giants, including Merck, Bristol-Myers Squibb, and Glaxo, had dominated their respective therapeutic categories for over half a century, and typically had not competed on price for leadership of individual categories. (See **Exhibit 2** for a comparison of pharma giant sales by therapeutic category.)

However, in the early 1990s, pharmaceutical company sales and earnings growth slowed dramatically. Company stock valuations fell precipitously: between 1991 and 1993 market capitalization for drug stocks plummeted by 35%. (See **Exhibit 3** for price movements of pharmaceutical stock indexes.) Downsizing followed. Merck, for example, announced it would reduce its workforce by 5% during the 1990s, while Pfizer announced plans to reduce its workforce by more than 10%.[6]

In the United States, which represented one-third of the world pharmaceutical market, pressure to reduce drug prices came from the growth of managed care organizations (MCOs), which sought to control prices through restricting the number of drugs offered to patients in a particular therapeutic category. In 1980 only 5% of the insured U.S. population was covered by managed care. By 1993 this figure had risen to 80%. Similarly, while in 1960 only 4% of prescription drug sales were funded by third-party payers, by 1995 MCOs alone accounted for 75% of drug purchases.[7] Increased buying power enabled MCOs to extract large price concessions from drug manufacturers.

Indeed, cost containment was the "name of the game" among health care payers worldwide. In the United States, virtually all health maintenance organizations (HMOs) used formularies, or lists of approved medicines, to control costs. In 1997 an estimated 65% of HMOs used "closed" formularies, which limited payment to those drugs listed on the formulary. This figure had risen from 52% and 35% in 1995 and 1994, respectively.[8]

Pharmaceutical manufacturers were also under attack from generic substitutes for their flagship patented drugs, priced typically at a 30% to 90% discount to brand-name drugs. Generics' share of the U.S. prescription drug market rose from 19% in 1984 to over 40% in 1996.[9] By 1996 an

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[4] One study estimated a rate of return on new drugs introduced between 1954 and 1978 of 21% (compared to a cost of capital of roughly 11%). See Meir Statman, *Competition in the Pharmaceutical Industry: The Declining Profitability of Drug Innovation*, Washington, D.C.: American Enterprise Institute, 1983, as quoted in Gary P. Pisano, *The Development Factory: Unlocking the Potential of Process Innovation*, Harvard Business School Press, 1997, p. 55. Several academic studies found that, once the industry's economic returns were adjusted to recognize R&D as an asset, returns were commensurate with the industry's cost of capital. See Grabowski and Vernon, "Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics*, Vol. 13, November 1994, pp. 383-406.

[5] See Dale O. Cox, Greg Keller, Anita McGahan, and John F. McGuire, "The Pharmaceutical Industry in the 1990s," Harvard Business School Case No. 796-058.

[6] See Pisano, *op cit.*, p. 57.

[7] *Ibid.*, p. 60.

[8] Source: PhRMA, *op. cit.*

[9] Source: IMS America, 1997.

estimated 86% of HMOs routinely substituted generic products for patented drugs when possible.[10] In a radical departure from normal pharmaceutical pricing, Eli Lilly became the first company to guarantee to match the Tariff price of a generic with a branded product.[11]

The growth of generics had been fueled by the 1984 Waxman-Hatch Act, which reduced the barriers to generic entry by accelerating the approval process for the drugs. Instead of forcing generic drug makers to conduct their own lengthy and costly clinical trials, Waxman-Hatch mandated they show only that their drugs were chemically and biologically equivalent to the original patented versions. Whereas before Waxman-Hatch generic entry had taken years, after Waxman-Hatch generic substitutes began appearing in the market immediately after branded drugs lost patent protection, giving drug makers less time to recoup their research and development costs. The industry faced the expiration of patents on many blockbuster drugs: 42 major drugs by 2002, which would cost the industry $32 billion in revenues.

Pharmaceutical companies also came under political attack following U.S. President Bill Clinton's election in 1992. The Clinton administration and many in Congress were highly critical of pharmaceutical companies for their high profit margins and their alleged contribution to runaway U.S. health care costs. Shortly after taking office, Clinton initiated a review of the entire U.S. health care system, which although not implemented, recommended a new system of federal controls on health care, including price controls on prescription drugs.

By the mid-1990s, price pressure had extended to Europe where governments had traditionally played a more direct role in the medical system. In 1994, the German government, having increased patient copayments the year before, imposed a 5% price reduction on many drugs. Drug sales subsequently declined 15% to 20% in the world's third-largest drug market. Price cutbacks initiated in Italy in January 1994 were expected to reduce annual state-reimbursed drug costs by one-third. Expectations for 1995 were that the combined pharmaceutical markets of the United Kingdom and Germany would grow by 3% to 4%, that of Spain would remain flat, and those of France and Italy decline by 1% and 9%, respectively. The Japanese government had also been reducing reimbursement amounts for prescription drugs, and this continued through 1997, when drug sales in Japan fell by 1% to $41.7 billion.[12]

## Rising Cost and Complexity

Downward pressures on prices coincided with growing complexity in drug development and approval cycles, which drove up R&D and capital expenditures. Industry R&D expenditures grew to $18.9 billion in 1997. In the United States, R&D as a percentage of sales rose to 21.2% in 1997, up from 15.9% in 1990, and 11.7% in 1980.[13] (In contrast, the average R&D to sales ratio for U.S. industries was less than 4%).[14] (See **Exhibit 4** for R&D and capital expenditures of the large pharma companies.)

The high risk and research intensiveness of the pharmaceutical industry made drug development costly. According to one estimate, as much as 50% of all development dollars were expended on products that never reached the market.[15] Only one in 5,000 compounds reached an end user. Of these, only 30% achieved the commercial success necessary to recover an average

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[10] *Ibid.*

[11] "GW's $2bn Golden Egg Loses its Lustre," *Community Pharmacy*, November 1997, p. 27.

[12] Daniel Green, "Prescription drug sales rise 6% to 166bn," *The Financial Times*, March 5, 1998.

[13] Source: PhRMA 1997 Annual Report.

[14] Source: PhRMA, *op. cit.*

[15] *Ibid.*

research investment. A study released in the early 1990s estimated that $359 million and approximately 10 years were required to move a drug from test tube to end user, compared with approximately $250 million in the mid-1980s. Total drug development time grew from an average of 8.1 years in the 1960s, to 11.6 years in the 1970s, to 14.2 years in the 1980s, to 15.3 years for drugs approved from 1990 through 1995.

Clinical trials—which in Phase 1 involved 50 to 100 healthy individuals, in Phase II 200 to 300 potential patients, and, in Phase III, more than 3,000 individuals in some cases—accounted for two-thirds of total product development costs. Firms applied to the authorities upon completion of testing and could begin marketing upon notification of approval.[16] The cost of worldwide testing for an initial application of a new product was estimated to be $20 to $75 million. Approval by local governments added another $1 to $2 million per country or region ($5 to $6 million in Japan).

The drug development process was monitored carefully by the U.S. Federal Drug Administration (FDA) and comparable institutions around the world. Rejection of one of the applications required at each stage of the drug development process or other regulatory delays could jeopardize the scheduling of a series of interdependent activities and greatly delay time to market. For a "blockbuster" drug, one day's delay could mean well over $1 million in lost revenues. Although the United States led the world in drug discovery and development, 67% of drugs approved in the United States between 1990 and 1996 were marketed abroad first. The U.S. FDA had been criticized for the length of its review process and was working to speed up its review of new drug applications. Mean FDA approval times for new drugs fell to 17.8 months in 1996, down from 19.2 months and 30.3 months in 1995 and 1991, respectively.[17]

Marketing expenditures in the industry also seemed set to grow. It was still important to have large sales forces to detail doctors and explain product features and benefits. However, in fall 1997 the U.S. FDA changed the advertising rules for prescription drugs. Although firms had been allowed to take their messages directly to consumers in magazines for roughly a decade, there had been strict guidelines for ad content. For instance, warnings for drug side effects had to be prominent in print ads, while in TV ads there was usually no identifying information for a drug, only a description of symptoms followed by encouragement to see a doctor if those symptoms appeared.[18] Under the new regulation, marketers of pharmaceuticals were allowed to name a prescription drug and the illness it treated in direct-to-consumer television advertisements. One of the first drug makers to take advantage of this change was Hoechst Marion Roussel, which launched a new TV ad campaign for its prescription antihistamine Allegra. Many observers believed that relaxed federal rules for consumer advertising would help firms increase pharmaceutical sales, and they expected advertising expenditures to increase significantly.

Pharmaceutical companies responded to these circumstances by challenging the success potential of products and compounds through centralized decision-making at the top management level, and by implementing control systems that would allow them to coordinate far-flung R&D activities. Ultimately, the major challenge for managers in the industry continued to be to mediate the legendary conflicts between R&D, production, and marketing.[19]

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16 For a complete discussion of the drug discovery, development, and approval process, see Cox, Keller, McGahan, and McGuire, *op. cit.*, pp. 5-6.

17 *Ibid.*

18 "Advertising drugs: pill pushers," *The Economist*, August 9, 1997, p. 56.

19 This section adapted from Jean-Pierre Jeannet, Carin-Isabel Knoop, and Michael Y. Yoshino, "Ares-Serono Abridged," Harvard Business School case No. 9-396-104.

## Increasing Scale and Scope

Intensified competition and price pressures in global pharmaceutical markets fueled merger and acquisition activity in what remained a highly fragmented industry. In 1995, even industry leaders Merck and Glaxo only claimed 3.5% and 4.4% of global market share each, respectively (1.3% earned a firm a place among the top 20). Through mergers and acquisitions firms sought global scale and scope advantages in research, manufacturing, marketing, and distribution. Merck, Eli Lilly, and SmithKline Beecham integrated *forward* by purchasing pharmaceutical benefits managers to gain greater control over drug distribution channels.[20]

Firms like Glaxo and Wellcome, Sandoz and Ciba Geigy, and Pharmacia and Upjohn merged. The pooling of product portfolios, referred to as "one-stop shopping," extended manufacturers' coverage of therapeutic areas to afford greater clout with managed care customers. Acquirers instantly gained new products and customers and realized opportunities to reduce costs by rationalizing, for example, sales forces and manufacturing and R&D facilities. (See **Exhibit 5** for mergers and acquisitions in pharmaceuticals.)

Other firms like Merck and Pfizer decided not to merge and to instead rely on their own R&D programs to fuel growth. They divested themselves of unrelated businesses, ramped up their investment in R&D, and rededicated themselves to producing blockbuster drugs through "breakthrough" research.

Firms also attempted to leverage their marketing and distribution resources by acquiring technology from external sources through licensing agreements, R&D contracts, joint ventures, equity investments, and other forms of collaboration. From 1986-1993 the number of strategic alliances in the pharmaceutical industry increased from 121 to over 400.[21]

Finally, in an effort to further reduce costs in the health care system, HMOs, first in the United States and later in Europe, began seeking ways to manage disease comprehensively, rather than by component part. Supported by pharmaceutical companies, HMOs began offering "disease management programs," which offered comprehensive disease treatment guidelines for health care providers and patients. An executive at Eli Lilly defined disease management as follows:

> [Disease management was] an integrated system of customized interventions, measurements, and refinements to . . . processes of care designed to optimize clinical and economic outcomes within a specific disease state by facilitating proper diagnoses, maximizing clinical effectiveness, eliminating ineffective or unnecessary care, using only cost-effective diagnostics and therapeutics, maximizing the efficiency of care delivery and improving continuously.[22]

Pharmaceutical companies used disease management programs to demonstrate the cost effectiveness of prescription drugs relative to hospital-based care, and to combat poor compliance

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[20] Pharmaceutical benefits managers (PBMs) typically provided a range of services to large self-insured employers, insurance carriers, managed care organizations, and other private and governmental institutions that provide prescription drug coverage to their employees, retirees, or members. PBM services included assisting in the design of pharmacy benefit plans; processing prescription drug claims submitted for plan members from retail pharmacies; reviewing prescriptions to prevent drug interactions; implementing programs to encourage the use of lower-cost generic and brand name drugs; and dispensing drugs through mail service pharmacies. For a detailed discussion of PBMs, see Marie Bell and V. Kasturi Rangan, "Merck-Medco: Vertical Integration in the Pharmaceutical Industry," Harvard Business School Case No. 598-091.

[21] Source: Windhover's Pharmaceutical Strategic Alliances, 1997.

[22] William C. Castagnoli, "Disease Management—Background," *Medical Marketing & Media*, January 1995.

rates for patients taking prescription drugs. Poor compliance was common across all chronic medical conditions, particularly when patients were asymptomatic, and encompassed a wide variety of behaviors: underuse (especially the failure to fill or renew prescriptions), overuse, the mistiming or skipping of doses, the sharing of drugs with family members, or the consumption of food or liquids that interacted with the prescribed drug. Poor compliance was believed to have large economic costs, as measured by the increased frequency of hospital admissions and readmissions, and costs associated with poor preventative health care (See **Exhibits 6 and 7** for patient noncompliance data; and **Exhibit 8** for types of disease management programs.) Disease management also went by other names—"population-based management of care," "disease state modeling," "outcomes management," and "care mapping."

Organizationally, pharmaceutical companies engaged in disease management in three basic ways. First, some companies used disease management programs as a "value-added" service to augment their traditional national accounts sales structures, which handled sales to hospitals, HMOs, and other group purchasers. Second, other firms like Merck, SmithKline Beecham, and Eli Lilly, developed and distributed disease management programs through their PBM subsidiaries. Third, firms set up separate subsidiaries to offer disease management programs, with the intent of making disease management a new, separate line of business unrelated to pharmaceuticals.

Some industry observers viewed disease management as an attempt by pharmaceutical companies to escape commodity status. According to a senior vice president at Merck-Medco Managed Care:

> Pharmaceuticals appear[ed] headed for commodity status pushed by generics, formularies, and other cost pressures. Regardless of lowering prices there [wa]s an upside for drugs. They represent[ed] only seven percent of the health care bill and through disease management, they c[ould] draw funds from less efficient treatment methods [such as] hospitalization, surgery, etc. A pharmaceutical company c[ould] get itself out of the commodity/price box by seeing itself as a manager of health. It c[ould] draw off some of that 93% of non-drug spending to itself and at the same time save money for providers based on the cost efficiencies of pharmaceuticals and the contribution they make to the efficient management of the disease.[23]

## New Science and Technology

While pharmaceutical companies attempted to cope with major changes in the drug market, a revolution in science and technology was changing the way drugs were discovered, developed, and tested. Advances in genetics, molecular biology, and biochemistry created new competitive dynamics.

The revolution in molecular biology had two important effects on pharmaceutical research and development. First, it offered new techniques for working backward from known disease biochemistry to identify or design chemical "keys" to fit the biochemical "locks" of that disease. This method, known as "rational drug design," stood the traditional approach to drug discovery on its head. In the past, drug discovery occurred through the random screening of large numbers of organic chemical compounds (called libraries), the success of which was determined largely by chance. With the advent of rational drug design came the opportunity for firms to discover organic therapeutic compounds more quickly and efficiently than ever before.

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[23] William C. Castagnoli, "Is Disease Management Good Therapy for an Ailing Industry?" *Medical Marketing & Media*, January 1995.

In competitive terms, however, the potential advantage was limited by the fact that all firms drew from the same publicly available knowledge base, which opened the door to fast follow-on products that were therapeutically similar, but different enough on a molecular level not to infringe on patents. New drugs once enjoyed, on average, a five-year monopoly before a competitor emerged. By 1998, the window had shrunk to a year or less. (See **Exhibit 9** for declining exclusivity periods for patented drugs.)

Second, the molecular revolution allowed the development of an entirely new class of drugs based on protein molecules synthesized through genetic engineering. Substances based on organic (or natural) raw materials were replaced by bio-genetically engineered products using a technique developed by Herbert Cohen and Stanley Boyer at the University of California in 1973. Within months of their invention they had formed Genentech, the first biotechnology company. Genentech's first commercial product, a growth hormone, was developed by the company in the mid-1980s and approved by the FDA in 1985. Within a few years, several hundred biotechnology firms had been formed to undertake commercial R&D.[24] Companies like Genentech, Amgen, Chiron, and Genzyme were among the first to demonstrate that competitive barriers in drug discovery could be breached. In addition, regulatory changes such as the 1994 European Community decision to grant pan-European product approval for prescription drugs were making it easier for these entrants to take their innovations to market. Shortly thereafter, biotechnology developer Biogen launched its beta-interferon drug on a pan-European level without the benefit of individual country organizations.

Traditional pharmaceutical companies became buyers of drug candidates—and the companies that discovered them. Large drug makers initiated a series of partnerships, alliances, and takeovers of biotechnology companies in the early to mid-1990s. In September 1990 Roche purchased a 60% stake in Genentech, one of the biotechnology pioneers, in a deal valued at $2.1 billion. In January 1995 Ciba-Geigy acquired a 49% stake in biotechnology developer Chiron for $2.1 billion. In exchange for marketing rights under licensing agreements, drug manufacturers provided biotech firms with development funds, production facilities, and access to large existing sales organizations. Research-based firms were being led increasingly beyond their traditional therapeutic strongholds.

By 1997 worldwide sales of the top seven biotech firms had climbed to $6 billion, while worldwide sales of recombined proteins were estimated at $13 billion. (See **Exhibit 10** for the top seven biotech companies ranked by 1997 global sales.) Nevertheless, more than half of the approximately 1,200 biotechnology companies throughout the world in 1993 were located in the United States. Only 2% of these companies had sales of at least $200 million, although the companies with the leading products ranged widely in size. The vast majority were in the process of developing a first product and hence reported no sales. Industry losses climbed from $2.2 billion in 1990 to $3.6 billion in 1993. R&D expenditures increased from $2.8 billion to more than $5.7 billion over the same period. It often took eight to ten years and more than $100 million before a drug would be approved for marketing. Finally, because most biotech companies produced only one product at a time, plants often stood idle while active substances were under development. Nearly half of the biotech industry's capacity was believed to be idle in 1994.[25]

Advances in science and technology promised breakthroughs beyond rational drug design and genetically-engineered drugs. Combinatorial chemistry allowed new organic molecules to be produced in vast quantities for the first time. Using traditional methods, an individual scientist would have been able to produce 50 to 100 new compounds per year. Using combinatorial chemistry that chemist could produce on the order of 2,000 new compounds per year. Because success in drug discovery had been correlated strongly with the size of a firm's chemical library of molecules, large libraries were prized assets. Moreover, only large companies could afford to develop large libraries. Combinatorial chemistry brought large libraries within many firms' reach. Another technique called

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[24] See Pisano, *op. cit.*, pp. 64-65.

[25] Adapted from Jean-Pierre Jeannet, Carin-Isabel Knoop, and Michael Y. Yoshino, *op. cit.*, pp. 3-4.