

Opportunity for Efficiency

The fate of large investments and health of many people depend on the results of clinical studies. For one recent trial of a new therapeutic agent for breast cancer, the stakes seemed particularly high. Successful completion of the study would lead to marketing approval for the new agent, bringing women with breast cancer a promising new therapy. The new agent would provide simpler administration and, based on previous work, improve prospects of longer survival. It was the first major product developed by a small biotechnology company. The company's founders were confident that the agent worked well, but the study would stretch their resources to the limit. The company needed both to control expenses and to start generating revenues soon. If the trial succeeded, revenues from the approved product would make the company viable and secure the reputations and livelihoods of the company's principals. If the trial failed, it would destroy the company and derail several careers. The company would have only one chance to get the study right.

In planning discussions for the study, tensions ran as high as the stakes. The small company and the contract research organization (CRO) hired to conduct the study disagreed about how many patients the study required and where to find them. Confirmatory studies of oncology drugs must include detailed assessments of tumor size and progression. Treating and assessing each patient often cost more than \$15,000. Furthermore, quickly enrolling enough patients for such studies often presented major challenges. Despite budgets that frequently exceeded \$10 million, enrollment delays often caused cost overruns and extended studies beyond planned completion dates. It was hardly surprising that questions about the number of patients required and the best enrollment strategy dominated planning discussions.

Determining the appropriate sample size for clinical studies challenges even the most experienced clinical researchers. For this oncology study, the main determinant of sample size was the size of the treatment effect that the new agent was expected to have on cancer tumors. The greater the treatment effect observed during the trial, the smaller the sample required to provide enough statistical power to demonstrate a difference with the comparator, an existing product representing the standard of care. The smaller the treatment effect, the greater the sample required. However, estimates of treatment effect are at best educated guesses based on limited information.

The principals of the small company believed a strong treatment effect was likely, and thus the study would require relatively few test subjects. The principals were concerned that testing the drug on too many subjects would not only waste scarce resources but also extend the study and delay market entry and revenue generation. Even worse, a larger trial would require the company to raise additional money, imposing substantial delays and a high risk of losing control of the company to outside investors. The company also took an optimistic view of the ability to enroll patients quickly and economically, believing a handful of sites in the United States would be sufficient to meet study timelines for enrollment.

Having seen inadequate sample size undermine other oncology studies, the CRO's statisticians and medical officer focused on the risks of testing the new agent on too few patients. That would prevent the study from producing statistically significant results, wasting the entire effort, and jeopardizing the company's future. The CRO considered a larger sample size based on a more modest estimate of treatment effect prudent. Furthermore, from experience with other oncology studies, the CRO questioned whether the study could enroll enough patients quickly without involving more sites, including some sites in more affordable countries outside the United States.

Despite lengthy discussions, the sponsor and the CRO found it impossible to reach agreement on likely treatment effect, sample size, and enrollment strategy. Both parties considered walking away. The sponsor could easily find another CRO willing to conduct the study with a smaller sample size. The CRO could decline the business to avoid conducting a study doomed from the outset by flawed planning assumptions.

The Adaptive Solution

Instead, the CRO proposed using a technique never before used in a confirmatory study of an oncology product: to wait until midway through the study, look at the actual magnitude of treatment effect observed in enrolled

patients, and then use the observed magnitude to recalculate the sample size. Sample-size reestimation (SSRE) is one of the most common techniques in the emerging field of adaptive clinical research. To date, most adaptive techniques allow adjusting a variety of study design elements, such as sample size and ratios for allocating patients to different treatment arms, based on data collected during the study. The principals of the small biotechnology company agreed to the use of sample-size reestimation.

The sponsor also approved an adaptive enrollment strategy based on the CRO's system for real-time monitoring of data on recruitment progress. At inception, the study would use only sites in the United States, but the CRO would arrange for backup sites in Russia to come online rapidly if necessary. Adaptive enrollment belongs to a second class of adaptive techniques aimed not at midcourse optimizations of the study design but at optimizing key study operations based on performance metrics continuously derived from study data. Operational adaptations can adjust enrollment strategy, the approach to monitoring study sites, allocation of key resources, and many other aspects of study operations.

The CRO launched the study based on a larger, more conservative sample size, with provision for adjustment based on actual trial data when enrollment reached half the expected number of patients. Real-time data on recruitment progress soon showed the need to activate the backup sites in Russia. The additional sites quickly accelerated enrollment, hastening the date of sample-size reestimation. At the halfway point, study managers declared an interim database lock (restricting write access to the database preparatory to analysis). Techniques for rapid data validation and analysis enabled completing the interim lock in a single day. That same afternoon, analysis of actual study data showed that the treatment effect fell between the initial conservative estimate and the more optimistic estimate by the sponsor.

The good news was that a 25% reduction in sample size would allow meeting statistical goals and saving more than \$1,000,000 in direct costs. The bad news was that completing the remainder of the study in typical fashion would still cost more than the sponsor had hoped. The CRO recommended the use of adaptive monitoring for the balance of the study. Instead of sending monitors to visit all remote sites the same number of times at the same intervals throughout the study, study managers would allocate site visits based on need, as indicated by metrics on site performance, such as query rate, the number of queries outstanding, and the mean time to resolve queries at each site. Monitors would also use an electronic tool to facilitate their work on site. Without compromising data quality, adaptive allocation of site visits and advanced monitoring tools reduced the need for expensive monitoring personnel, the amount of travel required, and overall monitoring expenses.

In the end, three key adaptive elements—sample-size reestimation, adaptive enrollment, and adaptive monitoring—allowed completing the study within the sponsor’s budget and a year ahead of schedule. Shortening the study and reducing sample size saved a relatively modest \$1.9 million in direct expenses. The indirect benefits were much greater. The breast-cancer treatment was the first in its category to reach the market. It had sales of \$329 million in the first year. Reaching the market earlier allowed an additional year to market the product with patent exclusivity and, over time, generated an additional \$299 million in profit. Best of all, the new therapeutic agent is helping improve the treatment of women with breast cancer today.

This story about one small biotech and its CRO may point to a better future for an industry that has struggled to develop new drugs in recent years despite vast R&D expenditures. The disappointing output of new drugs leaves no doubt about the need for greater efficiency in clinical research. This book explains an approach that uses information and communications technologies together with methodological improvements to make clinical development much more efficient. These changes can help shape a brighter future for the pharmaceutical industry.

An Industrial Success Story

For decades, the pharmaceutical industry has enjoyed numerous and impressive successes, both scientific and financial. Among the most spectacular examples, HmG co-A reductase inhibitors (“statins”) have contributed to a dramatic reduction in deaths from atherosclerotic heart disease, long a leading cause of mortality in western nations.¹ More than 300 drugs are now available for the treatment of rare diseases (defined as those that affect fewer than 200,000 people in the United States); fewer than 10 such drugs existed before the 1983 approval of the Orphan Drug Act.² Drugs such as insulin sensitizers have allowed improving glucose levels for people with type 2 diabetes, bringing hope to approximately 160 million individuals worldwide.³ HIV was a uniformly fatal disease only a decade ago, but an individual diagnosed with the infection today has a life expectancy approaching that of the general population.⁴ A new generation of anticoagulants greatly reduces thromboembolic complications of orthopedic surgery and thus reduces the risk of myocardial infarction.⁵

Providing such compelling health benefits has brought the drug industry substantial rewards. For example, Pfizer’s Lipitor (atorvastatin, the leading statin drug) generated sales of \$83.5 billion from its introduction in 1997 through 2007. Lipitor sales for 2006 and 2007 were \$12.9 billion and \$12.7 billion, respectively.^{6,7}

Signs of Trouble Ahead

Despite such striking medical and financial successes, the pharmaceutical industry today faces a deepening crisis: inefficiency in its core business, the development of new drugs. Impressive increases in research-and-development (R&D) spending have failed to produce corresponding increases in the output of drugs that are truly new, that is, not reformulations or combinations of existing drugs. Industry investments in R&D totaled \$214.3 billion just in the period from 2004 to 2007, culminating in a record expenditure of \$58.8 billion in 2007, including expenditures by biotechnology companies.⁸ However, according to one analysis, although the industry has doubled its annual investment in R&D over the past decade, output of new drugs has fallen 60%.⁹ This is consistent with a decline in approved new drugs from 53 in 1996 to 23 in 2007, a drop that occurred while members of the Pharmaceutical Research and Manufacturers of America (PhRMA) increased R&D expenditures from \$16.9 billion annually to \$44.5 billion (Figure 1-1).

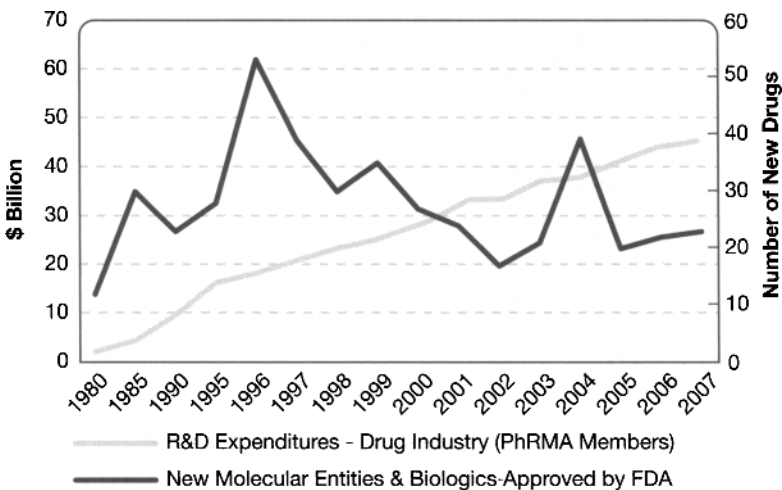


Figure 1-1. Expenditures to develop new drugs and biologics have surged in recent years to unprecedented levels but failed to increase output of approved novel products, that is, new drugs and biologics excluding reformulations and combinations of existing products.

Source: Pharmaceutical Research and Manufacturers of America, Food and Drug Administration Center for Drug Evaluation and Research.¹⁰

Critics charge the drug industry with exaggerating its R&D expenditures. They object to including indirect considerations such as potential gains from alternative investments.^{11,12} However, many businesses consider such

factors when making investment decisions. Furthermore, those estimating R&D costs argue that it is appropriate to assign a monetary value to time costs when any return comes only after lengthy periods of investment.¹³ Since the drug industry's out-of-pocket R&D expenditures have also increased significantly, there is no denying the general point: R&D expenditures have increased without a corresponding increase in the output of new drugs.

Converging Challenges

About 80% of the drugs that enter clinical trials never emerge and thus generate no revenues to offset development costs.¹⁴ Furthermore, the current round of development casualties comes as the industry faces an unprecedented series of business challenges, including:

- a proliferation of cost controls such as the formularies of private and public health insurers, which limit access to expensive new drugs;
- the rise of generic alternatives to brand-name products;
- a wave of patent expirations on an aging generation of highly profitable "blockbuster" drugs that sustain the industry's business model;
- the Food and Drug Administration's (FDA's) delaying or withholding approvals and requiring stronger warning labels following recalls of major medications such as Vioxx (rofecoxib).

Lipitor again illustrates. Pfizer reaped a bonanza from this blockbuster. Indeed, Warner Lambert's ownership of Lipitor inspired Pfizer's hostile acquisition of the company for more than \$90 billion in 2000.¹⁵ However, Lipitor's patent exclusivity begins to expire in 2010.* Pfizer was counting on its own promising candidate in the same therapeutic class, torcetrapib, to replace the revenues soon to be lost to generic versions of Lipitor and other statins. Pfizer's disappointing trials of torcetrapib had severe yet typical repercussions. After investing almost \$1 billion, Pfizer abandoned the drug in December 2006 without filing for regulatory approval.¹⁶ The announcement slashed Pfizer's market value by \$21.3 billion in a single day,¹⁷ precipitated layoffs, and underscored the risks of relying on a handful of blockbuster drugs. Pfizer litigated to delay the introduction of Indian manufacturer Ranbaxy Laboratories' generic version of Lipitor before Ranbaxy agreed to a 20-month delay in many markets.¹⁸ Pfizer's January 2009 agreement to purchase Wyeth for \$68 billion seems at least in part a response

* The first of a series of patents expires in March 2010, but because of ongoing litigation and other patents, precisely when market exclusivity in the United States will be lost remains unclear, and market exclusivity varies in different parts of the world. Most bets are that June 2011 will be the critical date. However, if Pfizer's recent deal with Ranbaxy stands, it puts that date in doubt in the United States.

to expected declines in sales of Lipitor and other drugs with expiring patents.¹⁹ Such maneuvers by Pfizer and other drug companies protect and extend exclusive market positions. However, expensive acquisitions are a poor substitute for the development and introduction of compelling new products. Mergers and acquisitions do not make a long-term strategy.

Disappointing trials hurt small companies even more than industry giants. Table 1-1 shows the harsh consequences of having a lead product fail in clinical testing.

Table 1-1. The effect of failed clinical testing of lead products on share prices of small companies.

Company	Lead Candidate	Indication	Share Price Effect
Renovis	NXY-059	Stroke	-76%
Nuvelo	Alfimeprase	Arterial obstruction	-79%
Telik	Telcyta	Lung, ovarian cancer	-71%
Dynavax	Tolamba	Ragweed allergy	-30%
Threshold	Glufosfamide	Pancreatic cancer	-57%

Source: San Francisco Chronicle, Mar. 11, 2007.²⁰

Like Pfizer, much of the drug industry clings to the blockbuster model despite growing evidence against its validity. Driven by cost concerns, especially as expressed through formulary preferences, sales of generics have flourished. In 2007, generics accounted for two-thirds of prescriptions written in the United States (Figure 1-2).

Many formularies already favor simvastatin, a generic version of Zocor, Merck's blockbuster statin. Simvastatin came off patent in 2006.²² Zocor's acceptance in formularies plunged after the introduction of a generic version. This foreshadows Lipitor's fate.

The Struggle to Replace Lost Revenues

In recent years, the drug industry has had far too many torcetrapibs and too few new Lipitors to sustain its current business model. Between 2007 and 2011, patents will expire on 14 major drugs, resulting in estimated losses of \$100 billion in sales of brand-name drugs to generic competitors.²³ No industry could easily replace such a huge loss of revenue. A recent analysis of 14 leading drug companies identifies corresponding peer groups of old drugs rolling off patent and new drugs coming on the market. A compari-

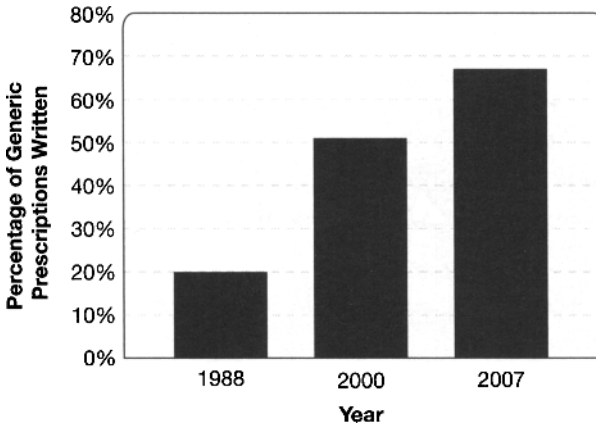


Figure 1-2. Prescriptions for generic drugs represented 67% of all prescriptions in the United States in 2007.

Source: The New York Times.²¹

son of expected revenues lost by the group of old drugs and gained by the new ones concludes that in 2007, the 14 firms generated only \$0.77 for each \$1.00 of lost sales. The worst is yet to come. The analysis projects a decline by 2012 to only \$0.23 in new revenue to replace each \$1.00 lost.²⁴ A 2006 report indicated Pfizer executives referred to the looming expiration of patents on five major drugs in a five-year period as “the cliff.”²⁵ Patent cliff has become part of the industry’s vocabulary.

The combination of rising generic sales, aging blockbusters, high development costs, and low success rates has taken a toll on the market capitalization of most large drug companies (Figure 1-3). Abbott was the only company whose market capitalization did not drop substantially between December 30, 2000 and June 30, 2008. It is probably not a coincidence that Abbott derives less than half of its revenues from pharmaceuticals. In another comparison over roughly the same period (December 2000 to February 2008), the stocks of 15 major drug companies lost \$850 billion in value.²⁶

Growth of the drug industry’s global profits has been slowing for almost a decade despite spectacular successes in the same period. Blockbusters like Lipitor, Plavix (clopidogrel), Advair (salmeterol/fluticasone), and Viagra (sildenafil) were not enough to reverse the trend. Between 2000 and 2007, the annual growth rate in global sales fell by almost one-half (Figure 1-4).

Although a declining growth rate raises concerns, a decline in revenues indicates a serious problem for any industry. IMS Health forecasts declining U.S. revenues for the drug industry in 2009. The industry has not experienced such a contraction for more than a half century. Murray Aitken,

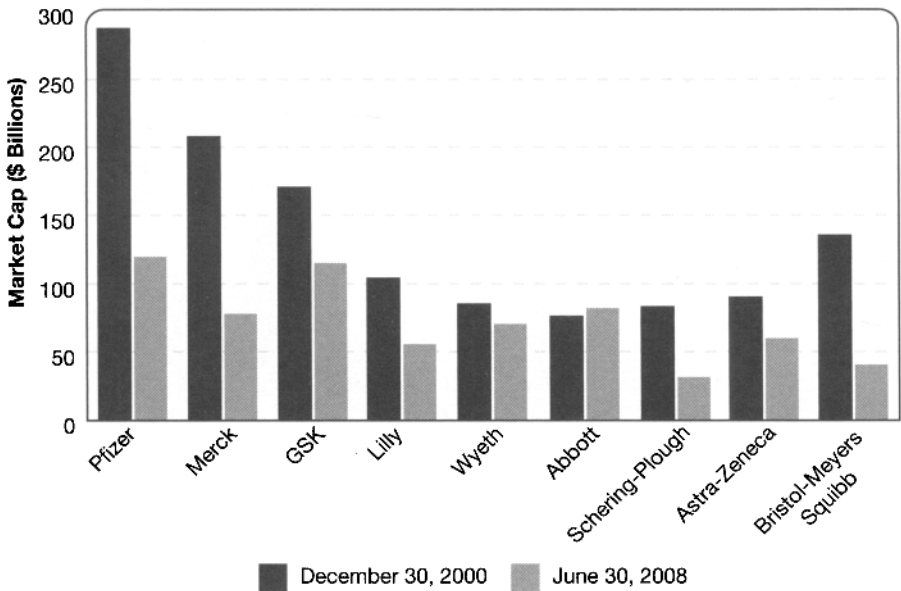


Figure 1-3. Almost all of the leading companies in the pharmaceutical industry saw their market capitalization decline substantially between December 30, 2000 and June 30, 2008, before the sharp across-the-board decline in financial markets in late 2008.

Source: CottonMoehrke Financial Group UBS; Wolfram Alpha LLC.

senior vice president of IMS Health, highlighted lack of innovation as an underlying issue. “It’s much more difficult now if you are not a very innovative product with a very strong clinical profile to be launching into a therapy area where leading generics are available, and expect to get a first-line position,” Aitken said.²⁸

The decline in revenues is but the latest sign that the drug industry should treat the disparity between R&D spending and output of compelling new products as an urgent problem. Certainly pharmaceutical development is expensive and inherently risky. Failure can happen anywhere on the long road from discovery through preclinical development, clinical testing, regulatory submission, and approval. Developing a new drug takes 10–15 years, failure is the norm, and the accumulating costs stagger the imagination. Four recent estimates of per-drug development costs are \$802 million,¹⁴ \$868 million,²⁹ \$882 million,³⁰ and \$1.65 billion.³¹ Although these figures include a variety of indirect costs, the out-of-pocket investments are themselves enormous, especially for clinical development (see below).

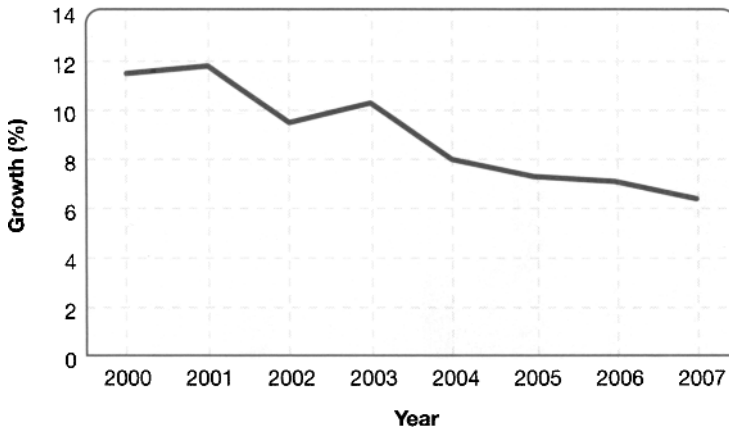


Figure 1-4. Global sales growth over previous year for pharmaceuticals. Between 2000 and 2007, the total world market grew from \$365 to \$712 billion, but the rate of growth fell by almost one-half.

Source: IMS Health Market Prognosis, Mar. 28, 2008.²⁷

Clinical Research Is the Key

Both costs and risks are greatest in the clinical stage of development. Most new drugs fail in clinical testing. Clinical studies also consume the bulk of the drug industry's out-of-pocket, per-drug R&D expenditures and development time. Clinical research accounts for 70% of the \$403 million in average out-of-pocket costs and 64% of average development time of 11.8 years¹⁴ (Figure 1-5).

Furthermore, the proportion of out-of-pocket R&D expenditures devoted to clinical studies is growing. Annual growth rates for out-of-pocket clinical R&D costs were 6.1% for approvals in the 1970s and 1980s and almost twice as great, 11.8%, for approvals in the 1980s and 1990s. Out-of-pocket preclinical costs declined from 7.8% to 2.3% on drugs approved in the corresponding periods.¹⁴

Thus, if the drug industry is to reduce the investment and time required to develop new drugs, clinical development demands scrutiny. There are two major ways to save on clinical development. The first is to conduct successful studies faster and in the process bring drugs to market at lower cost. The second, equally important given the high failure rate, is to find ways to identify drug failures earlier, before large, long, and expensive phase II and phase III trials. These trials consume most of the time devoted to clinical development, whether the therapeutic agent is a biologic or a more traditional compound³² (Figure 1-6). This makes a powerful economic argu-

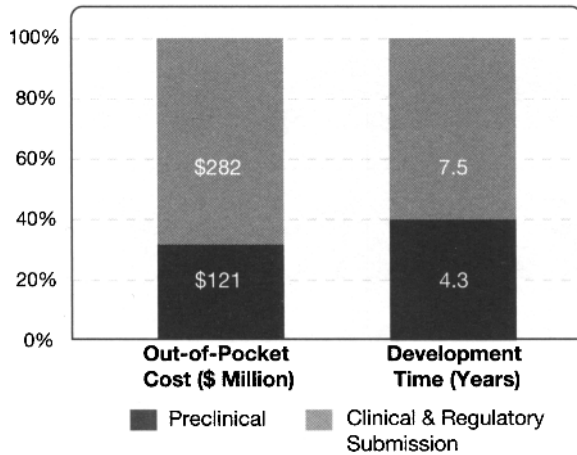


Figure 1-5. Clinical trials and submissions for regulatory approval account for an average of 70% of the direct costs of drug development and 64% of development time.

Source: DiMasi et al. 2003.¹⁴

ment for research methodologies that allow learning more about new drugs earlier in the development process. Every R&D budget should address the search for new methodologies as well as new drugs.

The comparable time required to develop biotech drugs—many from aggressive startup companies—suggests that pharma giants do not have a monopoly on inefficient development practices. The problem extends across different types of companies, therapeutic agents, and treatment classes. The time required to win approval does vary by therapeutic area. Oncology and neurological drugs (such as antidepressants and Alzheimer’s treatments) are most complex and take longest. Anti-infectives and gastrointestinal (GI)/metabolic drugs typically gain approval fastest. However, all therapeutic areas are experiencing longer timelines and disappointing approval rates.

Behind the High Costs of Clinical Development

Drug development has become considerably more complex in recent years. There are more studies, more subjects and procedures per study, and more restrictive criteria for entry into studies. Drug discovery is benefiting from the explosion of knowledge and technology associated with the genetics revolution, computational chemistry, and high-throughput screening. Preclinical timelines have decreased. However, longer clinical phases have offset preclinical gains, increasing overall development times.

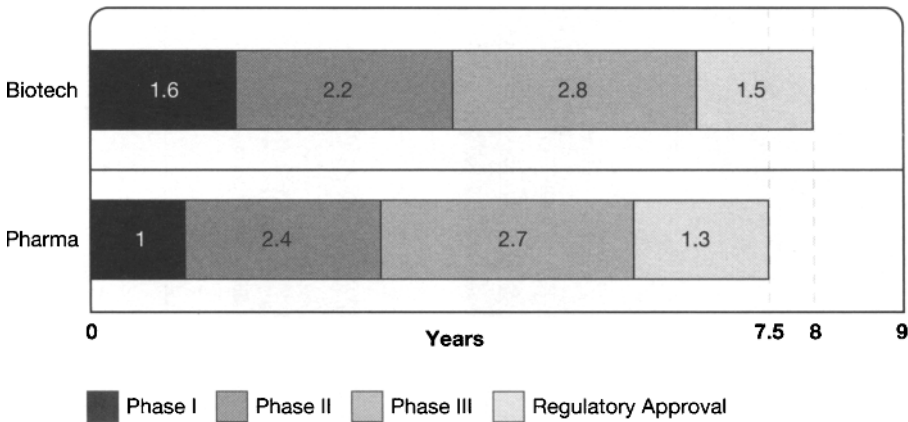


Figure 1-6. Expensive phase II and phase III clinical trials account for most of the time in clinical development.

Source: DiMasi and Grabowski 2007.³²

The growing size of clinical studies is a major contributor to growing costs. For example, the number of subjects involved in clinical testing for each submission to the FDA for approval of a new drug grew 562% between 1977–80 and 1998–2001, from 1,576 to 5,621³³ (Figure 1-7).

Increases in the number of inclusion criteria and the number of procedures required for each subject have also increased costs. The Tufts Center for the Study of Drug Development reports that the number of inclusion criteria for each study more than doubled between the 1999–2002 and 2003–2006 periods.³⁴ The same Tufts researchers obtained information from DataEdge showing large percentage increases in the number of medical procedures administered to each patient in phase I, phase II, and phase III trials from 1990 to 1997 (Figure 1-8). The largest increase, 120%, was in the number of procedures in large, expensive phase III trials.

Study protocols continued the trend of requiring increasing numbers of procedures between 1999 and 2005. The number of unique procedures across all therapeutic areas grew at an annual rate of 6.5%. In 2005, the median number of unique procedures per protocol in trials across all phases and therapeutic areas reached 35. The frequency of performing procedures grew even more rapidly, at an average annual rate of 8.7%.³⁵

High Costs and Increasing Prices

In sum, the complexity, magnitude, and cost of clinical testing have increased steadily in recent decades, driving R&D expenditures to new heights. The drug industry has maintained some growth in profits, but the

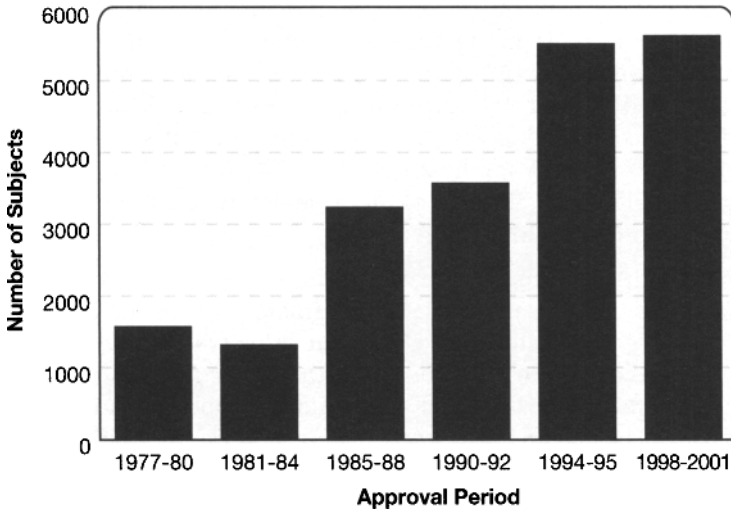


Figure 1-7. Mean number of test subjects in clinical trials for new drugs (new molecular entities or NMEs) by specified periods. The number of test subjects increased by a factor of 4 from the period 1981–1984 to the period 1998–2001.

Source: Boston Consulting Group, 1993; Peck, Food and Drug Law J, 1997; Parexel, 2002.³⁹

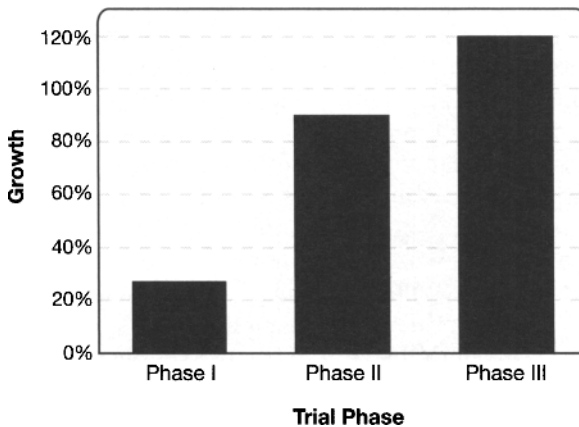


Figure 1-8. The number of medical procedures administered to each patient in clinical trials increased by large percentages from 1990 to 1997, especially in larger phase II and phase III trials.

Source: DiMasi et al. 2003.¹⁴

strain is evident. For example, pharmaceuticals have taken a larger and larger percentage of national health-care expenditures in the United States. During the decade of the 1990s, the average annual percentage increase in national expenditures for prescription drugs was 12%. That is double the increase in the same period for physician and clinical services and more than double the increase for hospital care. The annual expenditures are still increasing. However, the rate of increase declined from 15% in 2000 to 11% in 2003 and 6% in 2005³⁶ (Figure 1-9).

Prices for prescription drugs increased from \$28.67 to \$68.26 from 1994 to 2006, an average of 7.5% per year, approximately triple the annual rate of inflation. The average branded prescription price was higher still: \$111.02 in 2006. It is a reasonable inference that the drug industry has increased prices at such a rate at least in part to maintain some growth in profits. The rate of growth in profits has declined anyway. Although the industry argues that the treatments it provides remain less costly than surgical alternatives in some therapeutic areas, the trends in pricing and profitability speak for themselves. Presumably, the industry would rejoice if it could maintain growth in profits while moderating price increases. Reducing development costs and bringing greater numbers of new drugs to market would make this possible. Revenues would grow from additional sales of new products. The strategy of growth through price increases has given the industry a new set of problems (see below, “Cost of Inefficiency: Public Backlash”).

The prices of some innovative new oncology drugs have provoked extreme reactions. Patients believe their survival may depend on gaining access to the new treatments but costs are prohibitive. Erbitux (cetuximab), first used as a treatment for colon cancer, costs \$17,000 per month. Zevalin (ibritumomab), used to treat some rare forms of lymphoma, costs \$24,000 per month. Avastin (bevacizumab) costs \$4,400 per month.³⁸ A 2004 *New England Journal of Medicine* editorial noted that FDA approval of Avastin alone could add \$1.5 billion a year to the nation’s health costs.³⁹ *The New York Times* reported in July 2008 that the price of Avastin has increased to almost \$100,000 per patient per year, generating sales of \$3.5 billion globally, including \$2.5 billion in the United States. Yet the same article reports the drug prolongs life by only a few months, and recent research has called even this benefit into question.⁴⁰ The industry has indicated on many occasions that high development costs mandate such high prices for novel therapies. Nevertheless, high prices reveal the strain of high development costs.

The industry appears committed to substantial price increases as a strategy for growth despite hard economic times and widespread concerns about already unsustainable health-care costs. In April 2009, the industry increased prices on some drugs, including treatments for leukemia and erectile dys-

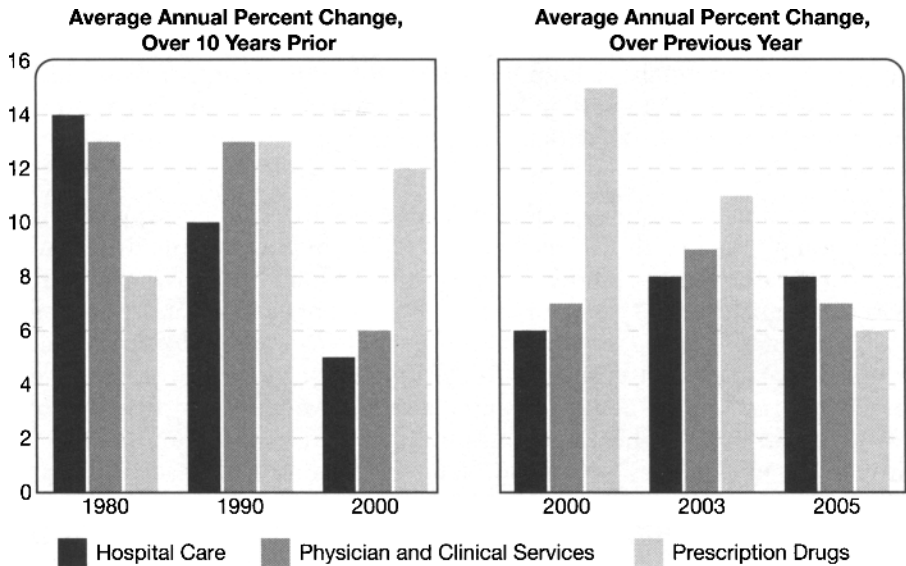


Figure 1-9. The drug industry has consumed an increasing percentage of national health-care expenditures, in part because of increases in prescription drug prices.

Source: Kaiser Family Foundation, Oct. 2004.³⁷

function, by more than 20%. Rates on other drugs increased by about 10%.⁴¹ The Consumer Price Index decreased 0.4% for the 12 months ending in March 2009, the first 12-month decline in more than half a century.⁴²

Cost of Inefficiency: Public Backlash

Aggressive price increases exact a cost in the goodwill of patients, health-care providers, and policymakers. Whether high drug prices fairly reflect actual development costs is debatable. However, there is no debate about how cancer patients react to such prices. When the monthly cost of some drugs can exceed the patient's annual income, many cancer patients believe they face the highwayman's ultimatum: your money or your life. The resulting outcries may exacerbate a backlash against the drug industry that is all too evident in public opinion surveys. Half of the U.S. public holds an unfavorable opinion of the industry, and one-quarter has a "not at all favorable" opinion.⁴³

Indeed, the public now ranks the drug industry with the pariahs of the business world. Like Big Oil, the drug industry ranks a little higher in public esteem than Big Tobacco. This result is startling for an industry in the business of providing treatments for human disease and suffering. How is it possible for an industry with this benign mission to earn public disdain

comparable to that of industries that sell lethal and addictive products or an essential and diminishing natural resource? Many people can remember a time when much of the public viewed the drug industry very differently. Today's corporate villain was once a modern miracle worker providing new classes of drugs with indisputable value, such as antibiotics and antidepressants.

The drug industry cannot dismiss measures of the public's disapproval as a reflection on the health-care system as a whole rather than the drug industry specifically. Surveys show the drug industry ranking below every other part of the health-care system in public esteem. For example, hospitals have a 78% favorable rating, of which 39% is very favorable. Physicians score even higher favorability ratings. In stark contrast, only 9% of Americans think pharmaceutical companies are "generally honest and trustworthy." No less than 69% of the American public considers high profits made by drug companies a very important factor in causing higher health costs.³⁷ The industry strategy of explaining high prices by simultaneously pointing to high development costs and running consumer advertising campaigns has not played well with the people who consume the products and the entities that foot the bill.

"Rightly or wrongly, drug companies are now the number one villain in the public's eye when it comes to rising health-care costs," according to Kaiser Family Foundation President Drew E. Altman. "People want to rein in the cost of prescription drugs, and just about anything we poll on with that aim gets public support."⁴⁴

Growing Pressures Mandate Greater Efficiency

Public opinion is not the only source of intensifying pressure on the drug industry to reduce development costs. Other noteworthy pressures include the trend toward segmenting populations by markers that predict response (genetics and proteins and metabolites), the sense that research has long since identified most potential "blockbusters," and growing competition from more nimble biotechnology companies and low-cost drug companies in emerging countries.

The Effect of Genetically Targeted Medicines

Despite its unquestioned benefits, the genetics revolution and its offshoots increase pressure for more efficient drug development. There are several reasons. First, with current methods, developing products such as recombinant proteins is even more costly than developing a conventional chemical compound. Developing a typical new biologic costs \$1.2 billion.³² Recovering such high development costs presents an enormous challenge. One of

the great scientific and medical by-products of the genetics revolution—the possibility of practicing individualized medicine based on the distinct genetic makeup of each patient—provides exciting benefits, such as increasing the odds of successful treatment and reducing the likelihood of side effects. However, the same genetic targeting also restricts the market for each product to patients with the appropriate genetic profile.

A recent analysis examines the likely effects on development strategy and market economics of the complex interplay between the benefits of such targeted medicines and potential economic drawbacks such as smaller market size. On scenarios characterized as “sustained future” and “bright future,” projected lifetime gross profit for such medicines declines from approximately \$4 billion today to estimated figures of \$2.15 billion and \$2.4 billion. The analysis takes an optimistic view on the ability to charge very high prices for such medicines. It concludes: “Stratified medicine changes the incentives for innovation, alters the drug and diagnostic development process, complicates regulatory review, and further extends the fragile reimbursement structure. But if all players adapt, patients will reap the benefits of better clinical outcomes, payers will spend less on ineffective treatments, and manufacturers will remain economically viable and continue to develop new products.”⁴⁵

Despite the economic challenges, the competition to develop new biologics is intense. Numerous nimble new biotechnology companies—by whatever definition of the admittedly vague category—are competing with the drug industry to develop biologic agents. These new companies often have deep expertise focused on specific areas of biologic research. As a result, these companies produce far more biotech products than the major pharmaceutical companies do. For example, a 2006 PhRMA survey listed 418 biotechnology medicines as under development. The survey indicated only 56 of the biotechnology medicines had a major pharmaceutical company as sole sponsor.⁴⁶ The survey listed another 21 medicines as jointly sponsored by a big pharma company and a biotech. The report suggests that, at most, the 12 largest pharmaceutical companies were participating in the development of about 18% of new biologic compounds. Major pharma companies played a somewhat larger role with respect to approved biotech products. The report listed major companies as sole sponsor on 37%. Wharton professors Sean Nicholson and Patricia Danzon found alliances between pharma companies and biotechs were responsible for 38% of the 691 approvals from 1963 to 1999.⁴⁷ Heavy reliance on collaborative development of biologics suggests that the major pharma companies will often have to divide any revenues generated.

The new biologics are thus more expensive to develop, may reach smaller markets because of genetic targeting, and may often force companies to

divide revenues with development partners. Although the genetics revolution offers boundless scientific possibilities, the economics of biologics will intensify pressures to reduce development costs.

Globalization, Costs, and Competition

The global drug industry is already trying to reduce development costs through outsourcing, a cost-reduction strategy that has swept modern industries. The drug industry has shifted many development activities to geographies with lower costs, especially to emerging economies such as those in India, China, and Eastern Europe. Since technological advances have simplified global communications, much of the planet now has the potential to host laboratory facilities and serve as a recruiting ground for patients to participate in clinical studies (time zone differences and the difficulty of face-to-face contact remain issues). The primary drivers of expanding the research universe to new geographies are cost and patient availability. Diverse genetic backgrounds, cultures, standards of care, and other local differences have not stemmed the tide of outsourcing.

While pharma giants downsize elsewhere, their operations in China are booming:

The combination of desperation outside China and promise within has convinced almost every big pharmaceutical player, including Roche, Novartis, GlaxoSmithKline, Eli Lilly and Pfizer, to collectively invest hundreds of millions of US dollars into research operations there over the past two to three years. The companies are somewhat cagey about how much they are investing at a time when they are laying off employees elsewhere, and when there is no guarantee of a return. But Kenneth Chien, an expert in cardiovascular medicine and an adviser to several large drug and biotechnology firms working in China, calls it “Basel on steroids,” referring to the throng of pharmaceutical companies in Switzerland.⁴⁸

A recent PricewaterhouseCoopers report finds that Big Pharma companies rank China and India as the best locations for outsourcing in Asia, followed by Korea and Taiwan. Among reasons for increased pharma outsourcing to Asia, the report cites the growing numbers of highly educated scientific professionals, declining concerns about intellectual property issues, and the availability of large patient populations for clinical testing.⁴⁹

There is no denying the business case for doing the same work, whether drug discovery or clinical testing, in a much less expensive setting. The geographic regions involved do indeed offer much lower costs. Starting salaries for life-sciences Ph.Ds. trained in the United States are \$8,000 to \$10,000 per year in China, far less than U.S. labs pay such Ph.Ds.⁵⁰ Employing a chemist in India costs \$60,000 vs. \$250,000–\$300,000 in the United

States. What is more, India is producing 120,000 chemists and chemical engineers each year.⁵¹

The trend to conducting clinical studies in new geographic regions is probably most obvious with the testing of oncology products. Until a decade ago, such testing largely took place in the United States. However, patient availability is the most common chokepoint on the speed of clinical research projects. Since cultural issues generally do not affect oncology projects (unlike Alzheimer's trials involving cognitive assessments), oncology trials are good candidates for relocation to areas with lower costs. Many low-cost areas are fertile recruiting grounds because large populations of oncology patients may ordinarily have limited access to chemotherapy. The combination of lower costs and high patient availability drove the shift to Eastern European sites for clinical studies of new oncology treatments over the past decade. Today, it is unusual to perform large-scale oncology programs entirely in the United States. An even larger shift of oncology studies to low-cost areas seems inevitable.

When Offshoring Comes Home

Although globalization presents some attractive possibilities for major pharma companies, it also introduces new challenges. In the long term, globalization seems likely to speed the emergence of new competitors from developing countries. Ultimately, these new competitors will operate their own robust drug development programs with enormous cost advantages. For cost reasons, drug companies already manufacture many drugs in less developed countries, including drugs primarily sold in the developed world. Indian drug firms are taking steps to ensure that their operations comply with FDA regulations, partly as a basis for sales of generic drugs in the United States. However, FDA compliance will also make it easier for Indian companies to bring their own novel compounds to the U.S. market. The labor forces in India and China are receiving on-the-job training in drug development because Western pharmaceutical companies are using growing numbers of Indian and Chinese personnel in their development projects, taking advantage of the pool of highly educated workers with lower salary demands than their Western counterparts. In addition, selective back-recruitment of native researchers who have worked for years as core members of Western pharma companies is proving a ready source of scientific and managerial leadership to propel this competitive evolution.

It would be foolhardy to believe that new low-cost competitors in emerging economies will pass up the enormous business opportunity presented by a global market with high demand, high prices, and high profits. The global drug market seems ripe for price competition driven by countries with significant and growing intellectual capital and a much lower cost structure. Both China and India have large and expanding domestic markets for drugs,

an important source of revenue to drive expansion into development of novel compounds. Both countries are major drug exporters as well. China was already exporting \$3.5 billion in Western medicines in 2004.⁵²

China's interest in developing novel drugs is growing, and China is investing accordingly. The CEO of a company that sells technologies for biotech research says China has "one of the most developed sets of scientific communities that we see outside the United States and is really quite strong in terms of agricultural biotech and gene therapy."⁵³

India's Ministry of Science and Technology has stated the goal of becoming a global leader. To that end, the Ministry noted the need for "a shift in the approach of pharmaceutical industry away from manufacturing only known drugs through innovative process routes to discovering and commercializing new molecules."⁵⁴ Established firms like Dr. Reddy's, Ranbaxy, and Sun Pharma have growing programs to develop new therapeutic compounds. According to an Ernst & Young report, there are at least 60 new compounds in development by 12 Indian pharmaceutical companies.⁵⁵ To be sure, India faces obstacles in advancing to the forefront of drug research, including consistently meeting global standards for good clinical practice (GCP) in clinical trials.⁵⁶ At this stage, Indian firms often make partnership deals to have their novel compounds marketed in specific regions by major global pharmaceutical companies. However, the long-term strategy is to make Indian companies robust competitors in the global pharmaceutical industry, leveraging the lower cost and ample supply of scientific expertise in India. This is particularly sobering in the United States, given the steady decline in U.S. nationals pursuing basic science careers at both the graduate and undergraduate levels.

As for clinical development capabilities, both India and China are experiencing rapid growth in the number of active investigators in drug development (Table 1-2). The cost of conducting a phase I clinical trial in China has been reported as anywhere from only 15% of U.S. costs for a phase I trial and 20% of U.S. costs for a phase II trial⁵⁷ to less than 50% for phase I and less than 60% of U.S. costs for phases II and III.⁵⁸ Total drug development costs in India are 30%–50% lower than in the United States.⁵⁹

Dispersing research operations to low-cost regions undeniably provides substantial savings. However, working across continents, time zones, and cultures inevitably increases the difficulty of managing trials. The problem of managing at a distance is more acute when a study sponsor has reservations about the experience and ability of staff in a new geographic region to provide the quality of GCP essential for clinical studies that provide the basis for successful regulatory submissions. Far-flung, cross-cultural operations may reduce some costs, but they also increase the challenge of managing development programs.

Table 1-2. The number of active clinical investigators developing new drugs in China and India is growing at annual rates of 24% and 18%, respectively.

Country	Number of Active Investigators (2004)	Annual Growth Rate (1999–2004)
North America	28,208	8%
Latin America	240	11%
China	160	24%
India	124	18%
Japan	1,486	6%
Western Europe	8,683	7%
Central and East Europe	327	15%

Source: Tufts Center for the Study of Drug Development 2006, from IMS Health and FDA 2005 data.

More importantly, moving work abroad does nothing to address the fundamental inefficiency of the current approach to clinical research. Inefficiency is inefficiency regardless of the nationality and location of the people involved. For the present, moving clinical operations to regions of lower cost partially relieves the heavy burden of inefficient processes. However, after industry players have completed the offshoring rush, the competition will again come down to how efficiently each player can perform essential tasks. This is especially true as market forces, including greater demands by Western sponsors, predictably shrink differential labor rates and narrow the cost gap. Thus, although outsourcing is an intelligent response to the industry's high development costs and poor productivity, it is at best a short-term solution. At worst, outsourcing places a Band-Aid on a large and growing sore that threatens its host.

The High Risk of Current Development Practices

Improving the efficiency of clinical research is essential if the drug industry is to thrive in an era that seems likely to have fewer blockbusters, the challenging economics of individualized medicine, and formidable new low-cost competitors from emerging countries. Furthermore, lowering development costs would enable the industry to reduce drug prices (or at the very least moderate increases) and defuse public hostility without destroying the profits that fuel research and reward investors.

The risks of continuing current development practices are enormous. Negative attitudes toward the drug industry suggest that the public may be receptive to a variety of proposals to control the cost of prescription drugs.

A familiar proposal modeled on practices in the United Kingdom would establish a single-payer health insurance system and a regulatory body to evaluate medicines not just for efficacy, but for cost-effectiveness as well, thus excluding medicines deemed too expensive from insurance coverage. Another proposal calls for radical restructuring of the entire drug industry, establishing two separate industries. One industry would perform R&D; the other would market drugs. Stan Finkelstein and Peter Temin of the Massachusetts Institute of Technology argue that such a step is necessary:

The crisis is real. Drug prices are high and getting higher. For those fortunate enough to have health insurance, co-payments are rising, too. Money—whether it has to do with spending it or making it—is an obstacle to getting needed medicines.⁶⁰

Finkelstein and Temin see dividing the industry as the solution: “By separating the risks of drug discovery and development from the chances inherent in marketing medicines, we can cut the Gordian knot that ties together high drug prices and the promise of new drugs.” A public nonprofit drug development corporation would acquire new drugs from the companies that develop them and transfer the rights to market the drugs to other companies.

Economic Consequences of Faster Clinical Development

Improved efficiency in clinical development reduces development costs, speeds market entry, and increases revenues and profits. More efficient research and management processes could not only reduce development timelines and the direct costs of conducting studies, but also identify less promising candidates earlier, reducing expenditures on futile projects. Reducing development timelines goes hand in hand with reducing costs (Figure 1-10). For example, a 10% reduction in development time saves 7% of capitalized costs. Cutting development time in half would produce savings of approximately \$350 million in total capitalized costs for a typical clinical development project.⁶¹

Thriving in a New Era

The industry’s problems clearly reflect an inability to produce novel products in reasonable time and at reasonable cost. The major reason for this reality is inefficiency in clinical testing, the most costly, time consuming, and risky portion of drug development. The inadequacy of the current approach and the lack of innovation point inevitably to the need for change in strategic thinking. The status quo, it is clear, will condemn the industry to continuation of its recent slump.

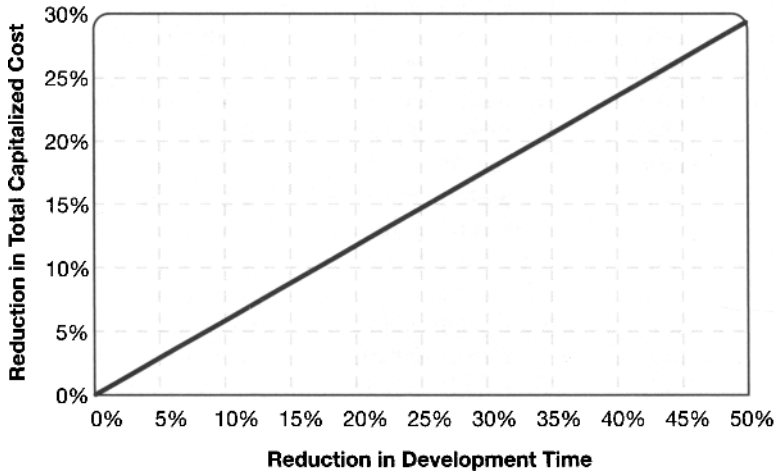


Figure 1-10. Reducing development time by one-half would reduce average per-drug R&D costs by almost 30%, saving an average of more than \$350 million. Source: DiMasi 2002.⁶¹

Although the drug industry's challenges seem daunting, a closer look provides cause for optimism. The root of the industry's problems is clearly the inability to produce novel products in reasonable time and at reasonable cost. It is equally clear that clinical trials consume most of the time and expense of drug development. However, few recognize that already available tools and techniques can enable the industry to streamline clinical trials and reach decision points faster and more efficiently.

The balance of this book discusses the concepts, principles, and specific techniques that will enable the drug industry to improve efficiency and reduce costs. Collectively, these items define adaptive research, an approach that allows midcourse changes based on data collected during trials.

The convergence of communications and computing trends makes the use of adaptive methods in clinical trials not just possible, but practical. Furthermore, the economic pressures on sponsors to improve the development process mandate the application of such technologies. Fundamentally, the adaptive approach involves bringing the tools and techniques of clinical research in line with those long exploited by other modern, efficient industries. There is little doubt that the companies that effectively implement such tools and techniques in drug development will enjoy distinct advantages over companies that do not. Similarly, investors stand to profit from backing companies that can save millions by taking a shorter path to the marketplace or identifying nonviable drugs sooner.

Shorter timelines can greatly reduce development costs. Typical timelines are long indeed. A retrospective study of 168 drugs approved in the period 1994–2002 found a median total post-IND (investigational new drug) development time of 6.3 years. The study found clinical trials consumed 5.1 years, or 81% of the post-IND development time.⁶² However, Joseph DiMasi, director of economic analysis for the Tufts Center for the Study of Drug Development, has stated that since 2002 development times have increased.⁶³ A January 2009 report indicated that average combined times for clinical development and approval are around eight years despite the FDA’s success in reducing average approval time to 1.1 years.⁶⁴ Based on this information, seven years seems a reasonable estimate for the length of a typical clinical development program. Assume that this includes everything from the first testing in humans through completion of confirmatory studies and preparation of regulatory submissions (Figure 1-11).

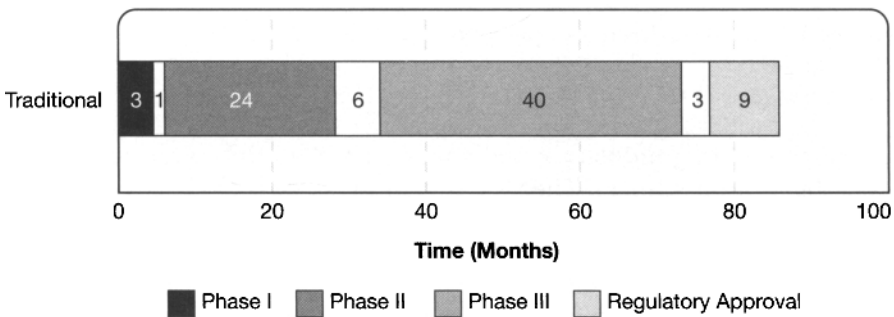


Figure 1-11. A clinical development program typically takes more than seven years from inception to the completion of regulatory submissions. The numbers below each segment indicate duration in months. White indicates between-phase pauses.

Source: Health Decisions, Inc. Used by permission.

For those laboring in the field, such timelines have seemed to lengthen in recent years, leaving the impression that there is little chance of accelerating clinical development. This impression is mistaken. This book will demonstrate principles and techniques that can reduce typical timelines by 25% or more.

Companies that lead the way to more efficient clinical development will reap huge rewards. Laggards will find that adhering to inefficient development practices progressively weakens their competitive standing. Once their descent begins, it will likely prove difficult to recover. On the other hand, industry-wide adoption of a more efficient approach to clinical research could provide enormous benefits. Most dramatically, it could al-

low the industry to break the dangerous cycle of introducing important new medicines at prices that infuriate the public and shatter the budgets of insurers, businesses that provide health insurance for employees, and individual patients. If that cycle continues, the public may demand radical changes in the status, structure, and role of the drug industry—changes in which the industry would have no voice. Breaking the cycle through greater efficiency could allow the industry to remain in control of its own destiny while also better serving the world's health needs. The principles, technologies, and techniques for breaking the cycle are available. There is no time to lose.

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