The Oxford Handbook *of*

THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY

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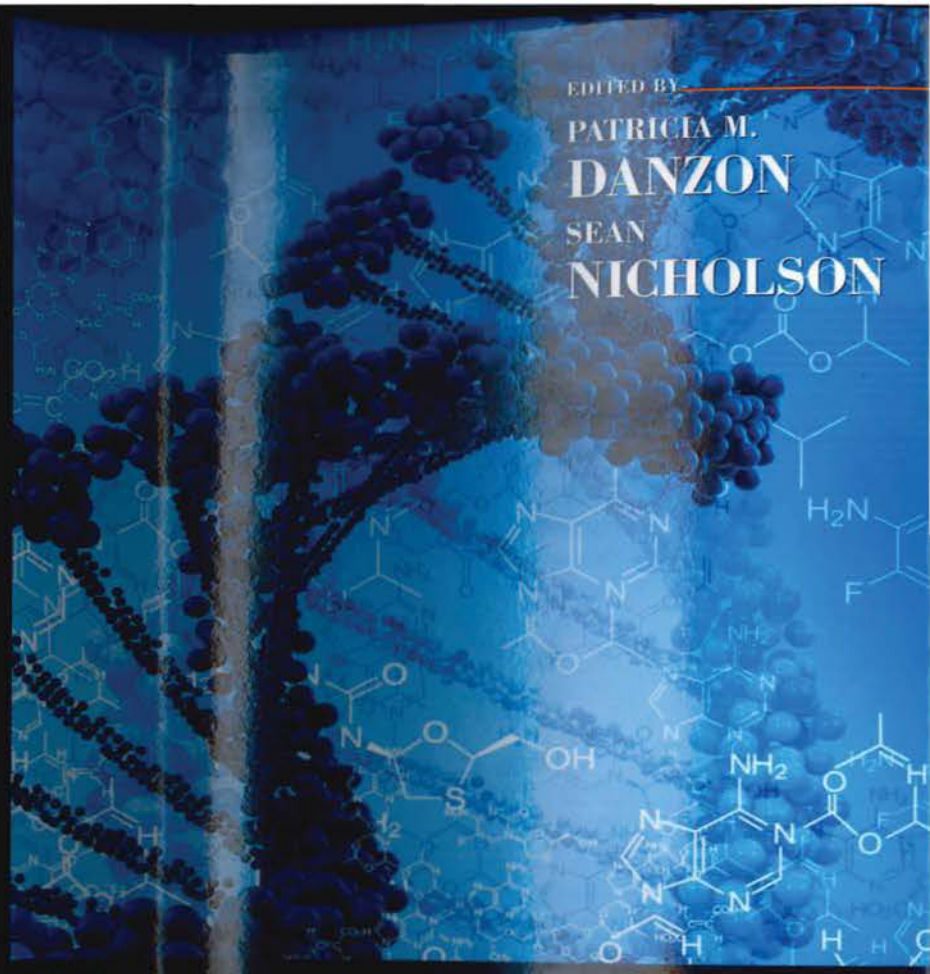

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Contents

CHAPTER 2

R&D COSTS AND RETURNS TO NEW DRUG DEVELOPMENT: A REVIEW OF THE EVIDENCE

JOSEPH A. DIMASI AND
HENRY G. GRABOWSKI

Economic analyses of research and development (R&D) costs and returns in pharmaceuticals have received prominent attention by scholars and policy makers. Investment cycles in pharmaceuticals span several decades. Trends in future R&D costs and returns shape the incentives for companies to pursue R&D opportunities for new medicines. Economic studies provide a basis for evaluating all the factors affecting R&D costs and returns and can be useful in assessing productivity changes in the pharmaceutical and biopharmaceutical industries (Munos 2009). They also can be used to consider how various policy actions (e.g., price regulation) affect innovation incentives (Giaccotto et al. 2005; Vernon 2005).

This chapter reviews the extensive literature on R&D costs and returns. The first section focuses on R&D costs and the various factors that have affected the trends in real R&D costs over time. The second section considers economic studies on the distribution of returns in pharmaceuticals for different cohorts of new drug introductions. It also reviews the use of these studies to analyze the impact

of policy actions on R&D costs and returns. The final section concludes and discusses open questions for further research.

Pharmaceutical Industry R&D Costs

Estimates of the cost of developing new drugs have varied methodologically and in terms of coverage, but taken together, they paint a picture of substantially rising costs for more than half a century. The resource cost increases are dramatic, even after adjusting for inflation. This section briefly reviews the literature on pharmaceutical R&D costs and then describes some of the more recent results.

Approaches to Estimating Pharmaceutical Industry R&D Costs

Early attempts to examine at least some of the costs of new drug development were quite limited in that they did not account for important aspects of the drug development process, such as non–drug-specific R&D, expenditures on drug failures, and the length of the development process and its relationship to opportunity costs. DiMasi et al. (1991) referenced and discussed the early economic literature on the R&D costs of new drug development. One of the earliest of these studies (Schnee 1972) examined data on 17 new chemical entities (NCEs) from the 1950s and 1960s for a single firm. However, only out-of-pocket (cash outlay) costs were considered (i.e., the time costs of R&D investments were not evaluated), and neither fixed discovery costs nor the costs of drug failures were counted. This was followed by several studies that also focused on individual drug out-of-pocket costs; taken together with the Schnee estimate of an average cost of $0.5 million per NCE, these studies suggested that R&D costs increased substantially from the 1950s to the late 1960s (Mund 1970; Baily 1972; Sarett 1974; Clymer 1970).

The early literature also included two attempts to develop R&D cost estimates from published aggregate industry data on R&D expenditures and lists of approved NCEs (Mund 1970; Baily 1972). These studies assumed fixed lag times between industry R&D expenditures and new drug approvals. Although these approaches implicitly accounted for the costs of drug failures, neither of them included capitalization of costs or accounted for varying lag times between expenditures and approvals.

The first study that attempted to capture the full costs of drug development (cash outlays for investigational drug failures as well as successes, fixed discovery and preclinical development costs, and time costs) was that of Hansen (1979). The study used Tufts Center for the Study of Drug Development (Tufts CSDD) survey data from a dozen pharmaceutical firms to obtain a random sample of their investigational drugs and aggregate annual data on their R&D expenditures broken down by development phase and compound source (self-originated or licensed-in). Hansen found an average capitalized cost of $54 million in 1976 dollars for development that occurred in the 1960s and up to the mid-1970s. As with most subsequent studies, Hansen estimated the R&D cost per approved drug, taking into consideration costs incurred on failed drugs and adjusting historical costs to take account of the opportunity costs of time.

Following the Hansen (1979) study, Wiggins (1987) applied a regression analysis using industry-reported aggregate annual R&D expenditure data combined with the development time profile used by Hansen. Wiggins found a capitalized cost per approved new drug of $125 million in 1986 dollars for drugs approved from 1970 to 1985. However, implicit in the analysis was the assumption of a fixed lag relationship for the time between R&D expenditures and ultimate new drug approval. This was not a shortcoming with the Hansen approach.

Since Hansen's (1979) study, the survey approach has been dominant, with similar studies from DiMasi and associates that found increasingly higher R&D cost estimates for later periods. Specifically, DiMasi et al. (1991) reported an average R&D cost of $231 million in year 1987 dollars ($318 million in year 2000 dollars), and DiMasi et al. (2003) reported an average R&D cost of $802 million in year 2000 dollars. Companion studies to these two survey-based articles examined how R&D costs varied by therapeutic category (DiMasi et al. 1995; DiMasi et al. 2004). Gilbert et al. (2003), using an internal Bain Consulting development model, found an estimate of $1.1 billion for 1995 to 2000 approvals, but the methodology was not described in any great detail and the results included launch costs. In two recent papers, Adams and Brantner (2006, 2010) attempted to validate the results reported by DiMasi et al. in 2003 using public data and found general support for them. Earlier, the Congressional Office of Technology Assessment concluded that the results in the 1991 DiMasi et al. study were reasonable (U.S. Congress, OTA 1993).

The highest estimate to date in the literature of the expected, fully capitalized cost of developing a single approved drug was $1.8 billion in year 2008 dollars (Paul et al. 2010). The authors obtained this result by using a mathematical model, some recent industry benchmark data on part of the process, and some internal data from a single firm. The most recent full capitalized R&D cost estimates based on industry survey data were reported by DiMasi and Grabowski (2007), although they focused on "biotech" drug development. The DiMasi et al. (2003) and DiMasi and Grabowski (2007) findings are discussed in some detail later in this chapter, along with some comparisons to the earlier findings to illustrate the extent to which pharmaceutical R&D costs have changed over time.

Risks, Times, and Costs for Traditional Pharmaceutical Industry R&D

Figure 2.1 indicates how inflation-adjusted aggregate industry pharmaceutical R&D expenditures have changed over a long period, measured against changes over the same period in the number of US new drug approvals (new chemical entities, or NCEs). Given that drug development phases are lengthy, spreading over many years (DiMasi et al. 1991), there is a substantial lag between when R&D expenditures are made and when new drugs get approved. Nonetheless, the data in Figure 2.1 strongly suggest that average R&D costs have risen at a rapid rate over time. A more rigorous analysis is needed to assess just how high pharmaceutical R&D costs have been during any period and how rapidly they have risen over time. It is also instructive to look beneath an overall estimate of drug development cost to important aspects of the drug development process that contribute to that cost.

Technical Risks

One of the most important contributors to cost of drug development is the amount of resources that are devoted to drugs that fail in testing at some point in the development process. The series of studies begun with Hansen (1979) involved estimates of the likelihood that a drug that enters the clinical testing pipeline (i.e., phase 1) will eventually be approved for marketing by the US Food and Drug Administration (FDA) and estimates of attrition rates for drugs during the three clinical phases of development. Hansen used a clinical approval success rate of one in eight (12.5 percent). The second study in the series, DiMasi et al. (1991), found that the clinical approval success rate between the two study periods had increased substantially, to between one in five and one in four (23 percent). If nothing else had changed from one study period to the next, the estimated cost per approved

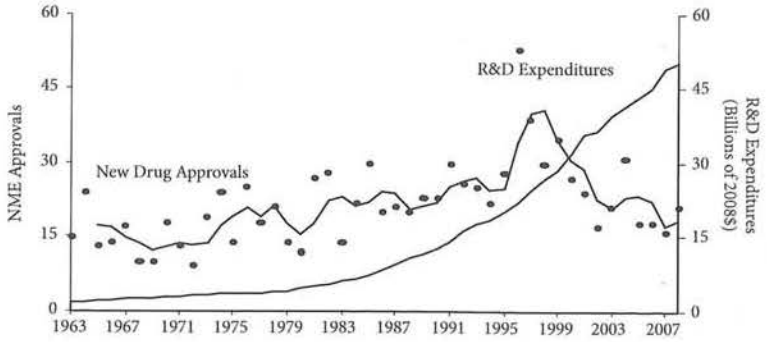

Figure 2.1 New drug approvals and R&D spending.
Source: Courtesy of Tufts Center for the Study of Drug Development (CSDD) and Pharmaceutical Research and Manufacturers of America (PhRMA), 2009.

new drug, inclusive of the cost of failures, would have declined significantly. This did not happen because, as described later, out-of-pocket preclinical and clinical costs also increased substantially, as did average development times and the cost of capital. The result was a much higher full average cost estimate.

The most recent study in the series, DiMasi et al. (2003), found that the success rate had worsened for drugs tested in humans between 1983 and 1994 relative to drugs tested on humans between 1970 and 1982, but only modestly. The estimate of the clinical approval success rate was 21.5 percent. The effect of failures on costs was modified somewhat by estimates showing that firms had terminated their clinical failures earlier. However, as discussed later, other factors contributed to produce a much higher full cost per approved drug for the most recent period.

Development Times

When the R&D process for pharmaceuticals is lengthy, development cycles will be an important indirect determinant of costs if cash flows are capitalized to the point at which revenues from the investment could be earned. As development times increase, so do capitalized cost estimates, other things equal. The time from synthesis of a new compound to first testing in humans increased by 6.6 months, on average, between the Hansen (1979) study and the DiMasi et al. (1991) study. The time from first human testing to regulatory approval increased by almost 21 months, on average, between the study periods. The extra 2.3 years in average total time from discovery to approval for the second study period accounted for approximately 24 percent of the increase in average costs between the studies.

In contrast, changes in development times had little impact on the increase in average cost between the DiMasi et al. (1991) study and the most recent study in the series, DiMasi et al. (2003). Although the time from first testing in humans to regulatory approval declined by an average of 8.6 months between the two study periods, the total time from discovery to approval remained, on average, virtually identical at 11.8 years. The increase in the cost of capital had a much greater impact on total capitalized costs than did changes in development times.

Opportunity Costs

Industrial R&D expenditures are investments, and there are potentially long lags between when the expenditures are made and when any potential returns can be earned. The three survey-based studies we focus on here attempted to capture these time costs, which, together with the out-of-pocket costs of development, yield a measure of the opportunity costs of bringing drugs from discovery to marketing approval. The approach is to capitalize costs to the point of first US approval using an appropriate discount rate. The discount rates used were estimates of the cost of capital for the pharmaceutical industry over the respective study periods. Average out-of-pocket costs by development phase were spread over average development times for each phase and capitalized to the point of marketing approval at the discount rate used for the study.

The real (i.e., inflation-adjusted) costs of capital used for the first two studies were 8 percent and 9 percent, respectively. The increase of one percentage point accounted for 13 percent of the increase in costs between the first two studies. The combination of longer development times and a higher discount rate for the second study accounted for 37 percent of the increase in average costs. As mentioned earlier, although there were some differences in development times between the second and third studies, the total development time was constant. Nonetheless, the estimated discount rate applied to the cash flows over the representative time profile was 2 percentage points higher for the third study (11 percent versus 9 percent). However, out-of-pocket costs increased enough that the time cost share of total capitalized cost remained virtually the same (50 percent for the third study, compared with 51 percent for the second).

Figure 2.2 shows the primary results for the DiMasi et al. (2003) study. In year 2000 dollars, the estimated preapproval capitalized cost per approved new drug was $802 million, with $403 million of that total accounted for by out-of-pocket cash outlays. Pharmaceutical R&D does not end with the approval of an NCE. Development often continues on new indications, new dosage strengths, and new formulations. The DiMasi et al. (2003) study provided an estimate of postapproval R&D costs. It found that approximately one-quarter of the total R&D life-cycle cash outlays per approved new drug were incurred after a drug product containing the active ingredient was first approved. Given that the analysis is focused on the point of first marketing approval, the postapproval costs must be discounted back in time to the date of marketing approval. Therefore, on a capitalized basis, postapproval R&D costs account for only 11 percent of the total life-cycle R&D cost per approved drug, $897 million.

Cost Trends

The three survey-based studies, taken together, demonstrate that pharmaceutical industry R&D costs increased dramatically over the first four decades of the modern era of drug development—that is, since enactment of the 1962 Amendments to

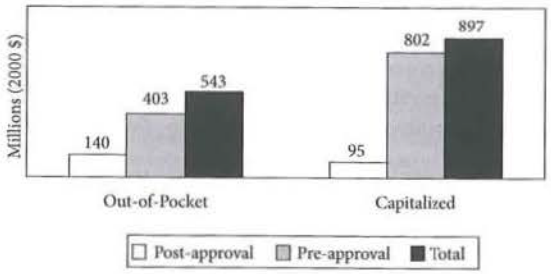

Figure 2.2 Pharmaceutical life-cycle R&D costs.
Source: From DiMasi et al. 2003.

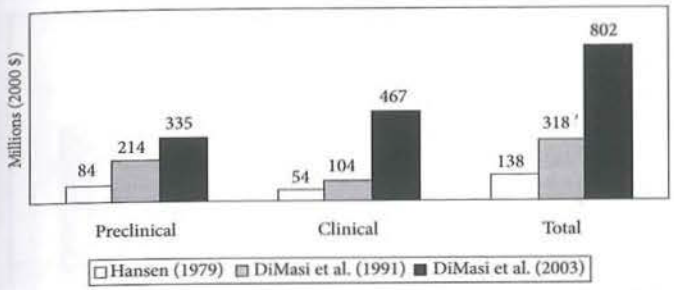

Figure 2.3 Pharmaceutical R&D costs gave increased substantially over time.
Source: From DiMasi et al. 2003.

the Food and Drug Cosmetic Act of 1938, which, for the first time in the United States, required proof of efficacy as well as safety. Figure 2.3 shows how preclinical, clinical, and total preapproval average costs increased across the three studies. Preclinical costs are all costs incurred prior to first human testing. This includes out-of-pocket discovery costs as well as the costs of preclinical development. Clinical costs include all R&D costs incurred from initial human testing to first marketing approval.

In constant dollars, total capitalized preapproval cost per approved new drug increased by a factor of 2.3 between the Hansen (1979) study and the DiMasi et al. (1991) study, and there was a similar increase of 2.5 between DiMasi et al. (1991) and DiMasi et al. (2003). However, at a more disaggregated level, there were substantial differences. From the first to the second study, preclinical costs increased somewhat more than did clinical period costs. However, between the second and third studies, clinical cost per approved drug increased substantially more rapidly than preclinical cost (an increase of 349 percent for the former, compared with 57 percent for the latter).

The length of time between the study periods was not identical. We can get a more precise estimate of the rate of increase in costs across the studies by estimating the average endpoint for analysis in each study. The endpoint is the date of marketing approval. The first study roughly corresponded to development that yielded approvals during the 1970s, development for the second study mostly resulted in approvals during the 1980s, and development for the most recent study was associated largely with 1990s approvals. DiMasi et al. (2003) found an average difference in approval dates of 9.3 years between the first and second studies and 13 years between the second and third studies. Using these time differences, we can calculate average annual rates of increase between the studies.

Figure 2.4 indicates that the annual rate of increase in inflation-adjusted total out-of-pocket costs was relatively constant across the studies (7.6 percent between the first and second studies and 7.0 percent between the second and third studies). However, the rates of increase in overall costs mask substantial differences in how

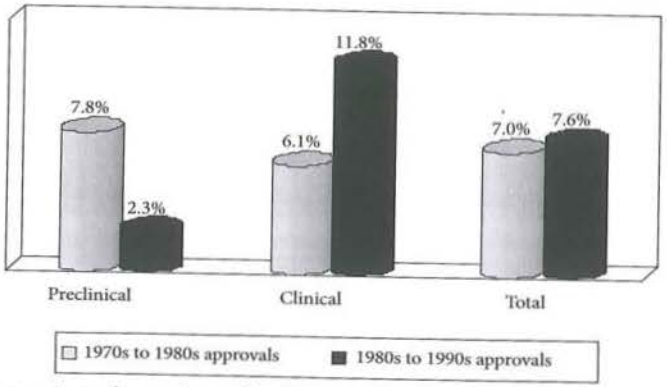

Figure 2.4 Annual growth rates for R&D out-of-pocket cost per approved new drug.
Source: From DiMasi et al. 2003.

costs changed over time for components of the R&D process. Figure 2.4 shows that, whereas preclinical costs continued to increase in real terms between the second and third studies, the rate of increase was less than one-third that between the first and second studies. On the other hand, the rate of increase in clinical period costs was dramatic for the most recent study—almost twice as fast as that between the first and second studies.

Large-Molecule R&D Cost Metrics

Almost all prior research on pharmaceutical R&D costs has focused on synthetic, so-called small-molecule drugs, as opposed to biologics, or large-molecule drugs. Although some of the molecules for the DiMasi et al. (2003) sample were biologics, the overwhelming majority of the drugs in the sample and in the pipelines of the survey firms at that time were small-molecule drugs. The study by DiMasi and Grabowski (2007) was the first to focus on so-called biotech molecules. Specifically, the sample they used consisted of approximately equal numbers of recombinant proteins and monoclonal antibodies (mAbs). Although out-of-pocket clinical costs were collected for a relatively small sample of large molecules (17), the other metrics used for the cost analysis (development times and success and attrition rates) were determined from large samples. The same methodology used to estimate average costs for the three survey-based studies of traditional pharmaceutical firm development, described earlier, was applied to the biotech sample.

Figure 2.5 shows some of the main results from the DiMasi and Grabowski (2007) study. The average overall capitalized cost per approved new chemical entity was $1.2 billion for large molecules. The study also compared development costs for small and large molecules. First, the results from the DiMasi et al.

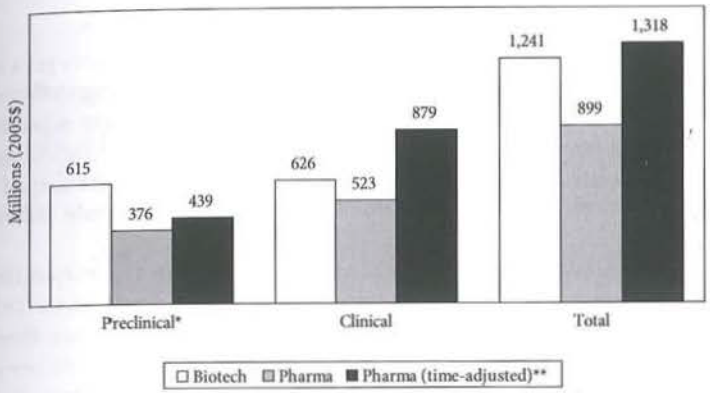

Figure 2.5 Preapproval capitalized cost by new molecule type.
Source: From DiMasi and Grabowski 2007.

(2003) study were adjusted upward for inflation, because the biotech results were expressed in constant 2005 dollars. This yielded costs for the preclinical and clinical phases, and overall costs, that were significantly lower for traditional small-molecule development. However, the molecules used for the biotech analysis were of a later vintage than the sample used for the 2003 study. The biotech sample was, in some sense, five years more recent. Consequently, the results from the DiMasi et al. (2003) study were not only adjusted for inflation but also extrapolated out five years using the growth rates implied by the differences between the second and third survey-based studies of traditional pharmaceutical development (see Figure 2.4). This produced an overall capitalized cost per approved new chemical entity for traditional pharmaceutical firm development similar to that for biotech development ($1.3 billion and $1.2 billion, respectively). However, there were substantial differences by development phase. Clinical period costs were higher for traditional pharmaceutical development, but preclinical phase costs were higher for biotech development.

Recent Metrics and Implications for R&D Costs

The studies in the academic literature on the costs of new drug development cover the period from the 1950s to part of the first decade of the 21st century. However, it is interesting to at least consider the trends for R&D costs during more recent years and for the near future. Without new data on cash flows, we cannot be conclusive about such trends, but there are many metrics that have an impact on full costs that can be examined for recent years. Taken together, these metrics may strongly suggest a direction of change.

Impact of Risk and Time on R&D Costs

Before we examine recent industry benchmark data, it is instructive to get a sense for the degree to which changes in certain key development parameters affect overall costs. DiMasi (2002) was the first to construct various thought experiments that examined how much the capitalized cost per approved new drug changes in response to isolated changes in individual development phase lengths, equal proportionate changes for all development phase lengths simultaneously, individual clinical-phase attrition rates, and clinical approval success rates.

Figure 2.6 is taken from the DiMasi (2002) study. It uses the results from the last survey-based study of traditional pharmaceutical industry development (DiMasi et al. 2003) as the base against which changes are measured. The figure shows, in percentage terms, the extent to which full capitalized cost per approved new drug is reduced if the overall clinical approval success rate is increased from its base case value of 21.5 percent to 35 percent. The results indicate that cost per approved new drug can be reduced by approximately 30 percent if the approval success rate increases from approximately one in five to one in three.

A similar improvement in average cost can be obtained instead from faster development times. Figure 2.7 shows that a 30 percent improvement in total capitalized cost per approved new drug would occur if all development phases and the regulatory approval phase were simultaneously reduced by half, other things equal. Since this work, Paul et al. (2010) has presented similar results for improvements in parameters of their mathematical model.

Development Time, Success Rate, and Trial Complexity Trends

Although comprehensive estimates of out-of-pocket cash flows for new drug R&D for recent years are not available, we can examine trend data for aspects of the development process that can be substantial determinants of changes in costs. As

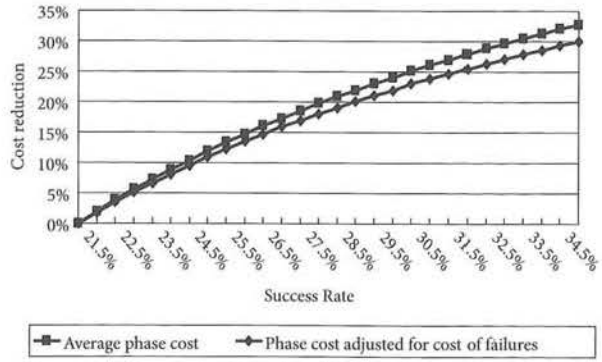

Figure 2.6 Cost reductions from higher clinical success rates.
Source: From DiMasi 2002.

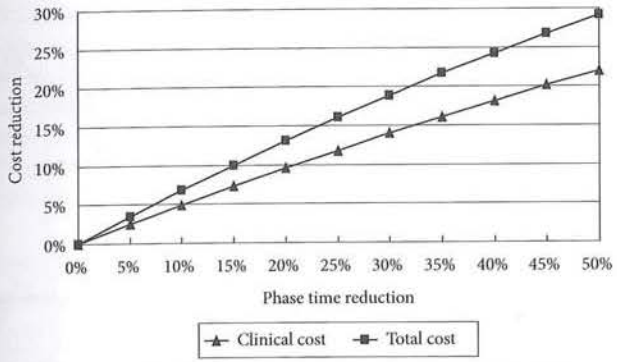

Figure 2.7 Cost reductions from simultaneous percentage decreases in all phase lengths.
Source: rom DiMasi 2002.

noted earlier, lengthier average development times, other things being equal, result in higher full cost estimates, because R&D cash flows are capitalized at a given discount rate over a longer period before first marketing approval. Kaitin and DiMasi (2011) examined US clinical development and regulatory approval phase trends since the early 1980s (Figure 2.8). Although these data do not account for clinical testing periods outside the United States prior to testing in the United States nor for preclinical development periods, the average total time from the start of clinical testing in the United States to US regulatory approval has varied little, ranging from approximately eight to nine years for each five-year period since the early 1980s.

Although development times have remained relatively stable over the last few decades, the data on technical risks in drug development indicate a worsening of conditions. The DiMasi et al. (2003) study found an estimated clinical approval success rate of a little more than one in five (21.5 percent) for investigational drugs that first entered clinical testing between 1983 and 1994. More recently, DiMasi et al. (2010) found an estimated clinical success rate of approximately one in six (16 percent) for investigational drugs that first entered clinical testing from 1994 through 2004 (Figure 2.9). Others have suggested even lower success rates for drugs tested in humans more recently (Paul et al. 2010).

We can also gain insight into changes in direct resource costs associated with individual investigational drugs from data on the complexity of clinical trials at a fairly micro level. Getz et al. (2008) examined a very large number of US-based pivotal clinical trial protocols to determine changes in protocol complexity over time. Unique procedures in these protocols were counted, as well as the frequency with which those procedures were to be employed in each protocol. In addition, eligibility criteria were examined, and a measure of investigator work effort was applied to the individual procedures. Data for 1992–2002 and 2003–2006 were compared.

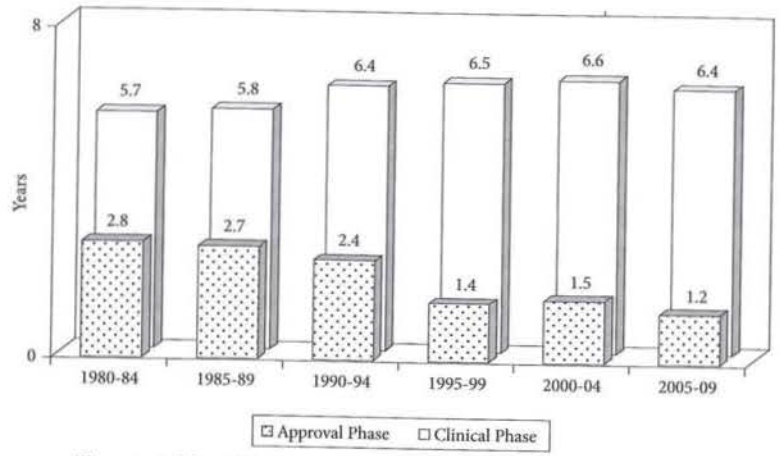

Figure 2.8 Mean US clinical development and regulatory approval phase times by period of approval.
Source: From Kaitin and DiMasi 2011.

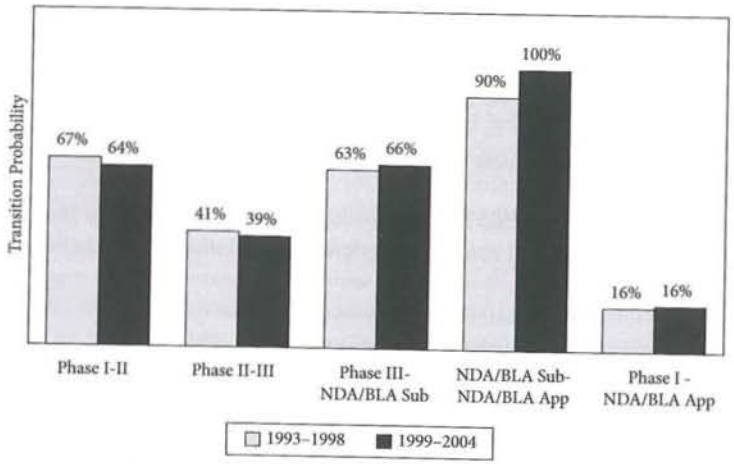

Figure 2.9 Phase transition probabilities and clinical success rates by period of first human testing.
Abbreviations: NDA, new drug application; BLA, biologic license application; Sub, submitted; App, application.
Source: From DiMasi et al. 2010.

As shown in Figure 2.10, the number of unique procedures per protocol, the frequency with which the procedures were applied, the work effort per procedure, and an overall measure of the burden of executing the protocols all increased. Of the measures depicted in Figure 2.10, only investigator fees declined, and those only slightly. In addition, the authors found that eligibility criteria for enrollment increased, patient enrollment and retention rates declined, and the number of case report forms per protocol increased.

Implications for R&D Cost Trends

The recent trends in aspects of the drug development process described in the previous section have implications for R&D costs in recent years. As was the case for differences between the second and the third survey-based studies, the data on approved drugs examined to date make it seem unlikely that changes in development and regulatory approval phase times will have had much impact on R&D costs in recent years. However, many in the industry have suggested that development times have begun to increase in the wake of high-profile safety concerns for approved drugs such as Vioxx and Avandia. It may be too soon to observe much impact from increased regulatory stringency for drugs that have been approved to date.

As indicated in Figure 2.6, other things being equal, a significant increase in technical risks (i.e., a decline in clinical approval success rates) will be associated with a substantially higher cost per approved new drug. The most recent data on success rate suggest that it has declined significantly since the period used for the DiMasi et al. (2003) study.

The evidence on clinical trial complexity (Getz et al. 2008) indicates that more resources have been applied to the trial process in recent years. Out-of-pocket

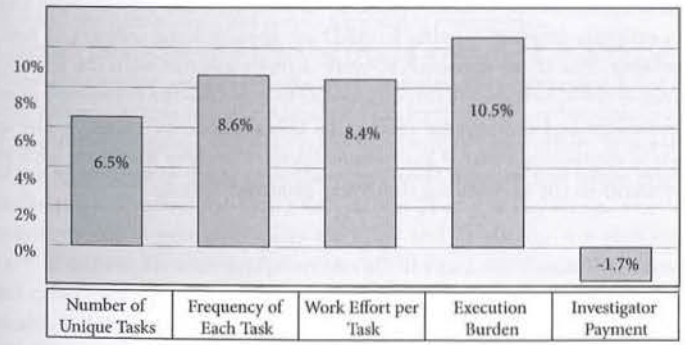

Figure 2.10 Protocol design trends: increased tasks, frequency, effort, and complexity. Comparison of data for 1992–2002 and 2003–2006.
Source: From Getz et al. 2008.

inflation-adjusted clinical costs could still have declined if the unit prices of the resources used in clinical trial development fell enough relative to general price inflation, but that seems unlikely. From 2000 to 2010, the Consumer Price Index for All Urban Consumers (CPI-U) increased at a rate of 2.4 percent per year, while the Gross Domestic Product Implicit Price Deflator increased at a similar rate (2.3 percent per year). Many of the inputs to the pharmaceutical R&D process are purchased in the health care sector. From 2000 to 2010, the medical care component of the CPI-U increased at a rate of 4.1 percent per year. Similarly, the Biomedical R&D Price Index, a measure of the rate of change of input prices for National Institutes of Health (NIH) research, increased at a rate of 3.7 percent per year over this period. These data suggest that out-of-pocket clinical trial costs have continued to increase in real terms.

Taken together, relatively stable development times, lower approval success rates, more complex clinical trials, and real increases in clinical trial input prices suggest that R&D costs have continued to increase in real terms.

Returns on Investment in the Pharmaceutical Industry

Analysis of returns in the pharmaceutical industry has comprised two main strands in the academic literature. The first approach has focused on accounting rates of return as reported in company income statements and balance sheets. Researchers have made various adjustments to accounting values in an attempt to approximate economic returns on investment (i.e., the *internal rate of return*). Researchers using the second approach have relied on life-cycle data on R&D investments and cash flows to estimate internal returns to R&D for specific time cohorts of new drug introductions. The latter approach is more directly aligned with the principles of economics and finance, and it also allows one to examine the variability of returns across products and therapeutic classes. In this section, we focus on the second approach to estimating returns but briefly discuss the older literature with respect to adjustments in the accounting returns in pharmaceuticals.

Accounting Rates of Return

One of the strong factors motivating researchers to investigate the returns in pharmaceuticals was the fact that accounting returns for pharmaceutical companies, as reported in *Fortune 500*, *Business Week*, and other trade publications, were high compared with most other industry sectors. The fact that these high returns

persisted led some to argue that a monopoly problem existed in pharmaceuticals. Individuals espousing this view associated the above-average returns with high entry barriers arising from regulation, R&D, and promotion.

Two alternative explanations for the higher returns also were advanced in the literature. One was that the above-average riskiness of investment in pharmaceutical R&D resulted in higher returns. This led to more detailed analyses of the cost of capital in pharmaceuticals using capital asset pricing model (CAPM) and other financial theories (see chapter 4). A second explanation was that accounting rates of return are biased upward in pharmaceuticals. Whereas several factors may affect the relationship between accounting returns and internal returns, the most important factor in pharmaceuticals is that R&D investments are expensed rather than capitalized in accounting statements. In particular, the pharmaceutical R&D process requires large outlays for preclinical and clinical trials over a decade or more before it leads to any marketed products. Hence, it is appropriate to treat R&D expenditures as capital expenditures. The same issue is applicable to advertising and promotion expenditures, but these expenditures have much shorter lifetimes (i.e., faster depreciation rates) and therefore are a less important potential source of bias.

Stauffer (1971, 1975) was the first to analyze the nature of the bias from a theoretical perspective and provide some initial sensitivity analyses. One of his findings was that, if the growth rate of expenditures on R&D (and advertising) is less than the book rate of return, the book rate overstates the true rate of return.[1] Numerous analyses point to this as being the usual case in pharmaceuticals.

Clarkson (1977), Grabowski and Mueller (1978), Baber and Kang (1996), and others subsequently obtained corrected rates of return using different cohorts of pharmaceutical firms and capitalized R&D and advertising expenditures. These studies were distinguished by use of different depreciation rates as well as other correction factors (adjustments for inflation, cyclical influences, and so on) All the studies resulted in a substantial movement of pharmaceutical industry returns back toward the mean observed across all industry categories.

Although these adjusted accounting returns studies were insightful in considering whether pharmaceutical returns were excessive, they were subject to a number of problems and uncertainties. In particular, the level of analysis necessarily involved use of an individual company's data as the basic unit of observation. However, companies are aggregates of many projects in the R&D pipeline and many products in the marketplace. Product life cycles vary across products and firms. The assumed lag structures and depreciation rates for R&D and promotion are also somewhat arbitrary in nature. In addition, pharmaceutical firms are diversified across other product categories (e.g., animal health, medical devices, consumer health products, chemicals). All these factors make adjustments on the macro level of a company's balance sheet subject to significant measurement errors.

1. This point was also made by Telser (1969) as part of a more general response to a paper on advertising by Comanor and Wilson (1969).

The issues surrounding accounting returns led to the second genre of returns studies, those based on R&D project data and product sales and cash flow data. This approach has become the center of attention by researchers and policy makers in assessing the returns to pharmaceutical R&D over the past two decades.

Internal Rate of Return Studies Based on Life-Cycle Data

Some earlier attempts to derive internal returns on pharmaceutical R&D expenditures using selective data samples and assumptions were performed by Schwartzman (1975), Grabowski and Vernon (1982), Statman (1983), and Joglekar and Paterson (1986). The first paper to use comprehensive samples of new product introductions for specific time cohorts and analyze returns in relation to an appropriate cost of capital for the industry was published in 1990 by Grabowski and Vernon. They used the R&D cost data from the study performed by Hansen (1979) as well as other life-cycle data inputs to analyze the internal rate of returns and present values for products introduced in the 1970s. Subsequent papers employed a similar methodology to analyze R&D returns for comprehensive cohorts of 1980–1984 new drug introductions and 1990–1994 introductions (Grabowski and Vernon 1994; Grabowski et al. 2002).

Figure 2.11 shows the pattern of mean cash outflows and inflows for new products introduced between 1990 and 1994. R&D outlays were based on the DiMasi et al. (2003) study. The analysis was performed on an after-tax basis, and all values were adjusted for inflation and expressed in 2000 dollars.[2] Figure 2.11 shows an average R&D investment period of 12 years. Negative cash flow outlays occur through this period and for the first few years after launch. Cash flows then become positive and escalate rapidly to year 10. Most of the drugs in the sample had post-launch patent lifetimes in the range of 9 to 14 years, so the rapid decline after year 14 reflects generic competition. Products subject to generic competition in the past five years in the United States market in fact have experienced more rapid declines than the pattern reflected in Figure 2.11 (Grabowski and Kyle 2007).

Grabowski et al. (2002) found that the mean industry return for new drug introductions was 11.5 percent. The corresponding estimated industry cost of capital was 11 percent. For most of the cohorts examined, the mean returns were moderately above or below the industry cost of capital. However, large variations were

2. Cash flows after launch are derived from sales data collected on an individual product basis for the full cohort of marketed products. Other inputs include information on profit margin on sales after taking account of production and distribution costs, the rate of erosion to generic competitors after patents expire, and the level and timing of plant and equipment capital investments, inventories, and accounts receivable. Some of these data points are available on an individual product basis, and others are based on representative industry values.

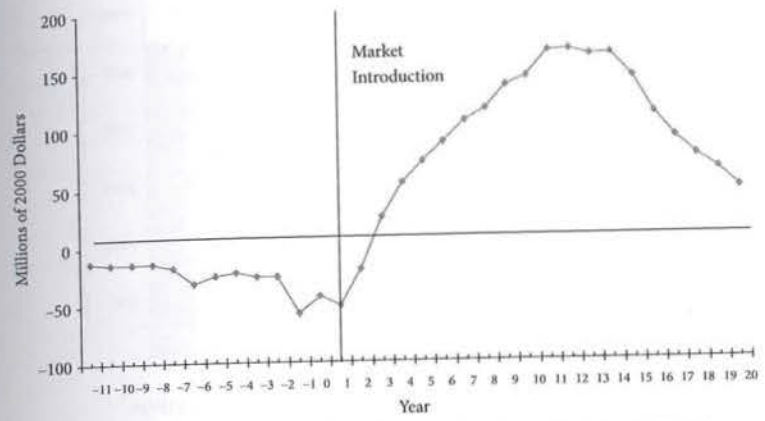

Figure 2.11 Mean cash flows for new chemical entities introduced between 1990 and 1994.

observed in present values and returns across products. The distribution exhibited a highly skewed pattern. This is discussed in further detail later.

One of the advantages of the internal rate of return investment approach is that one can undertake various simulation analyses on all of the parameters of the model (e.g., margins, tax rates, generic erosion rates, cost of capital). These analyses indicate that returns and present values are very sensitive to margins and the cost of capital. The results also underscore the importance of an efficient development regulatory review process, in that a one-year reduction in time to market is worth significantly more in present-value terms than an extra year of patent time at the end of the product life cycle.[3] This is intuitively plausible given the long gestation periods and product life cycles.

The life-cycle investment approach also has been used to conduct analyses related to various policy issues. For example, the Congressional Budget Office (US Congress, CBO 1998) used this analytical framework to estimate the impact of the Hatch-Waxman Act on the returns to pharmaceutical R&D. The Hatch-Waxman Act facilitated the entry of generics by enacting an abbreviated approval process while also restoring some of the patent terms lost in the clinical trial and regulatory review periods. Using the Grabowski and Vernon (1994) analysis on returns and taking account of the basic changes in patent lifetimes and generic competition resulting from the Hatch-Waxman Act, the CBO estimated that average returns to marketing a new drug declined by approximately 12 percent over the

3. This reflects the effects of discounting over long time horizons. A one-year shift at the beginning of the launch period has more impact on present values than an extra year of heavily discounted sales 12 to 14 years after launch even if sales are at peak or close to peak value.

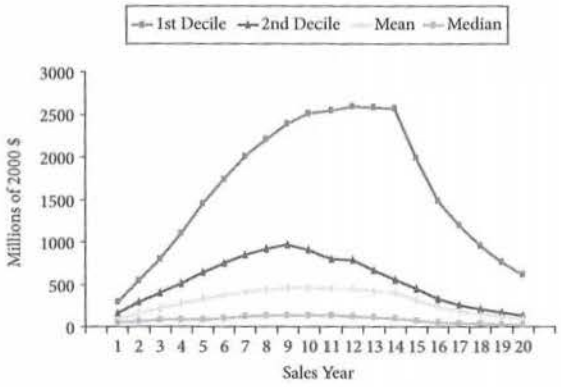

Figure 2.12 Worldwide sales profiles of new chemical entities introduced between 1990 and 1994.

initial decade after the Hatch-Waxman Act was enacted. In particular, the much faster erosion rates resulting from the Act on balance had a much greater negative effect on returns than the positive increases from patent term extensions.

Variability in Returns

The distribution of revenues across products exhibits a highly skewed pattern. As shown in Figure 2.12, the peak sales of the top-decile compounds in the 1990–1994 cohort (i.e., the top 10 percent of products in the cohort ranked by sales) are several times the peak sales of the second-decile set of compounds. Similarly, the mean sales are significantly greater than the median sales. This is representative of a highly skewed sales distribution.

Figure 2.13 provides another way of depicting the skewness present in the distribution of returns. This figure shows the present value of after-tax cash flows by decile for the 1990–1994 cohort of introductions.[4] It also shows the present value of the average after-tax R&D costs to discover and develop a product for this period. The majority of new introductions fail to cover average R&D costs (including the cost of projects that are terminated in the premarketing phase). Figure 2.13 shows that only the products in the top three deciles have returns in excess of average R&D costs. In particular, the top decile drugs have present values that are several times the R&D costs. In effect, the profitability of an extensive R&D program is dependent on occasionally achieving high returns from the "winners" of the top few deciles.

4. These cash flows are net of all expenditures except R&D expenditures.

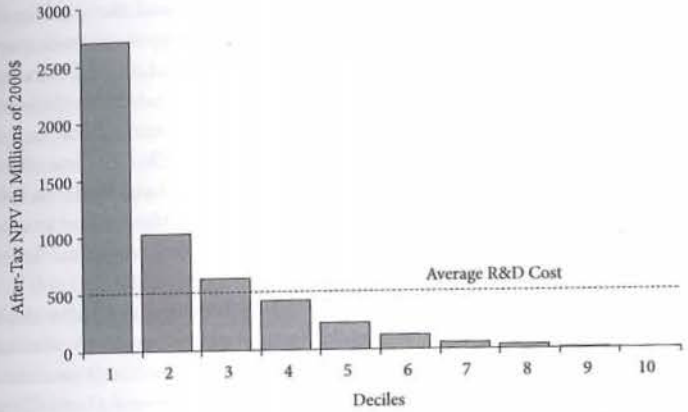

Figure 2.13 Net present values (NPV) by decile of new chemical entities introduced between 1990 and 1994.

In every cohort that Grabowski and Vernon (1994) and Grabowski et al. (2002) analyzed, a highly skewed distribution of returns was observed. Figure 2.14 provides a summary of these studies covering four time periods from the early 1970s to the mid-1990s. The vertical axis shows the percentage contribution of each decile to overall returns of the cohort. The top decile of new drug introductions accounted for approximately half the market value of the total sample in each of these four cohorts.

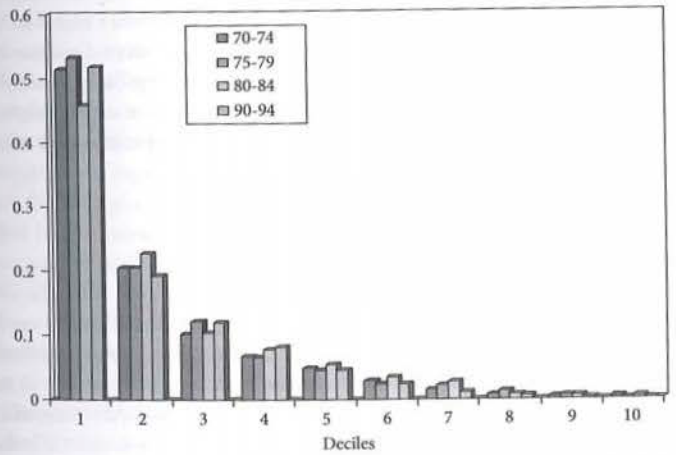

Figure 2.14 Proportional contribution to overall returns (net present values) for four samples of drug approvals by decile of sales.

In a series of papers, Scherer and colleagues examined the distribution of returns from several different sets of data on innovation outputs including venture capital investments, patented inventions from the United States and Germany, university inventions, and our pharmaceutical introduction databases (Scherer and Harhoff 2000; Scherer et al. 2000). They found that these innovation samples all exhibited distributions of returns that were highly skewed. The outcomes were best characterized by log-normal or Pareto distributions with long "tails" in which a few very successful projects accounted for a large part of the economic value. In particular, the most successful 10 percent of the innovations accounted for 50 percent to 90 percent of the total returns.

One of the implications of these highly skewed distributions is that the law of large numbers does not work as it does for normal distributions. In particular, a large, diversified portfolio of research projects does not necessarily produce a relatively stable pattern of realized returns over time. Scherer and Harhoff (2000a) concluded that when one assesses the innovative performance of companies in the pharmaceutical industry and other research-intensive industries, a long time perspective is essential, because short-term returns can be dominated by particularly favorable or unfavorable draws from a skewed distribution.

These findings also have important policy implications. Given the skewed distribution of returns, if regulators focus their efforts on significantly curbing the revenues of the product winners without providing an offsetting means for firms to capture innovation returns, this can have especially adverse consequences for innovation incentives. Some of the provisions of the reform health care plan proposed by the Clinton administration that applied to pharmaceuticals were subject to this critique (Grabowski 1994). Also, if regulators employ a rate-of-return constraint on company profits (an approach used with some flexibility by the United Kingdom), this can have particularly discriminatory effects on earlier-stage companies with fewer R&D projects and smaller asset bases. Scherer (1995) employed a Monte Carlo analysis using representative parameters from Grabowski and Vernon's (1994) research work to show how rate-of-return regulation would affect companies with R&D portfolios of different sizes. He found a strong relationship between realized returns and the size of a firm's R&D portfolio under a rate-of-return regulatory regime.

Cost and Returns for New Biologic Entities

Whereas most of the analyses of R&D costs and returns have focused on NCEs, new biologics are now the fastest growing segment of the pharmaceutical industry. As discussed earlier, the R&D costs of new biologics appear comparable in magnitude to those of NCEs, although the components of the costs differ significantly. As with NCEs, the distribution of sales in biologics is highly skewed (Grabowski 2008). One major difference in the product life cycle for biologics is the absence of generic competition (i.e., the rapid decline in sales observed for NCEs when generic

entry occurs, as shown in Figure 2.11). This results from the fact that the Hatch-Waxman Act that instituted abbreviated applications for market entry by generic products (which need only demonstrate bioequivalence to the innovator's product to gain approval) covers NCEs but not more complex biologic molecules.

As part of the Patient Protection and Affordable Care Act passed by Congress in March 2010, an abbreviated pathway was established for so-called biosimilars. Biosimilars are products that are not identical to the innovator's product structure but are similar enough in therapeutic outcomes to allow them to rely in part on the innovator's safety and efficacy data to gain approval. One of the most controversial areas of this legislation is the intellectual property provisions involving the minimum period of time before a biosimilar can enter with an abbreviated application (the so-called *data exclusivity period*). Data exclusivity is an "insurance policy" for innovators in that it provides a period of appropriability in cases in which patents are limited in time or uncertain in nature. The new law establishes a 12-year data exclusivity period for biologics.

Currently, the data exclusivity period for NCEs under Hatch-Waxman is five years. However, some scholars have found that biologics rely more on process and formulation patents than chemical entities do, and this may make them easier to invent around. At the same time, the nature of competition from biosimilars is likely to be different from that from generic drugs under Hatch-Waxman, given that biosimilars are not identical chemical compounds. For the foreseeable future, they are likely to compete as therapeutic options rather than interchangeable products subject to automatic substitution for the reference brand. The evolution of market competition between biologics and biosimilars will depend on a number of factors including how the FDA implements the law and how providers, patients, and payers respond to the availability of biosimilars (Grabowski et al. 2011a).

To gain insights into how market exclusivity periods affect innovation incentives, Grabowski (2008) used values of R&D investments and sales profiles for a representative portfolio of biologic products. The main outcome of this analysis was the finding of "breakeven lifetimes." A breakeven lifetime in this context is the time required for the mean product in the portfolio to earn a return commensurate with the industry cost of capital. The analysis found that breakeven lifetimes in biologics for a representative product in the portfolio are generally in excess of 10 years for a range of plausible input values.

This line of research was extended to a Monte Carlo analysis that considered a large number of draws from a representative range of values for the key parameters (Grabowski et al. 2011b). In particular, the distribution of products reaching breakeven status was considered for exclusivity periods ranging from 7 to 14 years. The analysis allowed for the innovator's brand to retain a significant share of the market in the face of biosimilar entry, given that biosimilars are not necessarily interchangeable with the reference brand but rather compete as therapeutic alternatives to it. The authors found that if products are subject to competition from biosimilars after seven years, only a small percentage of products are likely to break even (even when innovators are allowed to retain a significant share of the market

for 25 years or longer). However, as exclusivity periods increase to the 12- to 14-year range, the resulting distribution indicates that a much larger percentage of products achieve breakeven status.

This analysis underscores the need for a significant time period after product launch—secured by either patents or data exclusivity—for representative biologic products to earn risk-adjusted returns. In addition, Grabowski et al. (2011b) found that data exclusivity would extend the period of overall market exclusivity beyond patent protection only in those cases in which patents are easy to circumvent or long time periods have elapsed in the R&D process (i.e., cases in which the 20-year nominal life of a patent from date of filing has largely eroded, given that patents are filed early in the R&D process). Innovative products in particular often have longer timelines from invention to marketing, so there could be significant positive welfare effects associated with the longer data exclusivity provisions for biologics in the new law.

An important issue for further research is whether the longer data exclusivity period for biologics will tilt R&D incentives toward these new biologics rather than NCEs and thereby result in a loss of consumer welfare (Goldman et al. 2011). Biologics already have a large and growing share of R&D pipelines in pharmaceuticals (Trusheim et al. 2009). In this regard, the European Union (EU) has instituted a 10-year data exclusivity period for both NCEs and new biologics. The EU also provides for an additional year of data exclusivity for a significant new indication. Potential harmonization of US data exclusivity periods for biologics and chemical entities remains an important issue for both researchers and policy makers.

Conclusions

Analyses of pharmaceutical R&D costs using similar methodologies show that costs increased at high rates from the 1970s to the 1980s and from the 1980s to the 1990s. Over these periods, the full capitalized cost per approved new drug increased at average annual rates 7 to 8 percent greater than the general price inflation. However, the rate of increase was almost 12 percent per year for clinical-period costs between the 1980s and the 1990s. Undoubtedly, the increases were due to a combination of exogenous and endogenous (i.e., strategic) factors. Over these periods, to meet increasing medical demands and given the expansion of prescription drug coverage in the United States, firms likely shifted more of their R&D efforts toward treatments for chronic and degenerative diseases, which tend to have higher development costs. However, input prices also likely increased, and evidence presented by DiMasi et al. (2003, 2004) suggests that development complexity and costs increased substantially even at the therapeutic class level. Increasing exogenous costs, other things being equal, reduce innovation incentives.

Data on recent trends for components of full cost estimates suggest that R&D costs for recent and current development have continued to increase. Furthermore, in light of recent high-profile safety withdrawals in the United States and elsewhere, there is at least speculation that out-of-pocket costs and development times are increasing as a result of the heightened concern over safety. An increasing emphasis by payers and reimbursement authorities on obtaining information on the comparative effectiveness of new drugs relative to existing treatments may also result in higher out-of-pocket costs and longer development times. Lengthier development times are a concern not only for pharmaceutical firms but, more importantly, for patients. As Philipson and Sun (2010) demonstrated for several drug classes, the cost to patients of delayed access to effective treatments for life-threatening conditions can far exceed the costs of developing these new treatments.

The analyses of internal returns for drugs newly introduced in the 1970s, 1980s, and 1990s, based on life-cycle data of R&D costs and cash flows, provide important insights about R&D competition in pharmaceuticals. First, the distribution of returns in pharmaceuticals is highly skewed. In particular, only about 30 percent of the new drug introductions in these cohorts have present values in excess of average R&D costs. The top decile of compounds alone account for between 46 and 54 percent of the present value of the total returns from all introductions in these various cohort samples. The search for these blockbuster drugs, typically "first in class" or "best in class" compounds, has been a key driver of R&D competition over the past several decades.

A second major finding is that the estimated mean industry return for each cohort has been quite close in value to the industry cost of capital. These studies provide evidence in support of what Scherer (2001) labeled a "virtuous rent-seeking model" of R&D competition in pharmaceuticals. In particular, the rapid growth in real R&D outlays since the 1970s has resulted in the introduction of many important new therapeutic classes and compounds for AIDS, cholesterol reduction, ulcers, depression, and other conditions that have provided significant benefits to consumers. At the same time, most of the industry rents are dissipated as drug firms compete to exploit new technological opportunities, causing industry returns to converge to the cost of capital (Grabowski et al. 2002; Scherer 2010).

Whether this beneficial cycle of increasing R&D expenditures and innovative new product introductions will continue into the future is open to question. The last decade or so has been characterized by a downward trend in new product introductions (see Figure 2.1) and an increasingly rapid penetration of generic utilization after patents expire. This has resulted in a replacement problem for many firms as R&D pipelines have been insufficient to offset revenue losses to generics (see chapter 18). One bright spot over this period has been the growth of the biopharmaceutical sector and the growing number of significant new drug introductions based on recombinant biotechnology. Many companies are increasingly focusing on new biologic entities in their R&D pipelines and are engaging in partnership deals with smaller development-stage R&D firms as a means to deal with their product replacement problem.

Biologics are also the subject of evolving regulatory and public policy actions. A particularly notable event was the establishment by Congress of an abbreviated regulatory pathway for biosimilars in March 2010. The new law attempts to balance incentives for increased price competition with incentives for continued new product innovation by the biopharmaceutical sector. An important issue for further research is how competition will evolve in the face of this new law and related industry developments.

Future R&D competition will be shaped by scientific, regulatory, and other forces that in turn influence R&D costs and returns and the strategic responses of companies. Given these myriad factors, future competition may evolve in ways that are difficult to foresee at present. However, the search for innovative new products is likely to remain the key driver of competition in the pharmaceutical industry.

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CHAPTER 3

FINANCING RESEARCH AND DEVELOPMENT

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BIOPHARMACEUTICAL firms invested an estimated $61 billion in research and development (R&D) in the United States in 2008, an amount representing about 18 percent of their domestic sales (Pharmaceutical Research and Manufacturers of America [PhRMA] 2009; Biotechnology Industry Organization 2009). Historically, the new medical technologies resulting from such innovative activity have been the catalysts for both large real increases in medical spending (Newhouse 1992) and improvements in health (e.g., Cutler 2004). Profit-maximizing firms that cannot fully appropriate the returns from R&D will invest less than the social optimum (Arrow 1963). Even with patents there could still be underinvestment if firms have insufficient internal funds to finance all economically viable investments and the cost of external funds exceeds the cost of internal funds. Pharmaceutical firms with established products are able to finance all their economically viable projects with retained earnings; most biotech firms, which are important sources of innovation, must raise funds externally.[1] This raises the possibility that market failures in the capital market will result in less than the socially efficient amount of innovation.

There are two main reasons why the cost of external funds might exceed that of internal funds. First, a firm knows more about the quality of its drug compounds than potential outside investors do. The "lemons" problem (Akerlof 1970)

1. In this chapter, I follow the industry convention and define a "biotech firm" as a firm that conducts discovery research and was founded after 1970. All such firms draw on biotechnology science to varying degrees, even if they are developing small-molecule drugs (rather than large-molecule, biologic products).