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The Cost of Biopharmaceutical R&D: Is Biotech Different?

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The costs of developing the types of new drugs that have been pursued by traditional pharmaceutical firms have been estimated in a number of studies. However, similar analyses have not been published on the costs of developing the types of molecules on which biotech firms have focused. This study represents a first attempt to get a sense for the magnitude of the R&D costs associated with the discovery and development of new therapeutic biopharmaceuticals (specifically, recombinant proteins and monoclonal antibodies [mAbs]).

We utilize drug-specific data on cash outlays, development times, and success in obtaining regulatory marketing approval to estimate the average pre-tax R&D resource cost for biopharmaceuticals up to the point of initial US marketing approval (in year 2005 dollars). We found average out-of-pocket (cash outlay) cost estimates per approved biopharmaceutical of $198 million, $361 million, and $559 million for the preclinical period, the clinical period, and in total, respectively. Including the time costs associated with biopharmaceutical R&D, we found average capitalized cost estimates per approved biopharmaceutical of $615 million, $626 million, and $1241 million for the preclinical period, the clinical period, and in total, respectively. Adjusting previously published estimates of R&D costs for traditional pharmaceutical firms by using past growth rates for pharmaceutical company costs to correspond to the more recent period to which our biopharmaceutical data apply, we found that total out-of-pocket cost per approved biopharmaceutical was somewhat lower than for the pharmaceutical company data ($559 million vs $672 million). However, estimated total capitalized cost per approved new molecule was nearly the same for biopharmaceuticals as for the adjusted pharmaceutical company data ($1241 million versus $1318 million). The results should be viewed with some caution for now given a limited number of biopharmaceutical molecules with data on cash outlays, different therapeutic class distributions for biopharmaceuticals and for pharmaceutical company drugs, and uncertainty about whether recent growth rates in pharmaceutical company costs are different from immediate past growth rates. **Copyright © 2007 John Wiley & Sons, Ltd.**

INTRODUCTION

The financial viability of new drug and biopharmaceutical development depends on the expected costs of, as well as the returns to, R&D. When R&D costs are substantial it is important to examine approaches that could reduce those costs. If the productivity of new drug development can be improved, then more innovations may be pursued and eventually reach the patient. The Food and Drug Administration (FDA), through its Critical Path Initiative, has initiated a process to, in part, explore how the agency, industry, and academia can establish methods that would lower development costs (FDA, 2004).

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R&D costs for new drugs (including the costs of failures and time costs) have been estimated to average in excess of $800 million (in year 2000 dollars) for development that led to approvals in the 1990s, with a marked upward trend relative to earlier decades (DiMasi *et al*., 2003). These R&D cost estimates have used data on new drugs developed by traditional pharmaceutical firms (primarily new chemical entities). No study to date has focused on the types of molecules that are developed by biotech firms. One might conjecture that biopharmaceuticals are less costly to develop because biotech firms need to be more nimble and creative or that fewer safety issues arise for many biopharmaceuticals because they replace substances that exist naturally in the body. However, some industry insiders estimate that costs, even for biotech firms, exceed $1 billion.[1]

In this paper, we make a first attempt to examine the magnitude of R&D costs associated with developing the types of molecules on which biotech firms focus. Specifically, we use drug-specific cost, development time, and clinical success rate data for therapeutic biopharmaceuticals to estimate pre-tax R&D resource costs. We then compare these results to those obtained for development of new drugs by traditional pharmaceutical firms (DiMasi *et al*., 2003). Given that the biopharmaceutical data are, on average, more recent than the data used for DiMasi *et al*. (2003), we estimate the difference in study periods. Our results for biopharmaceutical development are then also compared to those for traditional pharmaceutical firms with costs extrapolated using estimated past growth rates for pharma costs to coincide with the more recent biopharmaceutical study period.

The rest of this paper is organized as follows. The next section contains a description of the data used for our analyses. Then, we describe the methods used to obtain our results. We further present our results. Finally, we summarize our conclusions and offer some discussion of the results.

DATA

Our data on project costs derive from two sources. First, the sample for our study of pharmaceutical R&D costs (DiMasi *et al*., 2003) contained a small number of biologic compounds developed by pharmaceutical firms. Second, we obtained project-level and aggregate annual expenditure data for a consulting project for a biotech firm.[2] We combined data by period and type of compound from these two sources. We focus on therapeutic recombinant proteins and monoclonal antibodies (mAbs), which are overwhelmingly the two most prevalent compound types in the biotech sector. The consulting project focused on compounds that first entered clinical testing from 1990 to 2003. With compound type and period of initial clinical testing as study criteria, we utilized data on four biologics from three companies used in the earlier study and 13 compounds from the biotech firm.[3]

While the data on cash outlays are limited to the 17 compounds noted above, we are able to use a much larger data set to estimate average development times, clinical success rates, and phase transition probabilities. These data are used to account for time costs and the costs of development failures.[4] We used a Tufts Center for the Study of Drug Development (CSDD) database of biopharmaceutical compounds. The Tufts CSDD database is constructed from information contained in a number of commercial business intelligence databases (*PharmaProjects*, *R&D Focus*, and *iDdb3*), trade press accounts, company reports and websites, and company surveys. For our analyses of development times, clinical success rates, and phase transition probabilities, we used a subset of this database. The compounds included are therapeutic recombinant proteins and mAbs that were first tested in humans from 1990 through 2003. There are 522 such compounds, and they include molecules that were abandoned during development, as well as those that have attained US Food and Drug Administration (FDA) approval.[5]

We compare our results for biopharmaceuticals to our previously developed estimates of R&D costs for new drugs developed by traditional pharmaceutical firms. The data underlying the 'pharma' results are described in DiMasi *et al*. (2003). These data included cash outlays for 68 new drugs and development times, clinical approval success rates, and transition probabilities for a larger data set of 534 new drugs.

METHODS

The methodology used for the analysis here is explained in detail in DiMasi *et al*. (2003). We shall only briefly outline the methods here.

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Out-of-Pocket Costs: Phase Means, Success Rates, and Expected Costs

We refer to actual cash outlays of the firm as out-of-pocket costs. We converted the data on clinical period expenditures by phase and year to 2005 dollars using the GDP Implicit Price Deflator. We determined mean costs for these molecules for phase I, phase II, and phase III. Long-term animal testing costs incurred during clinical development, regulatory approval submission costs, and chemistry, manufacturing and control costs related to development and incurred during clinical development are subsumed in the cost estimates for the clinical phases. The expenditures considered in this report for the sample of 17 molecules are only those that were incurred prior to original marketing approval.

To obtain a full R&D cost estimate that would account for the costs of failures and the time cost of new pharmaceutical development, we must build up to one through analyses of the expected costs for the clinical and preclinical periods. For purposes of this study, by the clinical period we mean the time from initial human testing of a compound to original marketing approval. The preclinical period refers to activities engaged in prior to the start of human testing. Thus preclinical R&D costs include expenditures for both basic research and preclinical development.

Expected costs take into account the fact that not all compounds will progress all the way through development to approval. We first work at the investigational molecule level. For the clinical period this means that we must estimate the probabilities that a compound that enters the clinical testing pipeline will make it to each phase. These values can be estimated from the data in the Tufts CSDD database of biopharmaceutical compounds. Statistical inference using, in part, survival analysis to account for censoring of the data has been implemented in a number of studies of drug industry success rates.[6] However, given lengthy drug development times, such an approach requires that there be a substantial period of time between when the most recent drug enters clinical testing and when the analysis is conducted. Since we must include here drugs that have entered the clinical testing pipeline relatively recently, we have estimated success and phase attrition rates in a more mechanistic manner. We estimated a phase transition probability to be the percentage of drugs in the sample that have proceeded from one phase to another among the set of drugs that entered the first phase and either proceeded to the next phase or were terminated in the first phase. This approach should provide reasonable estimates of phase transition probabilities since the lengths of individual phases are short relative to total development times. The implicit assumption needed for such an approach is that those drugs that are still active at the time of analysis will proceed to later phases more or less in accordance with the estimated transition probabilities. The overall clinical success rate is then determined as the product of the phase transition probabilities. Clinical success is defined as US regulatory approval for marketing.

Expected out-of-pocket cost per investigational drug is the weighted average of mean phase costs, where the weights are the estimated probabilities that an investigational molecule will enter a given phase. Finally, the out-of-pocket cost per approved new molecule is obtained by dividing the out-of-pocket cost per investigational molecule by the estimated clinical approval success rate.

Preclinical costs are obtained in a manner similar to the method we used in DiMasi *et al.* (2003). We examined time series data on aggregate preclinical and clinical expenditures for new molecules at the firm level. These data, along with our estimated clinical period costs per investigational and per approved molecule, were used to infer the corresponding values for preclinical costs. The time series data on preclinical and clinical expenditures were linked, as was done in DiMasi *et al.* (2003), via an estimated 5-year lag between the middle of the preclinical period and the middle of the clinical period.[7]

Capitalized Costs: Development Times and Discount Rate

Drug development is a very lengthy process. As such, there are substantial time costs to investing in R&D years before any potential returns can be earned. We capture the time costs of drug development in a single monetary measure by capitalizing costs forward to the point of original marketing approval at an appropriate discount rate. The discount rate used is a cost of capital estimate for a sample of firms obtained from applying the Capital Asset Pricing Model (CAPM). More detail on this process is explained

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below in the context of a discussion of the result we obtained for a biotech discount rate.

Capitalized costs are the sum of out-of-pocket and time costs. To obtain time costs we not only need an appropriate discount rate, but also a timeline over which out-of-pocket costs are capitalized forward to marketing approval at the discount rate. Thus, we estimate average clinical phase and regulatory review lengths from the data in our subset of therapeutic recombinant proteins and mAbs. As noted above, we use the estimate in DiMasi *et al*. (2003) for the time from discovery to first human testing.

RESULTS

Our focus is on biopharmaceutical development, but we will also make some comparisons to estimated costs for traditional pharmaceutical firms.

Clinical Phase Costs per Investigational Molecule

Table 1 shows our estimated average clinical period phase costs for the sample of compounds for which we obtained detailed data. Mean clinical phase costs are higher than those that we had obtained in our R&D cost study for traditional pharmaceutical firms when adjusted for inflation. For the period we analyzed, the sum of the clinical period mean phase costs for biopharmaceuticals ($166 million) is 14% higher than what we had found for pharma development ($146 million).[8]

Success Rate and Phase Transition Probabilities. Using information from the Tufts CSDD biopharmaceutical database, we estimated the phase transition probabilities shown in Figure 1. For comparative purpose, we also reproduce the phase transition probabilities for the DiMasi *et al*. (2003) study. Multiplying the phase transition probability estimates for biopharmaceuticals yields an overall clinical approval success rate of 30.2% (as opposed to 21.5% for pharma). To obtain an estimate of the expected clinical period cost per investigational molecule we need estimated probabilities that a molecule that enters clinical testing will reach a given phase. Those values can be derived from the transition probabilities and the overall clinical approval success rate. To be conservative, we assume a 100% success rate for regulatory approval submissions to the FDA so that the probability that a regulatory submission will be made is assumed to be the same as the overall clinical approval success rate. Previous studies have shown 100% success rates for regulatory submissions for biopharmaceuticals for almost every period analyzed (Reichert and Paquette, 2003; Reichert, 2005). Altering this value within reason does not have an appreciable effect on the results. Applying the probabilities as weights for the mean costs yields an estimated out-of-pocket cost per investigational molecule of $169 million for biopharmaceuticals.

Out-of-Pocket Clinical Cost per Approved Molecule. What we are mainly interested in are costs per approved new molecule. We obtain such values by dividing costs per investigational molecule by the estimated clinical approval success rate (30.2%). This yields an estimate of the out-of-pocket clinical period cost per approved new molecule of $361 million for biopharmceuticals.

Table 1. Out-of-pocket Preclinical and Clinical Period Cost per Investigational Biopharmaceutical Compound (In Millions of 2005 dollars)[a]

Testing phase	Mean cost ($)	Probability of entering phase (%)	Expected cost ($)
Preclinical	59.88	100	59.88
Phase I	32.28	100	32.28
Phase II	37.69	83.7	31.55
Phase III	96.09	47.1	45.26
Total			168.97

[a] All costs were deflated using the GDP Implicit Price Deflator.

Out-of-Pocket Preclinical Cost per Investigational Molecule

Preclinical cost per investigational molecule is obtained by multiplying our estimated clinical phase cost per investigational molecule by a ratio of preclinical to clinical expenditures obtained by applying the lag noted above to the aggregate expenditure time series data. The aggregate data, with a lag imposed, implies that clinical period phase costs should account for 65% of total out-of-pocket cost. These estimates yield an out-of-pocket preclinical cost per investigational molecule of $59.9 million, and, using a 30.2%

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clinical approval success rate, a preclinical out of-pocket cost per approved new molecule of $198 million.

Capitalized Costs

As noted above, to obtain estimates that include the time costs of new drug development we need to estimate development times and choose an appropriate discount rate.

Development Times. Our data on biopharmaceutical compound development histories for the period analyzed yielded the mean clinical development and approval phase lengths shown in Figure 2. The phase results are averages across all compounds that completed the phase, regardless of whether the compound was ultimately approved for marketing. For comparative purposes we also show the pharma development time results from DiMasi *et al*. (2003). Total clinical plus approval time is 8% longer for the biopharmaceuticals, with nearly all of the difference accounted for by phase I.

Cost of Capital. In our prior analysis of traditional pharmaceutical firms, we utilized a cost of capital of 11% as a discount rate for R&D activities that were first taken into clinical trials between 1983 and 1994 (DiMasi *et al*., 2003; Grabowski *et al*., 2002). This cost of capital estimate was based on concepts from modern finance theory.

Utilizing the CAPM framework (Brealey and Myers, 2000), the firm's cost of capital, r^*, is a weighted average of its cost of capital on its debt and equity capital.[9] Given the low debt values of large pharmaceutical firms, the equity cost of capital becomes the key factor driving the weighted cost of capital for the firms. In the case of biotech firms the debt component is negligible,

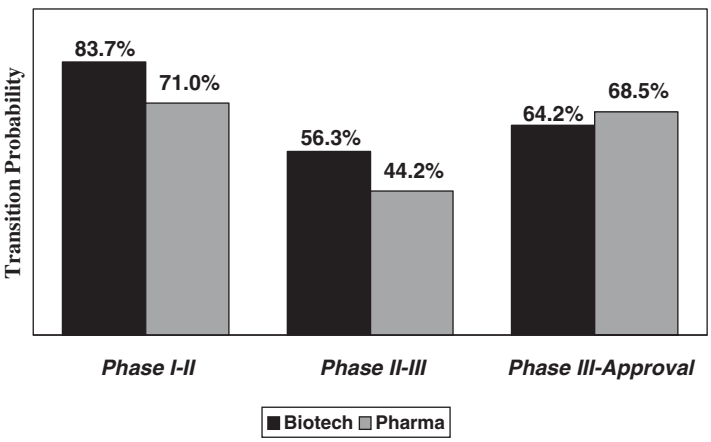


Figure 1. Transition probabilities for clinical phases.

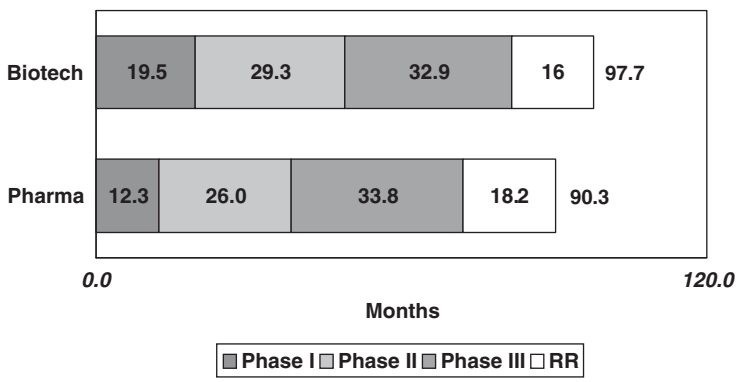


Figure 2. Clinical development and approval times.

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given that long-term debt after 1990 is less than 1% of market valuation. Thus, for all practical purposes the equity cost of capital for biotech firms is the same as their weighted cost of capital.

In the CAPM framework, investors require a risk premium for holding equity in a particular company. This premium is based on the relative riskiness to investors of that company's assets. The formal measure of relative riskiness is the beta coefficient, or the firm's contribution to the variance in the returns from a diversified portfolio of equity shares. The CAPM assumes that investors hold well-diversified portfolios.

The CAPM implies that the expected return on a firm's assets (the equity cost of capital) is equal to the risk-free rate plus a risk premium which is positively related to the riskiness of the firm's assets relative to other stock market assets

$$r_E = r_f + beta(r_m - r_f).$$

In this equation r_f is the risk-free rate (the return in treasury bonds minus a horizon premium is typically used as a proxy for the risk-free rate); r_m is the long-term rate of return for a market basket of common stock (usually the S&P index); $(r_m - r_f)$ is the equity premium, and beta is a measure of the relative riskiness of a specific firm (based on a regression analysis that yields the covariance of returns with the overall S&P index).

Under CAPM, a firm with a beta of one would have the same riskiness as the overall S&P index, whereas those with values greater than one are more risky, and correspondingly, those with betas below one are less risky. Company specific values for beta can be found in Value Line's Investment Surveys and other security analyst publications. Betas in these sources are typically updated on a periodic basis.

Myers and Shyam-Sunder (1995) examined the cost of capital for seven smaller biotechnology and specialty pharmaceutical firms for 1989. These firms had higher betas and costs of capital than the major pharmaceutical firms. The greater betas or riskiness exhibited by these firms were consistent with the fact that the smaller biotech firms had fewer commercialized products and proportionately more earlier-stage R&D projects. The average cost of capital for the full sample of seven biotech and specialty pharma firms was 19% in nominal terms and 14% in real terms.

Using the same methodology as employed by Myers and Shyam-Sunder (1995) and other financial economists, we estimated cost of capital values for a sample of biotech firms at roughly five year intervals from their 1989 estimate. The lower value in 2004 reflects declining value in the risk free rate and the equity premium in recent years compared to the 1994–1999 period. The focus of our analysis is on R&D projects initiated since the mid 1990s through the early 2000s where a 10% to 12.5% rate was observed. We therefore use the average of the three values for the cost of capital in Table 2, 11.5%, as the benchmark value for biopharmaceuticals. We also perform simulations around this baseline value to analyze the sensitivity of the capitalized R&D cost to this cost of capital value.[10]

Discussions with a few of the leading pharmaceutical firms suggest that a nominal cost of capital in the range of 12–15% was being utilized by many large pharma firms in 2001–2002 (Grabowski, *et al.*, 2002). Given a 3% rate of inflation, this would imply a 10–12% real cost of capital for major pharmaceutical firms. This is roughly consistent with estimates of the cost of capital derived from the CAPM in this period.

Capitalized Costs per Investigational Molecule. We obtain capitalized costs by spreading our estimated expected out-of-pocket phase costs per investigational molecule over estimated mean phase lengths and then capitalizing them forward to marketing approval at an 11.5% discount rate using a representative time profile. The results are shown in Table 3.

Preclinical capitalized cost per investigational molecule is obtained by spreading the out-of-pocket cost per investigational molecule determined above ($60 million) over an estimated preclinical period (52.0 months) and then capitalizing forward to marketing approval at an 11.5% discount rate over the representative time profile. Doing so yields a capitalized preclinical period cost per investigational molecule of approximately $186 million. Capitalized clinical cost per investigational molecule is obtained by capitalizing

Table 2. Nominal and Real Cost of Capital (COC), 1994–2004

	1994	2000	2004
Nominal COC (%)	17.0	15.0	13.0
Inflation rate (%)	4.5	3.0	3.0
Real COC (%)	12.5	12.0	10.0

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Table 3. Capitalized Preclinical and Clinical Period costs per Investigational Biopharmaceutical Compound (In Millions of 2005 dollars)[a]

Testing phase	Expected out-of-pocket cost ($)	Phase length (mos.)	Monthly cost ($)	Start of phase to approval (mos.)	End of phase to approval (mos.)	Expected capitalized cost[b] ($)
Preclinical	59.88	52.0	1.15	149.7	97.7	185.62
Phase I	32.28	19.5	1.66	97.7	78.2	71.78
Phase II	31.55	29.3	1.08	78.2	48.9	56.32
Phase III	45.26	32.9	1.38	48.9	16.0	60.98
Total						374.70

[a] All costs were deflated using the GDP Implicit Price Deflator.
[b] Expenditures capitalized forward to the point of marketing approval for a representative time profile at an 11.5% real discount rate. The estimated length of the approval phase is 16.0 months.

out-of-pocket clinical phase cost forward to marketing approval according to the time profile in Figure 2. This yields a capitalized clinical period cost per investigational molecule of approximately $189 million.

Total R&D Costs per Approved Molecule

To get estimates of fully allocated total cost per approved new molecule, we need only add estimates of cost per approved molecule for the preclinical and clinical periods. Applying the clinical approval success rate of 30.2% for biopharmaceuticals to the capitalized preclinical cost per investigational molecule noted above yields a preclinical period cost per approved new molecule of $615 million. Similarly, applying the success rate to our estimate of capitalized clinical period cost per investigational molecule yields a capitalized clinical period cost per approved molecule of $626 million. Total capitalized cost per approved molecule for biopharmaceuticals is then $1241 million. Out-of-pocket, time, and capitalized costs per approved new molecule are shown in Figure 3.

R&D Cost Comparisons: Biotech and Pharma. Our estimates for biopharmaceutical out-of-pocket preclinical, clinical, and total out-of-pocket R&D costs are shown in Figure 4. For comparative purposes, we also show the corresponding figures for pharma from our most recent study of R&D costs for traditional pharmaceutical firms (DiMasi *et al*., 2003). The overall figures for pharma firms are significantly lower than those for biotech development. Biopharmaceutical costs are 46% higher for the preclinical period, 14% higher for the clinical period, and 24% higher in total.

It may be the case, however, that the appropriate figures for R&D costs for traditional pharmaceutical firms to compare with our biotech estimates should be much higher than those shown by the middle bars of Figure 4. The reason is that the biotech data are somewhat more recent than the data used for DiMasi *et al*. (2003). We conducted two types of comparisons to judge the extent to which the period is shifted. Examining both actual approval dates for biotech compounds in the Tufts CSDD database and for those used in the DiMasi *et al*. (2003) sample, as well as average approval dates on which phase I testing began for biopharmaceutical compounds and for the data in DiMasi *et al*. (2003), suggested a shift of approximately five years in the study periods. Thus, we should consider what new drug development costs for pharma firms would be five more years into the future. In DiMasi *et al*. (2003) we compared costs for the current sample to those for an earlier period covered by a previous study (with more than a decade difference in time). We applied the growth rates (over and above inflation) for the preclinical and clinical periods that we observed between our two earlier studies on pharma costs to the most recent pharma data assuming a further five-year shift. The results are the pharma time-adjusted values given by the third set of bars in Figure 4. The unadjusted figures can be viewed as what the outcomes for pharmaceutical firms would be if they had kept cost increases in the later five-year period in line with general inflation.

The time-adjusted out-of-pocket biotech costs for the preclinical period are still somewhat higher than for pharma even with the period adjustment (32% higher). However, for the clinical period and

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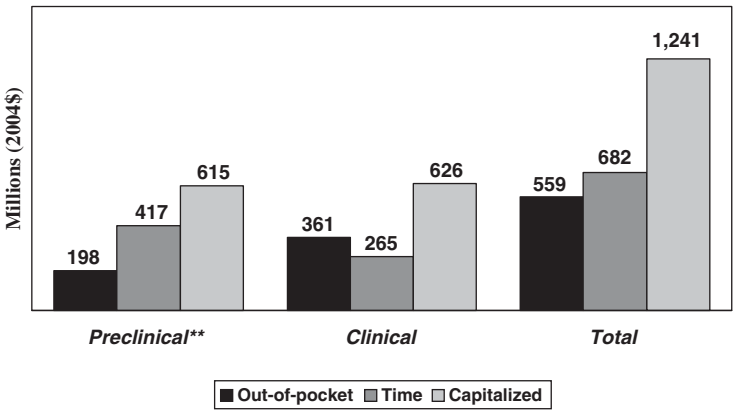


Figure 3. Pre-approval out-of-pocket (cash outlay) and time costs per approved new biopharmaceutical.*

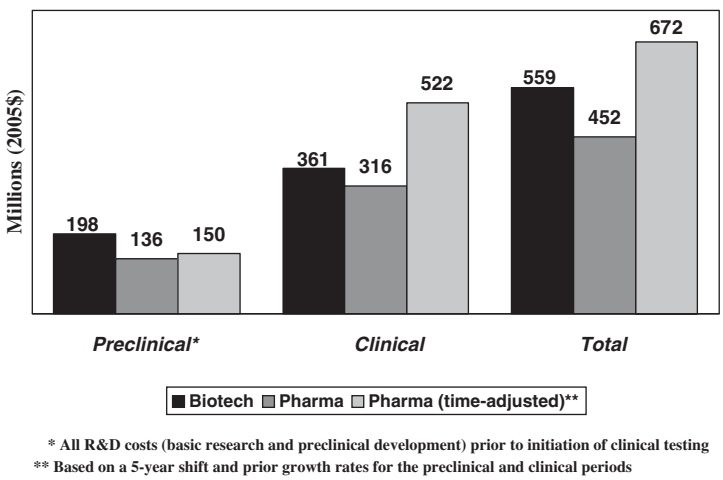


Figure 4. Pre-approval cash outlays (out-of-pocket cost) per approved new molecule.

in total, biopharmaceutical out-of-pocket costs are lower than our reported pharma costs adjusted for a later period. Specifically, clinical period costs are 31% lower and total costs are 17% lower for biopharmaceuticals. Of course, we do not know if pharma costs continued to increase at the same rates as they had in the past.

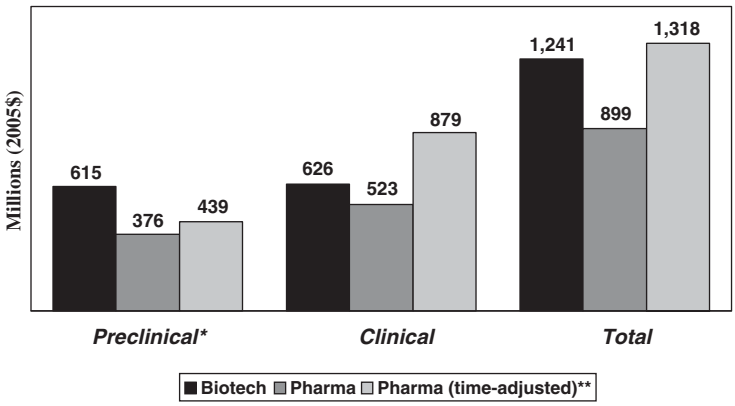
Our main results for capitalized costs are shown in Figure 5. Capitalization increases biopharmaceutical costs relative to pharma costs because of a longer development timeline and a higher cost of capital.[11] As a result, the capitalized preclinical costs for biotech are proportionately higher (40%) relative to time-adjusted pharma costs than are out-of-pocket costs. However, capitalized clinical period and total costs are proportionately closer to pharma costs than are out-of-pocket costs. Capitalized clinical period costs for biopharmaceuticals are 29% lower than for time-adjusted pharma costs. However, total capitalized cost per approved biopharmaceutical ($1241 million) is only 6% lower than total capitalized time-adjusted pharma cost ($1318 million).

CONCLUSIONS

While estimates of the level of, and trends in, R&D costs for traditional pharmaceutical firms have been published, to date no studies have focused

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* All R&D costs (basic research and preclinical development) prior to initiation of clinical testing
** Based on a 5-year shift and prior growth rates for the preclinical and clinical periods

Figure 5. Pre-approval capitalized cost per approved new molecule.

specifically on biotech firms or particular types of biopharmaceutical development. We have taken a first step toward getting a sense for the magnitude of what the full R&D resource costs associated with discovering and developing biopharmaceuticals to the point of initial regulatory marketing approval had been for recent years. Using compound-specific costs for a sample of 17 investigational biopharmaceuticals from four firms, a time series of annual preclinical and clinical expenditures for a biotech firm, estimated average development times and phase transition probabilities for over 500 therapeutic recombinant proteins and mAbs, we estimated average preclinical period, clinical period, and total costs per approved new biopharmaceutical. We found out of-pocket (cash outlay) cost estimates of $198 million, $361 million, and $559 million per approved new biopharmaceutical for the preclinical period, the clinical period, and in total, respectively (in year 2005 dollars). These figures include the costs of compound failures. Adding time costs to cash outlays, we found cost estimates of $615 million, $626 million, and $1241 million per approved new biopharmaceutical for the preclinical period, the clinical period, and in total, respectively (in year 2005 dollars).

Our estimates for biopharmaceuticals are higher than those we found for our previous study of pharma costs (DiMasi *et al*., 2003). However, the biopharmaceutical data that we used is of a more recent vintage. If past growth rates in R&D costs for traditional pharmaceutical firms are applied to the results in DiMasi *et al*. (2003), then total capitalized biopharmaceutical cost per approved new molecule appears to be essentially the same as estimated total capitalized per approved new drug for traditional pharmaceutical firms. However, total out-of-pocket costs for biopharmaceuticals were found to be somewhat lower, both out-of-pocket and capitalized clinical period costs for biopharmaceuticals were lower, and preclinical period costs for biopharmaceuticals were somewhat higher.[12] Determining what the actual growth rates in costs for pharma firms had been in recent years awaits further study.

Several caveats to our results should be mentioned. The results are preliminary in that the sample size for mean phase costs is relatively small, although the sample sizes for development times and success rates are quite large. Beyond this, the comparisons with pharma costs should be viewed with some caution for two reasons. First, as noted, pharma costs may not have changed to the same degree in recent years as they did in the past. Second, costs can vary by therapeutic class (DiMasi *et al*., 2004). The distributions of investigational compounds by therapeutic class for traditional pharmaceutical firms do differ from the distributions by class for the recombinant protein and mAb biopharmaceuticals that we examined. Specifically, investigational biopharmaceutical molecules were more concentrated in the oncology and immunologic categories than were pharma molecules for the period analyzed in DiMasi *et al*. (2003), while the pharma distribution was more concentrated in the cardiovascular and neuropharmacologic classes. It is unclear how these differences affect the comparative results; while full clinical period costs for new cardiovascular and neuropharmacologic

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drugs were found in DiMasi *et al.* (2004) to be about average for pharma development, not enough information was available to determine costs for oncology and immunologic drugs. Additional research is needed to fully resolve these issues.

NOTES

1. Gottschalk (2004) notes that a manager at a biotech company estimated that his company spends in excess of one billion dollars to get a drug to market (lecture to Professor Fiona Murray's MIT Sloan Management class 15.968, 'Building a Biomedical Business,' by Bill Anderson, VP Business Planning, Biogen Idec Inc., 3 December 2003).
2. The firm provided data on its R&D expenditures in the form required to apply the basic methodology used in DiMasi *et al.* (2003). The purpose was to test their hypothesis that their R&D costs were in fact significantly lower than the estimate in DiMasi *et al.* (2003) for traditional pharmaceutical firms.
3. The sample consisted of nine recombinant proteins and eight mAbs.
4. Given that we use development times and success rates for what is essentially the universe of biopharmaceuticals developed by all firms, it is not possible to infer what costs per approved new molecule are for the biotech firm that provided molecule-specific cash outlays to us. Company-specific success rates, in particular, can have a substantial impact on total R&D costs for a given company. One might wonder, however, about the internal consistency of all of the data. It is unlikely that company-specific mean clinical phase expenditures will have an appreciable effect on success rates. It is also likely that mean clinical phase costs for an investigational molecule of a given type and therapeutic class will not vary much across firms. One potential concern, though, is the possibility that there were some time–cost tradeoffs for the phase data (Scherer, 1966). This is more of a concern for molecules that fail in testing than for those that succeed, since the total amount of testing for molecules that are eventually approved for marketing is likely to be essentially the same, regardless of whether some testing is done in parallel rather than sequentially. We have no reason to believe that the biotech firm in question here differed from other firms with regard to time–cost tradeoffs.
5. This data set consisted of 278 recombinant proteins and 244 mAbs.
6. See, for example, DiMasi *et al.* (1991), DiMasi (1995), Gosse *et al.* (1996), DiMasi (2001), DiMasi *et al.* (2003).
7. In the absence of precise data on the length of the preclinical period for these molecules, we used the value estimated for DiMasi *et al.* (2003). Managers at the biotech firm from which we obtained cost data agreed that the estimate was reasonable.
8. See, however, our discussion below about differences in time periods between our previous study and the data used for this report.
9. The weighted average company cost of capital can be expressed in terms of the following equation:

   $$r^* = r_D(1 - T_C)(D/V) + r_E(E/V),$$

   where r_D and r_E are the expected rates of return on assets of comparable riskiness for the firm's debt and equity securities, respectively. T_C is the firm's corporate tax rate, and D/V and E/V are the proportion of the firm's market valuation represented by debt and equity securities, respectively. The debt component of the cost of capital is multiplied by $(1 - T_C)$, because interest on debt obligations is tax deductible, while earnings on equity shares are not.
10. Financial economists suggest that the risk and cost of capital of an individual R&D project will depend on the stage of the project and, correspondingly, on the amount and timing of follow-on investments required to achieve commercial success. By contrast, the estimates derived from corporate financial data by Myers and Shyam-Sunder (1995) and other financial economists represent an average cost of capital for a firm's aggregate portfolio of R&D projects as well as their complementary capital investments in manufacturing and marketing assets. Some analyses of the pharmaceutical industry have utilized a higher cost of capital for earlier stage R&D projects based on cost of capital estimates from firms at different stages of the life cycle. For example, the Office of Technology Assessment (U.S. Congress, Office of Technology Assessment, 1993) utilized a 14.5% real cost of capital for the earlier pre-clinical stages of pharma R&D based on the Myers and Shyam-Sunder (1995) biotech and small firm sample, and lower values for later stages of the life cycle. Myers and Howe (1997) generate a 'stair-stepped' cost of capital using a Monte Carlo simulation model and an option value approach. To our knowledge, none of the big pharma firms use a stair-stepped cost of capital in their NPV and return calculations, but some are considering this approach.
11. The discount rate has a modest effect on total capitalized costs. If we use a 10.5% discount rate for biotech, then its total capitalized cost falls by 6.8%. If we use a 12.5% discount rate for biotech, then total capitalized cost is 7.3% higher.
12. The higher preclinical expenditures per approved biopharmaceutical may, to some extent, help explain the higher clinical approval success rates for biopharmaceuticals.

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