Research and Development Costs for New Drugs by Therapeutic Category
A Study of the US Pharmaceutical Industry

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Summary

The clinical period (i.e. clinical trial and long term animal testing) development costs of a random sample of new chemical entities (NCEs) were examined for differences in average cost. All of the NCEs studied were first tested in humans between 1970 and 1982, and were classified for the purposes of the study by therapeutic class. The costs of unsuccessful projects were included with those of projects that resulted in US marketing approval. Including income forgone from expending funds before returns are earned (‘time costs’), the capitalised (i.e. out-of-pocket plus time) clinical period costs per approved NCE were $US70, $US98, $US103 and $US163 million (1993 dollars) for anti-infective, cardiovascular, neuropharmacological and nonsteroidal anti-inflammatory drugs, respectively. Combining the data for all therapeutic categories, the mean clinical period cost per approved NCE was $US93 million.

Omitting costs associated with unsuccessful projects, the mean capitalised clinical period costs for approved NCEs ranged from $US7.1 million (for topical steroids) to $US66.7 million (for cardiovascular agents) [1993 dollars]. The estimates of total clinical period costs per approved NCE depend on average out-of-pocket clinical phase costs, attrition rates across phases (i.e. the rates at which compounds drop out of active testing), the probability of marketing approval, and development and regulatory review times. Phase attrition and approval rates are the most important sources of variability in total clinical period costs between therapeutic categories.

Development cost estimates by therapeutic category did not correlate strongly with US sales in the fifth year of marketing. Cardiovascular NCEs had much higher than average sales revenues, but clinical development costs for these drugs were only slightly above average. Conversely, nonsteroidal anti-inflammatory drugs attained average sales revenues, but had much higher than average development costs.

Growing concern over escalating pharmacy budgets of national healthcare authorities and managed care providers has led to pressures on pharmaceutical firms to offer cost-effective therapies. Regardless of whether or how healthcare reform in the US develops, the pharmaceutical industry will continue to face a marketplace where cost containment is a critical element. As a result of these de-
velopments and of rapidly rising research and development (R&D) costs for new drugs.[1] Pharmaceutical firms have paid increasing attention in recent years to improving the drug development process.

Although a given firm can examine its own development costs, it cannot know how its experience compares with that of the industry as a whole unless a third party provides that information. Elsewhere,[1] we have estimated the average cost of getting a new drug approved in the US and compared the results with those of another study that covered an earlier time period.[2] The development costs for individual drugs were, however, found to be highly variable. Part of that variability may be associated with the therapeutic category to which the drugs belong. In this study, we examine that issue in detail by providing estimates of the clinical costs of developing drugs in several therapeutic classes.

In addition to providing development cost benchmarks, the results of our study can serve as inputs for analyses of the profitability of drug development in various therapeutic programmes. These analyses, in turn, could be useful in developing insights into the R&D budget process for individual firms and for the pharmaceutical industry as a whole. Specifically, they may help us to learn more about how sensitive budgetary allocation decisions are to economic factors.

**Methods**

In estimating new drug development costs, we treated drug development as an investment with potential future returns. We also fully recognised the substantial risks in new drug development by including the costs of research failures along with the costs of the successes (drugs that eventually reach the marketplace). With the exception of anti-infective drugs, no data on preclinical period (time from drug synthesis to first testing in humans) expenditures were available, so most of our analysis was restricted to development that occurs after clinical testing has begun.

The basic methodology that we used to calculate clinical period costs (that is, the costs of clinical trial and long term animal testing) is described in detail elsewhere.[1] An overview of the data, how component cost estimates are derived and how these estimates are used to construct full development cost estimates is presented here.

**Data**

We obtained data on the cost and timing of development for a stratified (according to time in testing and regulatory fate) random sample of 93 new chemical entities (NCEs) first tested in humans in any country sometime between 1970 and 1982. The NCEs belonged to 3 broad and 1 very specific therapeutic categories: anti-infectives, cardiovascular agents, neuropharmacological and nonsteroidal anti-inflammatory drugs (NSAIDs). The data were taken from a confidential survey of 12 US-owned pharmaceutical firms. The sample includes NCEs that the firms abandoned without obtaining US marketing approval as well as NCEs that were approved. The full R&D costs for licensed or acquired NCEs are not reflected in the R&D budgets of the firms that acquired them, making it difficult to track those costs. Therefore, we restricted our analysis to self-originated NCEs (i.e. NCEs discovered and developed by one of the survey firms).

The sample was selected from a Tufts Center for the Study of Drug Development (CSDD) database on NCEs tested clinically in any country by US pharmaceutical firms. The CSDD obtains its information from a triennial survey of US pharmaceutical firms. Using this database, we were able to select a random sample of NCEs that met our inclusion criteria (i.e. self-originated and first tested in humans between 1970 and 1982) and were developed by firms that agreed to participate in our cost survey. Thus, no firm could pre-select drugs on which to report costs.

The surveyed firms provided clinical testing phase start and finish dates, clinical phase costs by year, animal testing costs incurred during the clinical testing period by year, and the date that testing
was suspended for those NCEs for which research was abandoned. New drug application (NDA) submission to the US Food and Drug Administration (FDA) approval dates were obtained from CSDD databases of investigational and approved NCEs. The firms reported clinical period development expenditures until 1987, inclusive. All reported R&D expenditures were converted to 1993 dollars using the Gross Domestic Product (GDP) Implicit Price Deflator (i.e. a price index for the output of the US economy).

**Phase Costs for Investigational New Chemical Entities**

To reduce sampling error, NCEs in the sample were grouped into strata according to their fate. Specifically, we noted: (i) the time spent in active testing for those NCEs that failed; (ii) whether or not research was still in progress; and (iii) whether or not an NDA had been submitted or approved. Within each stratum, sample NCEs were selected at random. NCEs that reached NDA submission or approval and NCEs that spent a relatively long time in testing before being abandoned were oversampled. The rationale behind this is that if the variance of costs is higher for drugs that spend longer in testing, then oversampling drugs that proceed further in the development process will, on average, reduce sampling error.

Weights were then applied to the data for the sampled NCEs to yield a sample that is representative of all NCEs. We developed separate sets of weights for each therapeutic category examined. Both mean and median phase costs for investigational NCEs entering a phase were computed based on these weights.

The number of NCEs from a group of investigational NCEs that remain in active testing will diminish as testing progresses from one phase to the next. The expected cost of developing an NCE that enters the clinic will depend on these attrition rates (i.e. the rates at which compounds drop out of active testing). We estimated the probability that an investigational NCE from a therapeutic class will eventually enter a given clinical or animal testing phase by using weighted survey responses about the development histories of NCEs in the class.

The estimated expected phase cost for a therapeutic class is the product of the weighted mean cost for investigational NCEs that entered the phase, and the estimated weighted probability that an investigational NCE from the class will reach that phase. The sum of these estimates for a therapeutic class yields an estimated out-of-pocket clinical period cost per investigational NCE for that class.

**Clinical Success Rates and Cost Per Approved New Chemical Entity**

While estimates of the expected development cost for an investigational NCE are important for planning purposes, the productivity of the pharmaceutical industry R&D process is measured by the cost of producing its final output: approved NCEs. Estimates of cost per investigational NCE can be linked to cost per approved NCE via a clinical success rate. We defined the clinical success rate for a therapeutic class as the percentage of investigational NCEs in the class that will eventually be approved for marketing. An estimate of out-of-pocket clinical period cost per approved NCE for a therapeutic category is obtained by dividing the estimate of cost per investigational NCE for the category by an estimate of the category’s clinical success rate.

We estimated clinical success rates for therapeutic categories using a 2-stage statistical process described in detail by DiMasi et al. The population of NCEs for which success rates were sought consisted of self-originated NCEs first tested in humans from 1970 to 1982 by firms that responded to our cost survey. Data on these NCEs were obtained from a CSDD database on investigational NCEs that tracks their development until 1989.

The first stage of the process is a survival analysis, where survival time for an NCE is modeled as the time from when the NCE is first tested in humans anywhere in the world to when either: (i) research on the NCE is abandoned; or (ii) the NCE is approved. Since some of the NCEs in the database were still active (i.e. they were either still...
under development or they had an NDA still under review) at the end of 1989, the data contain some right-censored values (i.e. their ultimate fate was unknown at the time of analysis). Consequently, nonparametric statistical procedures such as life-table analysis or the Kaplan-Meier technique were helpful.\cite{11} The Weibull and exponential parametric models were tried, but they did not fit the data well. Thus, life-table analysis was used to estimate NCE survival times.

The second stage in estimating clinical success rates for NCEs consists of estimating the conditional probability of approval, given a survival time for an investigational NCE in a therapeutic class. Probit and logit specifications were tried for this stage of the analysis, and the choice of specification was made on the basis of how well each of the models fitted the data. The probability that marketing approval will be obtained a given number of years from the initiation of clinical testing can be estimated from the product of: (i) the estimated probability of survival to that point in time; and (ii) the estimated conditional probability of approval given that the NCE survives that many years.

**Phase Lengths**

We used the phase-testing start and finish dates that the firms provided for our cost survey to determine: (i) average phase lengths for phase I, phase II, phase III and long term animal testing; and (ii) a time profile for a representative NCE passing through all phases to approval. Mean phase times were calculated using the stratified sample weights for the therapeutic classes. The NDA phase is defined as the time from NDA submission to NDA approval. Average NDA phase lengths were determined from a CSDD database on NCEs approved for marketing in the US. The NDA phase lengths for self-originated NCEs of US-owned firms that were first tested in humans during 1970 to 1982 were used to calculate the mean NDA phase lengths for the therapeutic classes investigated in this study.

Successive phases do not usually end and begin at the same time. Often, testing for one phase ends after (sometimes substantially after) the next phase has begun. In addition, clinical testing for a phase sometimes ends before the next phase begins. Thus, adding the mean clinical and NDA phase lengths would not necessarily give us an accurate average development time profile. To construct a representative time profile, we calculated the weighted mean overlaps or gaps between successive phases. Combining these average overlaps/gaps with the results on average phase lengths, we determined the mean time from the start of one phase to the start of the next phase.

**Capitalised Costs**

Development expenditures are treated here as an investment, with returns delayed until marketing approval. With development viewed in this manner, firms have costs in excess of what is paid out-of-pocket. We refer to this type of cost as 'time cost'. Time cost measures the income forgone from investing in development for a period before returns are earned. The sum of out-of-pocket and time costs is the opportunity cost, or capitalised cost, of new drug development.

To capitalise out-of-pocket costs, we used a discount rate that is applicable to the US pharmaceutical industry for the period studied. A 9% discount rate, as described by DiMasi et al.,\cite{11} was used to capitalise expenditures on the NCEs investigated in this study. This rate is an estimated long term cost of equity capital for a sample of pharmaceutical firms.\cite{14}

The Office of Technology Assessment (OTA) capitalised the out-of-pocket R&D costs given in DiMasi et al.\cite{11} at a variable discount rate.\cite{51} The OTA varied the discount rate from 14% for the earliest preclinical expenditures to 10% for the final clinical expenditures. The discount rate range was chosen from cost-of-capital estimates given by Myers and Shyam-Sunder\cite{66} for a group of small, mainly biotechnology, firms and a group of large traditional pharmaceutical firms. The rationale for this approach derives from noting that the sequential nature of R&D requires higher costs of
capital for funding of early stage than for late stage projects.

Ideally, however, cost-of-capital estimates for R&D projects would be estimated directly, as opposed to being inferred from cost-of-capital estimates for firms of different types and sizes. In the best of all worlds, we would also have empirical analysis available that determines the rates at which costs of capital should decrease from the earliest to the latest stage development for specific therapeutic classes. Furthermore, traditional pharmaceutical firms tend to acquire their financing based on the performance of the firm as a whole, rather than that of individual R&D projects. Finally, we are mainly interested here in relative costs for therapeutic categories. Varying discount rates has a second-order impact on relative costs; that is, the primary effects are on absolute costs, while the effects on relative costs are minimal.

For these reasons, we retained 9% as the discount rate to use for our base-case analysis. However, we did perform sensitivity analysis on this parameter. We report on costs by therapeutic category at discount rates of 5, 10 and 15%. Costs obtained via an analysis like that performed by the OTA would necessarily fall between the estimates for discount rates of 10 and 15%.

We also examined results for a variable discount rate using the OTA range for the cost of capital for R&D projects. The OTA varied rates linearly according to the time profile for all NCEs described by DiMasi et al. However, time profiles for NCEs vary according to therapeutic class. Thus, expenditures incurred a given number of years before marketing approval will, on average, be applied to different developmental stages depending on the therapeutic class.

To apply the concept of a variable discount rate to estimating costs for therapeutic classes, we determined the discount rate ranges that are implicit in the OTA formulation for each clinical phase (and the long term animal testing period). We then applied these ranges to the corresponding phases for each therapeutic class. For this analysis, we must therefore assume that the cost of capital depends only on the stage of development.

Preclinical Costs for Anti-Infectives

Discussions with pharmaceutical industry R&D personnel led us to consider the possibility that low clinical development costs per approved NCE for anti-infectives may be offset by high costs for preclinical development. Consequently, for our survey, we asked firms to allocate aggregate annual preclinical development expenditures between anti-infectives and all other compounds. Basic research expenditures were not broken down in any way. If we assume that these expenditures follow the same allocation to anti-infectives as do preclinical development expenditures, then we can provide estimates of total expected anti-infective costs in a manner similar to that described by DiMasi et al. for all NCEs in the sample.

Results

Enough data from the sample of 93 NCEs were available to develop clinical period cost estimates that incorporated the costs of development failures for those NCEs. The sample contained 21 cardiovascular NCEs, 16 neuropharmacological NCEs, 15 anti-infective NCEs and 8 NSAID NCEs. These 4 classes accounted for two-thirds of the sample. One of the anti-infectives was an extreme high outlier in terms of development costs and was therefore unrepresentative of the class. The results given below exclude this outlier.

Uncapitalised Phase Costs

Mean phase costs for NCEs by therapeutic category are given in figure 1. Firms reported costs for some animal testing during the clinical period that they did not classify as long term animal testing. In the absence of a better term, we refer to these expenditures as 'other animal testing' costs. These costs constitute a small part of the total animal testing costs for NCEs in every therapeutic category in which they appear.
Relative costs across clinical phases are consistent in that categories of NCEs with above- or below-average costs in one phase tend to have above- or below-average costs, respectively, in other phases. Despite relatively short development times, investigational anti-infective NCEs have above average clinical phase costs. For example, the median phase III cost for anti-infective NCEs is 40% above the phase III median for all NCEs in the sample (approximately $US13.7 million vs $US9.8 million) and 61% above the medians for phases I (approximately $US1.9 million vs $US1.2 million) and II (approximately $US4.3 million vs $US2.7 million).

In addition, even though development times tend to be long for neuropharmacological NCEs, their clinical development phase costs are generally below average. Although the mean phase III cost for neuropharmacological NCEs is approximately the same as that for all NCEs, the median phase III cost for neuropharmacological NCEs is 39% below the full sample median.

The most notable phase costs are for NSAIDs, which are substantially above average. Compared with costs for the full sample, mean phase costs for NSAIDs are 54 and 44% above average for phases I and II, respectively. However, the mean phase III cost for NSAIDs is more than double that for all NCEs. These differences with the full sample are even more pronounced for median values. Median phase costs for NSAIDs compared with all NCEs are 166, 143 and 254% higher than for all NCEs combined for phase I, II and III, respectively.

Cardiovascular NCEs have clinical phase costs that are moderately above average. Mean phase costs for cardiovascular NCEs compared with the
full sample values range from 13% above average (phase III) to 20% above average (phase II). Median costs for cardiovascular NCEs range from 12% above average for phase III ($US11 million vs $US9.8 million) to 22% above average for phase I ($US1.46 million vs $US1.2 million).

Long term animal testing costs were, on average, lowest for anti-infective and greatest for cardiovascular NCEs. These results reflect usage patterns for many of the drugs in these 2 categories. Anti-infectives are generally intended for short term use, while cardiovascular NCEs are often used for long periods. NSAIDs had median long term animal costs that were 50% below average ($US0.83 million vs $1.66 million). Mean long term animal costs for NSAIDs, however, were 7% above average (fig. 1).

The phase cost distributions, for the most part, are highly positively skewed. That is, for the full sample of NCEs, mean phase I, II, III and long term animal testing costs were 61, 62, 82 and 124% greater than their respective median costs. In addition, mean values substantially exceed medians within each therapeutic class, with the exception of the NSAID category. Although mean long term animal testing costs are more than 4 times as large as median costs for NSAIDs, the clinical phase means for NSAIDs were only 26, 9 and 4% greater than phase medians for phases I, II and III, respectively. However, the sample size for NSAIDs was smaller than for the other classes.

**Phase Success Rates**

To determine expected phase costs for NCEs entering clinical testing, we used cost survey data to estimate phase-to-phase success rates by therapeutic class. The results are shown in figure 2. The
estimated probabilities that an investigational NCE will reach phases II and III are greatest for neuropharmacological NCEs. While 75% of all investigational NCEs reach Phase II, nearly 90% of neuropharmacological NCEs enter that phase. The deviation of the NCEs in the neuropharmacological category from the average is also substantial for long term animal testing: 76.8% of investigational neuropharmacological NCEs last long enough in the clinic for long term animal testing to be done, compared with 56.1% for the full sample.

Multiplying each of the mean phase costs in figure 1 by the corresponding phase-to-phase success rates in figure 2 yields expected phase costs (fig. 3). Although the estimated probabilities that a randomly selected investigational NSAID will reach the later testing phases are roughly equal to or less than those for all NCEs, mean phase costs for NSAIDs are so high that the expected phase costs for NSAIDs are well above average. Because out-of-pocket phase costs and probabilities of entering the later clinical testing phases are both above average for anti-infective NCEs, these drugs also have above-average expected clinical phase costs.

Estimated total out-of-pocket costs per NCE taken into the clinic can be obtained by adding the expected costs in figure 3 together. The out-of-pocket cost per investigational NCE for neuropharmacological ($US12.1 million), anti-infective ($US14.8 million) and cardiovascular ($US16.3 million) categories are all within 20% of the overall average ($US13.7 million). NSAID out-of-pocket cost per investigational NCE ($US22.1 million), however, is 61% above average.
Clinical Success Rates

The statistical procedures to predict clinical success rates (see Clinical Success Rates and Cost Per Approved New Chemical Entity in Methods) were applied to the data in the CSDD database of investigational NCEs for self-originated compounds. NCEs were included if they were first tested in humans between 1970 and 1982, and if they were originated by firms that responded to our cost survey.

The fates of the 43 anti-infective NCEs in the larger CSDD database that met these criteria, however, were known. Therefore, we used the actual percentage of investigational anti-infectives that gained marketing approval (30.2%) in our cost calculations.

Three of the 18 NSAIDs that met the above criteria have been approved. Only 1 NSAID of the 18 is ‘active’ and an NDA for it has been submitted. Since the vast majority of NDAs submitted eventually get approved and the cost per approved NCE is inversely related to the clinical success rate, we conservatively assumed that the submitted NDA for the active NSAID will be approved. This yields a clinical success rate for NSAIDs of 22.2%.

Statistical estimation is helpful in predicting clinical success rates for the other 2 therapeutic classes. We determined the predicted final success rates for NCEs in these 2 categories in the following way.

The number of neuropharmacological NCEs in our database that had been approved by the end of 1989 was 10 of 64 (15.6%). If all 4 of the 64 NCEs in this class that were still active at the end of 1989 are approved, then the final success rate for the neuropharmacological class will be 21.9%.

However, in general, we would not expect all of the active NCEs in this class to be approved. Each of the active NCEs has been active for 8.1 years or longer. Our statistical model predicts that 67.5% of
Table 1. Percentage of new chemical entities (NCEs) first tested in humans between 1970 and 1982 that were abandoned during a given development phase. An NCE was considered to have been abandoned during a phase if research on it was abandoned before the next testing phase was initiated.

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>Phase of clinical development</th>
<th>Total abandoned (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>phase I</td>
<td>phase II</td>
</tr>
<tr>
<td>AID-infective</td>
<td>21.6</td>
<td>35.8</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>36.1</td>
<td>27.7</td>
</tr>
<tr>
<td>Neurapharmacological</td>
<td>19.3</td>
<td>50.0</td>
</tr>
<tr>
<td>NSAOs</td>
<td>25.0</td>
<td>43.7</td>
</tr>
<tr>
<td>NF</td>
<td>25.0</td>
<td>38.8</td>
</tr>
</tbody>
</table>

a. Includes NCEs that were abandoned after submission of a new drug application.
b. Based on data for all 93 NCEs in the sample.

Abbreviation: NSAOs = nonsteroidal anti-inflammatory drugs.

neuropharmacological NCEs that have been active for at least 8.1 years will be approved. This translates into the approval of 2.7 of the 4 active NCEs. Additionally, of the 11 neuropharmacological NCEs whose fate is known and that were active for at least 8.1 years, 7 (63.6%) have been approved.

Applying this approval rate to the 4 still-active neuropharmacological NCEs suggests that 2.5 of them will be approved. We assume, then, that 3 of the 4 active NCEs will be approved, and so choose a clinical success rate of 20.3% for neuropharmacological NCEs.

Similarly, 11 (18.0%) of the 61 cardiovascular NCEs in our database were approved as of the end of 1989. The 8 active NCEs in this class have been active for 7.1 years or longer. The statistical model predicts that 48.2% (5.3) of the active NCEs will be approved. Six of the 11 cardiovascular NCEs whose fate is known and that had been active for at least 7.1 years have been approved. This suggests that 4.4 of the 8 active NCEs will be approved. Thus, we assume that 5 of the 8 active cardiovascular NCEs will be approved. Consequently, our choice of a clinical success rate for cardiovascular NCEs is 26.2%.

Estimated success rates are shown in figure 4, expressed as the probability of marketing approval (by the US FDA) for NCEs that enter phase I, II and III testing. Success rates for drugs entering phase I are those given earlier in this section. Rates for phases II and III were determined from the information in figure 2 and the clinical success rates given in this section.

There is substantial variation in success rates between therapeutic classes. For example, while more than 75% of the anti-infective NCEs that reach phase III will be approved, only just over half of the neuropharmacological NCEs that enter this costly phase will be approved.

The results on clinical success rates and the probabilities of entering a phase (fig. 2) can also be used to determine phase attrition rates. The results (table I) show that there is substantial variation in attrition rates between therapeutic categories. Most notably, cardiovascular NCEs tend to be screened out relatively early in clinical development, while testing on neuropharmacological NCEs extends more often than average into the later clinical phases before research is abandoned. Research on approximately one-third of all the investigational NCEs that fail is abandoned before phase II testing is undertaken. However, nearly half of the investigational cardiovascular NCEs that fail are abandoned during phase I. In contrast, research on only 13% of eventual neuropharmacological failures is terminated in phase I. Approximately 24% of neuropharmacological failures occur during phase III or later, while only 13.6% of cardiovascular failures occur this late in the process. For comparison, 17% of all failures occur in phase III or later.

The clinical success rates can be combined with the estimated expected out-of-pocket cost per in-
vestigational NCE to determine estimates of out-of-pocket cost per approved NCE. Although the expected out-of-pocket cost per investigational anti-infective is 8% above average, a higher than average clinical success rate for anti-infectives (30.2%) results in a cost per approved NCE of $US49.0 million, which is 18% below the overall average ($US59.6 million). Conversely, a below-average clinical success rate for neuropharmacological NCEs (20.3%) yields a cost per approved NCE of $US61.1 million (2.5% above average) despite a cost per investigational NCE that is 9.0% below average. Costs per approved NCE for cardiovascular and NSAID NCEs are 4.4% ($US62.2 million) and 67.0% ($US99.5 million) above average, respectively.

Phase Lengths

Figure 5 shows weighted mean phase times for NCEs in each therapeutic class. Anti-infectives have the lowest average clinical phase and regulatory review times. In contrast, NSAIDs have an unusually long average phase III length. The average regulatory review time is more than 18 months longer for neuropharmacological NCEs than for anti-infective compounds.

To capitalise costs, however, we need to know how expenditures are distributed over the time from first testing in humans to marketing approval. Specifically, we must construct a time profile that accounts for both: (i) average phase lengths; and (ii) average overlaps with or gaps between phases. The gaps and overlaps for the early clinical phases...
were generally found to be small. However, the overlaps between phase III testing and the NDA phase were, on average, larger. In particular, NSAID phase III testing ended, on average, more than halfway through the NDA phase (24.3 months after NDA submission).

Representative time profiles for NCEs passing through all clinical phases to marketing approval are shown in figure 6. The variation in time profiles between therapeutic categories is substantial. For example, the time from the start of phase I testing to NDA approval for anti-infectives is nearly 2 years shorter than average. Although the total pre-NDA clinical development time is slightly longer for cardiovascular and NSAID NCEs than for neuropharmacological compounds, NCEs in the latter category have longer average regulatory review times and the longest time profile overall.

**Capitlised Costs**

Expected out-of-pocket phase costs (fig. 3) can be distributed over the estimated time profiles and capitalised to the time of marketing approval. Expected phase costs capitalised at a 9% real discount rate are shown in figure 7. Adding the capitalised phase costs for a therapeutic category yields estimates of the total expected capitalised cost for an NCE in that category entering the clinic. Capitalised costs per investigational NCE for neuropharmacological ($US20.9 million) and anti-infective ($US21.2 million) NCEs are very close to the average for all NCEs ($US21.5 million). However, capitalised costs per investigational NCE for cardiovascular NCEs ($US25.8 million) are 20% above average, and capitalised costs per NSAID ($US36.1 million) are 68% above average.

Differential clinical success rates (fig. 4) can result in more variable costs per approved NCE. Capitalised clinical period costs per approved NCE are shown in figure 8. Despite an expected capitalised cost for anti-infective NCEs entering the clinic that is about average, an above-average success rate for anti-infectives produces a capitalised cost per approved anti-infective NCE that is 25% below average. Similarly, even though cost per investigational NCE for neuropharmacological compounds is slightly below average, an above-average failure
rate for neuropharmacological agents yields a cost per approved NCE that is 10% above average.

Throughout the analysis, NSAID development costs have been substantially above average. Concordantly, we found that capitalised costs per approved NSAID were 74% greater than those for all NCEs.

Capitalised costs are very sensitive to the discount rate used to calculate them. Therefore, we calculated estimates for a wide range of discount rates, as well as a capitalisation regime where the discount rate varied with the development phase (table II). The results for a variable discount rate can also be approximated using a fixed rate of 11.6%. Capitalised costs rise by 47 to 79% when the discount rate increases from 5 to 15%. However, despite varying development time profiles for the therapeutic classes, the relative ranking of categories by cost does not change at discount rates greater than 5%.

Costs for Approved NCEs

The out-of-pocket and capitalised costs presented above link the costs of developmental failures to those of successes. It is also interesting to investigate the costs of successes considered in isolation. We examined these costs for therapeutic categories that had at least 3 approvals with full cost data. Data were analysed for anti-infective, cardiovascular, neuropharmacological and topical steroidal NCEs. Mean out-of-pocket costs and capitalised costs, using a 9% discount rate, for approved NCEs only are presented in figure 9.

Both neuropharmacological and anti-infective successes have about average out-of-pocket and capitalised total clinical period costs. Costs per
neuropharmacological and anti-infective NCEs are both much closer to the average value than in figure 8, primarily because of below- and above-average clinical success rates, respectively. Despite ranking only third among the categories in capitalised cost per approved NCE (fig. 8), with development costs only 5% above average, cardiovascular NCEs had the highest development costs among NCEs that were eventually marketed (27 and 26% above average for out-of-pocket and capitalised costs, respectively).

The most notable results, though, are for topical steroids. Their costs are 86 and 87% below average for out-of-pocket and capitalised costs, respectively. Each of the drugs in this group had very low development costs. The highest out-of-pocket clinical period cost of any NCE in the group was only $US8.7 million. The least expensive topical steroid

![Diagram showing cost distributions for different categories of NCEs](image)

**Fig. 8.** Estimated capitalised clinical period cost per approved new chemical entity (NCE). Data are from the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases (NADDK). The 'all' category results are the full sample of 90 NCEs. Costs were deflated using the Gross Domestic Product Implicit Price Deflator, and a 9% real discount rate was used to capitalise out-of-pocket costs per approved NCE.

Abbreviation: NSAID = nonsteroidal anti-inflammatory drug.
Fig. 9. Estimated mean out-of-pocket (top) and capitalised (bottom) phase and total clinical period costs for new chemical entities (NCEs) with US marketing approval by therapeutic category. The 'all' category results are taken from a sample of 93 investigational NCEs. Data are for self-originated NCEs that first entered clinical testing during 1970 to 1982. Costs were deflated using the Gross Domestic Product Implicit Price Deflator. A 9% real discount rate was used to capitalise out-of-pocket costs.
to develop cost $US1.5 million, less than the phase 1 cost of 45% of the 93 drugs in the original sample.

Total Cost for Anti-infectives

Preclinical anti-infective development accounted for 25.3% of total preclinical development expenditures (in inflation-adjusted dollars). Information in the CSD database of investigational NCEs indicates that 15.4% of the survey firm investigational NCEs that met study inclusion criteria were anti-infectives. These 2 percentages, together with a base case estimate of uncapitalised preclinical period expenditure per NCE tested in humans ($US18.7 million) for the sample as a whole, imply an out-of-pocket preclinical cost per anti-infective NCE of $US30.7 million. The anti-infective approval success rate (30.2%) can then be used to determine preclinical and total uncapitalised cost per approved NCE.

Thus, we estimated that the uncapitalised preclinical R&D cost per approved anti-infective NCE is $US102 million (25% above the full sample average) and that the total uncapitalised cost is $US151 million (7% above the full sample average). Hence, in terms of out-of-pocket costs, our results indicate that increased preclinical R&D costs more than offset reduced clinical costs for anti-infectives.

However, because R&D times are significantly shorter than average at both the clinical and preclinical stages for anti-infectives, this is not the case for capitalised costs. Costs were capitalised using a 28.9 month preclinical period. This value is the mean preclinical period for the anti-infective NCEs in a CSD database of approved NCEs that met the inclusion criteria.

In particular, we estimate that capitalised preclinical R&D costs per approved anti-infective NCE are $US171 million (13% below the full sample average) and that the total capitalised cost per approved anti-infective NCE is $US241 million (19% below the full sample average of $US287 million). The anti-infective category therefore illustrates the value of a relatively short discovery and development period in containing total R&D costs.

Sales Revenues for Therapeutic Classes

Drug development in therapeutic classes with above-average costs can be sustained if returns are also above average. To examine the relationship, if any, between development costs and returns, sales in the fifth year of marketing and estimated capitalised clinical period costs were compared (table III). The reported average sales are based on US sales to hospitals and retail pharmacies. Data are reported for NCEs that meet our cost survey inclusion criteria.

Although clinical development costs for NSAIDs are well above average, their fifth year sales are only about average for all NCEs. Anti-infectives have both below average costs and below average sales. Although the cost estimate for cardiovascular NCEs is slightly higher than average, average sales for drugs in this category are substantially above average.

Although we do not have full cost estimates for each therapeutic class, the exceptionally high returns relative to clinical development costs for cardiovascular NCEs could explain the shift in R&D expenditures over time to this therapeutic area. Figure 10 shows that Pharmaceutical Manufacturers Association firms increased the percentage of their total R&D budget that was spent in the cardiovascular area from 11.1% in 1971 to 27.0% in 1987. However, this share subsequently declined to 19.6% in 1991.

Discussion

Although the average capitalised cost of new drug development is high, we have shown that the average cost varies substantially according to therapeutic class. Clinical period costs per approved anti-infective are appreciably lower than average, while NSAIDs have much higher than average costs. Average clinical development costs for the cardiovascular and neuropharmacological classes are modestly above the full sample average. Capitalised development costs per approved NCE are influenced by out-of-pocket phase costs, the rate of attrition across phases, the probability
Table III. Development costs and US sales 5 years after marketing for self-originated new chemical entities (NCEs) approved in the US and first tested in humans between 1970 and 1982. All costs are in 1993 dollars.

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>NCE approvals</th>
<th>Clinical period capitalised cost (US$ millions)</th>
<th>Mean US fifth year sales (US$ millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-infective</td>
<td>19</td>
<td>70</td>
<td>51</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>13</td>
<td>98</td>
<td>175</td>
</tr>
<tr>
<td>Neuropharmacological</td>
<td>15</td>
<td>103</td>
<td>79</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>6</td>
<td>163</td>
<td>86</td>
</tr>
<tr>
<td>All</td>
<td>69</td>
<td>93</td>
<td>87</td>
</tr>
</tbody>
</table>

a Excludes NCEs approved in the US after 1989.
b Costs and sales were deflated using the Gross Domestic Product Implicit Price Deflator. A 9% real discount rate was used to capitalise costs to the time of marketing approval.

Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.

of eventual marketing approval, and the length of time for development and regulatory review. However, little of the variability in clinical period costs associated with the broad therapeutic classes that we examined can be attributed to differences (by class) in out-of-pocket phase costs. More of the variability is attributable to differences in the length of the development and regulatory review processes.

Most of the differences in costs that we observed are attributable to variable phase attrition and clinical success rates. For example, even though mean phase costs for anti-infectives are close to the full sample means, anti-infectives have an appreciably higher probability of marketing approval, and shorter than average development and review times. The shorter phase lengths and, particularly, the higher probability of approval account for this category’s lower than average capitalised cost per approved NCE.

Although we found the differences in average costs for broadly defined classes to be moderate, the costs for some narrowly defined therapeutic categories are more extreme. Among the approved drugs in our sample, the topical steroids were notable for their low clinical development costs. Presumably, their relatively inexpensive and rapid development programmes can be attributed largely to the relative ease with which efficacy and safety can be established for compounds that are applied externally.

Conversely, NSAIDs have unusually high clinical development costs. Development and regulatory review times for this class are long and their out-of-pocket phase costs are very high. Regulatory and political pressures associated with this class may have been factors in producing these differences. Three of the compounds in this class that have been approved in the US (ibuprofen, naproxen and suprofen) have been withdrawn from the US market for safety reasons (hepatotoxicity, anaphylactic shock and renal failure, and flank pain and renal problems, respectively).

These withdrawals, in addition to the fact that there are numerous NSAIDs with acceptable safety profiles already on the market, led to scrutiny and criticism from the US Congress and consumer organisations of the NSAID development process.

![Fig. 10. Percentage of annual total Pharmaceutical Manufacturers Association member firm expenditures on research and development (R&D) of anti-infective, cardiovascular and CNS drugs.](image)
These factors may have made the approval process for NSAIDs more exacting than would otherwise have been the case.[12] In fact, mean NDA review times for NSAIDs approved after benoxaprofen and zomepirac were withdrawn in 1982 and 1983, respectively, tended to be much longer than for NSAIDs approved earlier (69 vs 27 months) [unpublished observations].

Development costs were not strongly correlated with fifth year sales revenues for NCE introductions over the study period. In particular, cardiovascular drugs had much higher than average sales revenues per NCE but only average clinical development costs. This is consistent with the observed increase over time in the cardiovascular share of pharmaceutical industry R&D budgets. In contrast, NSAIDs realised only average sales revenues, with much greater than average development costs. However, as noted above, NSAID development costs may have been affected by events during the period of analysis.

Nonetheless, the profitability of new drug development can be expected to affect decisions on how to allocate R&D resources. Although individual firms may pursue promising scientific leads in areas in which they have established programmes, firms will, over time, develop new programmes or expand existing ones if the potential returns relative to development costs in these areas become more financially attractive. Our results on cardiovascular drugs provide some evidence supporting such an 'R&D follows profitability' hypothesis.

We have not, however, examined the full product life cycle cash flows of NCEs by therapeutic class, or modelled the manner in which expectations about the profitability of NCE development are formed. With the exception of the anti-infective class, we also do not have data on preclinical costs. Much more comprehensive work on the relative profitability of development in therapeutic classes needs to be done before a relationship between expected profitability and the allocation of R&D resources can be firmly established.

Previous studies have examined the average R&D cost of new drug development as a whole.[1,2] Results from these studies indicate strongly that average R&D costs have increased substantially over the last several decades. It would be interesting to know, however, if these sharp cost increases were common to all therapeutic classes or confined to only a few. Unfortunately, we do not have comparable results from earlier studies to track changes in development costs for the therapeutic classes that we examined in this study. The results from this study can, however, serve as benchmarks against which to measure clinical development costs by therapeutic area in future work.

References

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