

R&D Costs and Returns by Therapeutic Category

Objectives: This study examines the degree to which therapeutic class accounts for variability in drug development costs. It also scrutinizes how sales levels vary across the associated therapeutic classes for those drugs that have reached the marketplace. **Data and Methods:** A stratified random sample of 68 investigational drugs that first entered clinical testing anywhere in the world from 1983 to 1994 was selected from the pipelines of 10 pharmaceutical firms. Clinical period cost data were obtained for these compounds by phase. The sample consisted both of drugs that failed in testing and drugs that obtained marketing approval. We grouped the drugs by therapeutic category. Clinical period costs per approved new drug (inclusive of failures) were obtained for the analgesic/anesthetic, antiinfective, cardiovascular, and central nervous system (CNS) therapeutic classes. Worldwide sales profiles for new drugs approved in the United States from 1990 to 1994 over a 20-year product life cycle were computed based on IMS Health sales data. All costs and sales were expressed in year 2000 dollars. **Results:** Out-of-pocket clinical period cost per approved drug (inclusive of failures) for cardiovascular (\$277 million) and CNS (\$273 million) drugs was close to the overall average (\$282 million). However, antiinfective drug costs were considerably above average (\$362 million) and anal-

gesic/anesthetic drug costs were modestly below average (\$252 million). The results were qualitatively similar when the development timelines were used to determine capitalized (out-of-pocket plus time) costs. In comparison to the overall average of \$466 million, the capitalized cost per approved drug was slightly lower for CNS (\$464 million) and for cardiovascular (\$460 million) drugs. The capitalized costs were \$375 million for analgesic/anesthetic drugs and \$492 million for antiinfective drugs. The mean net present values of life cycle sales for new drugs approved in the first half of the 1990s were \$2434 million, \$1080 million, \$2199 million, \$3668 million, and \$4177 million for all drugs, analgesic/anesthetic drugs, antiinfective drugs, cardiovascular drugs, and CNS drugs, respectively. **Conclusions:** Development costs vary substantially from drug to drug. A drug's therapeutic class can explain some of that variability. The sales of new drugs by broad therapeutic category did not correlate well with average development costs. However, given the dynamic nature of pharmaceutical markets and changes over time in research and development (R&D) expenditure shares, the results are still consistent with a model of firm behavior that posits that R&D efforts will generally shift toward high net return, and away from low net return, therapeutic areas.

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INTRODUCTION

Studies have shown that R&D costs for new drugs as a whole have increased substantially over time (1,2). New drug sales have also increased significantly, but new drug profitability studies have shown that sales and costs have more or less increased in tandem (3). At the same time, the political and economic environment for pharmaceutical firms has become increasingly tenuous. Double-digit annual percentage increases in pharmaceutical expenditures have given rise to numerous efforts to rein in those costs in the United States and abroad. The studies on new drug development prof-

itability have shown, though, that new drug sales are highly skewed. The temptation for proponents of stringent pharmaceutical cost containment to focus most attention on controlling expenditures for certain drugs is, therefore, quite strong. Such drugs, however, may provide the profits needed to cover the high R&D costs for drug development as a whole. Added to these developments are reports that drug company pipelines have thinned in recent years (4).

Given the economic, scientific, and political pressures and concerns weighing on the pharmaceutical industry, it is imperative that policy and business decisions be made on the basis of detailed data and analyses about components of

the drug development process. Regardless of the merits of various drug cost containment proposals, efforts to improve the efficiency of the drug development process can be productive for both pharmaceutical firms and patients. Analysis has shown, for example, that reducing development times, making decisions on drug failures sooner, and increasing approval success rates can have a substantial impact on R&D costs (5). The recent analyses of drug development costs and returns have provided insight into the economic outcomes of a complex process for drugs and the industry in general. It is useful to begin to develop a picture of the nature of new drug development from a financial perspective over recent periods at a more micro level. To that end, this study provides new results on the costs, risks, and length of the new drug development process at the therapeutic class level; compares these results to those from an earlier study on R&D costs by therapeutic area (6); and utilizes recent data to examine sales profiles over product life cycles by therapeutic class.

DATA AND METHODS

The R&D cost data for our analyses are described in detail in DiMasi et al. (2). Information was provided by 10 pharmaceutical firms on 68 randomly selected investigational compounds that were first tested in humans anywhere in the world from 1983 to 1994. The 68 compounds included four recombinant proteins, two monoclonal antibodies, and one vaccine. Both successful and failed compounds were included. Development costs for these compounds were collected through 2000.

The drugs in the sample that had attained United States marketing approval did so from 1990 to 2001. Five compounds were still in active testing at the time of analysis. The firms also provided data on their annual pharmaceutical R&D expenditures from 1980 to 1999, decomposed according to whether they occurred during the prehuman testing period or during the clinical testing period. In addition, they provided breakdowns according to whether the expenditures were for self-originated (develop-

ment up to initial marketing approval conducted under the auspices of the surveyed firm) compounds, licensed-in compounds, or improvements to existing (ie, already-approved) compounds.

Since it was not feasible to track all R&D costs for licensed-in drugs, the sample consisted of self-originated compounds. Approximately 99% of the United States new drug approvals obtained by the survey firms during the 1990s originated from industrial sources. Data were sufficiently robust for analysis of a number of broad therapeutic categories. Specifically, we provide clinical cost estimates for analgesic/anesthetic, antiinfective, cardiovascular, and CNS drugs.

COSTS FOR INVESTIGATIONAL DRUGS

We used a stratified random sampling process to select compounds for the survey firms from the Tufts Center for the Study of Drug Development (CSDD) ongoing database of investigational compounds. The stratification was done to reduce overall sampling error. Prior analyses had indicated that the variance of cost increased for later development stages or for longer periods in development. Four strata were chosen: compounds that failed in four years or less from the initiation of human testing, compounds that failed after more than four years from the initiation of human testing, compounds that had a New Drug Application (NDA) or Biological License Application (BLA) at least submitted for regulatory approval at some point, and compounds that were still in active testing. We over-sampled compounds that lasted long in development or had an NDA/BLA submitted and under-sampled drugs that failed relatively quickly. The costs for the drugs in the resulting sample were weighted so that the sample, after weighting, mirrored the population distribution for the strata.

CLINICAL SUCCESS AND ATTRITION RATES

Since the development process is risky, with drug candidates dropping out at various stages of development, our cost estimates are based on expected values. The clinical cost per investiga-

tional drug is a weighted average of mean phase costs. The weights are estimated probabilities that an investigational drug will make it to a given phase. The estimates needed to determine expected phase costs can be found by examining data on drugs that failed in testing. An estimate of cost per approved drug requires an estimate of an overall clinical success rate; that is, the probability that a drug that enters the clinical testing pipeline will eventually be approved.

The Tufts CSDD database of investigational drugs contains information on whether research on the drug has been terminated and the latest development phase the drug was in when research was terminated. This information can be used to estimate both the overall clinical success rate and the probabilities of an investigational drug entering a phase. Since some compounds are still in active testing at the time of analysis, the data are right-censored. Survival analysis and qualitative choice statistical techniques can be used in a two stage-model to estimate final success rates for the group of investigational drugs that first entered clinical testing in a given period. The methodology we use to estimate a final clinical success rate is described in detail elsewhere (1,7). The methods are applied to individual therapeutic classes. The data on research terminations by phase can be used in conjunction with the results on clinical success rates to determine the probabilities that an investigational drug will enter a given clinical phase.

PHASE DEVELOPMENT TIMES

R&D expenditures are incurred before any financial returns can be earned. Thus, there is a time cost to investing in pharmaceutical R&D. Determining the opportunity cost of new drug development requires, then, that a development timeline be constructed. Given that the approved drugs in the sample were approved from 1990 to 2001, with a concentration in the late 1990s, we analyzed data from Tufts CSDD databases of approved chemical and biopharmaceutical drugs for self-originated drugs that were approved from 1992 to 1999 by therapeutic class.

Mean clinical and regulatory approval phase lengths are determined from the Tufts CSDD data and used to establish a timeline from the initiation of clinical testing to NDA/BLA approval by therapeutic class. For some drugs, development is not strictly or continuously sequential. Some development occurs with gaps in time between successive phases, and, in some cases, a new phase will be initiated prior to the conclusion of the previous phase. We estimate the average gaps or overlaps between phases and include them in the representative timelines.

CAPITALIZED COSTS

The full economic cost of drug development is an opportunity cost. We measure it as the sum of out-of-pocket cost and the time cost of development. We use an estimate of the average pharmaceutical firm weighted cost of capital for the relevant time period as a discount rate. The methods and results are described in our earlier work (2). As is standard in these analyses, the flow of out-of-pocket costs are capitalized at the discount rate to the point of marketing approval. We assume that phase costs are distributed uniformly over the duration of the phase, and costs are compounded continuously.

SALES BY THERAPEUTIC CLASS

We sought worldwide sales by year for 118 new drugs approved in the United States from 1990 to 1994. We obtained data on the 118 drugs from company annual reports, financial analyst reports, industry publications such as *MedAdNews* (8), and a commercial information services provider to the pharmaceutical and other healthcare industries (IMS Health) which collects drug sales data (retail and hospital) from surveys and extrapolates them to the market as a whole. The sample drugs include biopharmaceuticals, as well as traditional chemical compounds. Three new drugs approved during the study period were excluded because they did not appear in the IMS Health sales audits. They are distributed outside normal channels and are likely to have unrepresentative R&D costs. We classified the drugs in the sample by therapeutic class.

We obtained data on worldwide sales for 66 compounds. These drugs accounted for more than 90% of the United States sales of all the drugs in the sample. Worldwide sales for the remaining compounds were obtained by applying a representative global sales multiplier to their United States sales. Additional details about the sample are described elsewhere (3).

We utilized a 20-year product life cycle for drugs in the sample. For the typical drug, sales beyond 20 years will contribute little since they will be small in undiscounted terms, and, therefore, quite small on a present discounted value basis. The worldwide sales experience of drugs coming off patent during 1994 to 1997 was used to determine the pattern of generic drug sales erosion after patent expiration for the highest selling drugs in the sample (31% in the first year, 28% of the remainder in the second year, and 20% per year thereafter). Lower selling drugs are less likely to face generic drug competition. For drugs in the bottom four sales deciles (determined by sales in the 10th year), we assume a more moderate rate of sales decline based on a reference life cycle curve that was estimated based on the period prior to patent expiration.

RESULTS

We used data collected for a study of the average cost of new drug development as a whole (2) to examine clinical period development costs by therapeutic class. The data were robust enough to provide separate estimates for four therapeutic categories. The sample included 10 analgesic/anesthetic drugs, 9 antiinfective drugs, 12 cardiovascular drugs, and 13 CNS drugs. These categories accounted for 65% of the total sample.

OUT-OF-POCKET COSTS FOR INVESTIGATIONAL DRUGS BY CLASS

Weighted mean phase costs are shown in Figure 1. Some animal testing occurs concurrent with clinical testing and these costs are also shown. These expenditures are low in relation to clinical phase costs. Costs by class are most variable for phase 3 and least variable for phase 2.

Mean clinical phase costs are uniformly below

average for the cardiovascular and CNS classes. Mean clinical costs for cardiovascular investigational drugs range from 7% below average for phase 3 to 40% below average for phase 1. Mean costs for CNS investigational drugs range from 4% below average for phase 2 to 27% below average for phase 1. For expensive phase 3 testing, CNS mean costs are 23% below average. In our earlier study on R&D costs by therapeutic category (6), cardiovascular and CNS (neuropharmacologic) investigational drugs had mean clinical phase costs that were about average or slightly above average.

The estimates for the analgesic/anesthetic and antiinfective investigational drugs are mixed. Mean phase 1 and phase 2 costs for analgesic/anesthetic drugs are above average (20% and 29%, respectively), but phase 3 costs are 24% below average. Antiinfective mean costs are 17% below average for phase 2, but substantially above average for phase 1 (53%) and phase 3 (59%). The high out-of-pocket clinical phase costs for investigational antiinfective drugs were driven largely, but not exclusively, by relatively high costs for AIDS antiviral drugs. In contrast, the results from our previous study (6) show that costs for nonsteroidal antiinflammatory drugs (NSAIDs), an important subclass of the analgesic/anesthetic category, were substantially above average (particularly for phase 3), and out-of-pocket phase costs for antiinfective drugs were modestly above average.

As is the case for all drugs, the phase cost distributions for the therapeutic classes are all positively skewed. Weighted means exceed weighted medians in all cases. However, the ratios of the mean to the median are in some cases smaller than for drugs as a whole and in other cases larger. As measured by the ratio of the mean to the median, phase costs for analgesic/anesthetic drugs and for cardiovascular drugs are more skewed than those for drugs as a whole for all clinical phases. For antiinfective drugs, costs were more skewed than for all drugs for phase 1, but less skewed for phases 2 and 3. CNS costs are more skewed than drugs as a whole for phases 1 and 2, but less skewed for phase 3.

The evidence suggests that the variability of

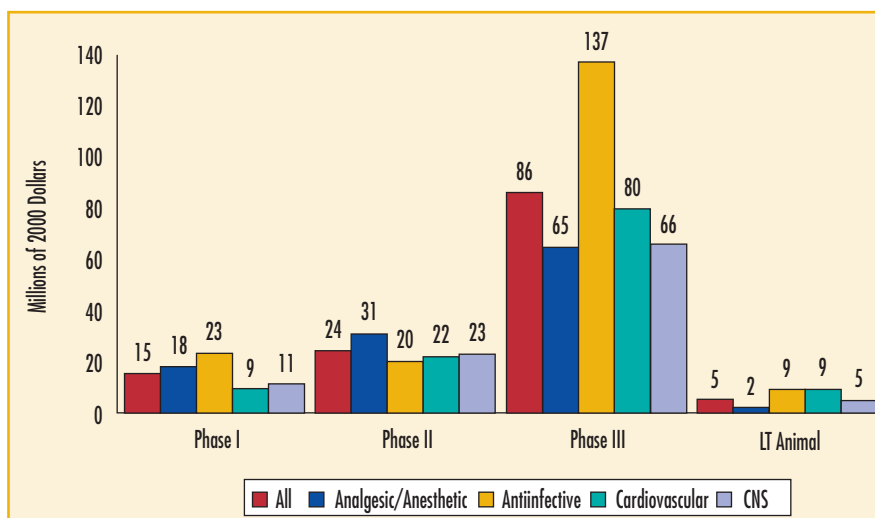


FIGURE 1

Mean phase costs by therapeutic class for investigational drugs entering a phase. LT animal = long-term animal testing concurrent with clinical trials.

drug costs is partially explained by therapeutic class. Although it is not the case for all classes in all phases, the relative variability of phase costs is generally less for therapeutic classes than it is for drugs as a whole (Table 1). The coefficient of variation is lower for two classes (antiinfective and CNS drugs) for phase 1, but higher for the other two classes. Similarly, the variability of the data for phase 2 costs is lower for two classes (analgesic/anesthetic and antiinfective drugs) and higher for the other two. However, variability is lower for all therapeutic classes analyzed than for drugs as a whole for the phase 3 testing period (particularly for CNS drugs).

SUCCESS RATES, PHASE ATTRITION RATES, AND EXPECTED COSTS BY CLASS

Statistical analysis of data from the Tufts CSDD database of investigational drugs was used to determine predicted final clinical approval success rates by therapeutic class for self-originated drugs first tested anywhere in the

world during 1983 to 1994. The estimates show a distinct clustering on either side of the success rate for all drugs (21.5%). The results indicate that approximately one in four investigational drugs in the analgesic/anesthetic and antiinfective classes will ultimately attain United States marketing approval (24.6% and 24.9%, respectively). Conversely, approximately 18% of the drugs in the cardiovascular and CNS categories will be approved for marketing (18.4% and 18.0%, respectively). In our previous study(6), the range of success rates by class was somewhat wider (20.3% for neuropharmacologic drugs to 30.2% for antiinfective drugs).

Antiinfective and analgesic/anesthetic drugs also have relatively high approval success rates for those compounds that reach phase 2 (37.7% and 34.8%, respectively), while success rates for cardiovascular and CNS drugs are below average (26.0% and 24.6%, respectively). In the previous study, antiinfective and cardiovascular drugs had above average success rates for drugs

Coefficient of Variation by Phase and Therapeutic Class					
	All ^a	Analgesic/Anesthetic	Antiinfective	Cardiovascular	CNS
Phase 1	0.84	1.15	0.42	1.04	0.82
Phase 2	0.94	0.77	0.45	1.12	1.17
Phase 3	0.70	0.60	0.44	0.51	0.28
Long-term animal	0.92	1.87	0.30	0.83	0.44

^aThe "All" category results are for all 68 investigational drugs in the sample.

TABLE 1

that entered phase 2, NSAIDs had an average success rate, and neuropharmacologic drugs had a below average success rate. For the current study the success rate for drugs that reach phase 3 is above average only for the analgesic/anesthetic class (78.3%). The phase 3 success rates for antiinfective, cardiovascular, and CNS drugs are 65.2%, 67.9%, and 61.0%, respectively, compared to an overall success rate of 68.5%. In our previous work, we found that antiinfective and cardiovascular drugs, and NSAIDs had above average success rates for phase 3, while neuropharmacologic drugs had a success rate for the phase that was substantially below average (51.1% compared to 63.5%).

While the success and failure rates noted above provide interesting perspectives on risks in drug development, the risk rates needed to compute fully-loaded costs are the probabilities that an investigational drug will enter the various testing phases. These estimates are shown in Figure 2. The values for phase 2 in the figure are transition probabilities. Each represents the probability that an investigational drug will proceed from phase 1 to phase 2. They range from approximately two in three for antiinfective drugs to nearly three in four for CNS drugs. Overall, fewer than one in three drugs that enter clinical testing will ever make it to phase 3. The likelihood is greatest for antiinfective drugs and lowest for cardiovascular drugs.

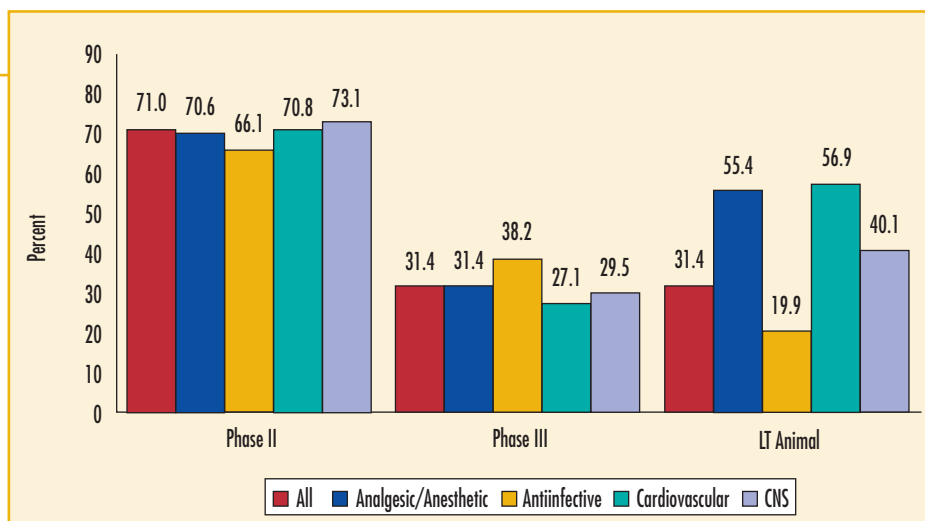
The relatively high probability of getting to

phase 3 for antiinfective drugs is, as noted above, associated with both a particularly low percentage of antiinfective failures occurring in phase 2 and a relatively high clinical approval rate for the class. Conversely, the relatively small percentage of investigational cardiovascular drugs that make it to phase 3 is linked to a high share of the class failures occurring in phase 2 and a low overall clinical approval rate. The likelihood that long-term animal testing will be initiated during the clinical period likely depends to some extent on how long a drug lasts in clinical testing and whether the drug is meant for long-term use. Cardiovascular, CNS, and analgesic/anesthetic drugs have relatively high chances that long-term animal testing will be conducted, while the antiinfective class has a relatively low likelihood of animal testing.

The product of the probabilities in Figure 2 and the mean out-of-pocket costs in Figure 1 yield expected costs per investigational drug. We can sum across phases to get an expected clinical period cost per investigational drug. Doing so for all drugs yields an expected cost of \$61 million. Expected clinical period cost per investigational drug by class are \$61 million for analgesic/anesthetic drugs, \$90 million for antiinfective drugs, \$52 million for cardiovascular drugs, and \$49 million for CNS drugs. Thus, out-of-pocket cost per investigational drug is average for analgesic/anesthetic drugs, 48% above average for antiinfective drugs, 15% be-

FIGURE 2

Probability of an investigational drug entering a phase by therapeutic class. LT animal = long-term animal testing concurrent with clinical trials.



low average for cardiovascular drugs, and 20% below average for CNS drugs. In contrast, for our previous study, out-of-pocket cost per investigational drug was 61% above average for the NSAID subclass, 8% above average for antiinfective drugs, 19% above average for cardiovascular drugs, and 12% below average for neuropharmacologic drugs.

DEVELOPMENT AND APPROVAL TIMES BY CLASS

The full economic cost of new drug development includes the cost of investing in R&D years before any returns can be earned. Determining these time costs requires detailed estimates of clinical and regulatory approval phase lengths. Representative time profiles for all drugs and for our four therapeutic classes are shown in Figure 3. The clinical phase is the time from first human testing to submission of an NDA/BLA to the Food and Drug Administration (FDA). The approval phase is the time from first submission of an NDA/BLA to regulatory marketing approval. The clinical phase is built up from estimates of mean phase lengths and mean gaps/overlaps between phases. Time costs depend on how the overall times are decomposed across specific phases and on how out-of-pocket costs are distributed across these phases.

The clinical phase for analgesic/anesthetic drugs, antiinfective drugs, and cardiovascular drugs is 36%, 30%, and 15% below the average for all drugs, respectively. The average clinical phase for CNS drugs is 28% above average. The mean approval phases for analgesic/anesthetic and antiinfective drugs are also below average (31% and 15%, respectively), while those for cardiovascular and CNS drugs are above average (15% and 21%, respectively). The mean overall time from the initiation of clinical testing to marketing approval is 32% below average for analgesic/anesthetic drugs, 30% below average for antiinfective drugs, 9% below average for cardiovascular drugs, and 27% above average for CNS drugs. For comparison, the mean times from the start of clinical testing to approval in our earlier study were 16% above average for NSAIDs, 23% below average for antiinfective drugs, 6% above average for cardiovascular drugs, and 17% above average for neuropharmacologic drugs.

CAPITALIZED COSTS PER APPROVED DRUG BY CLASS

Out-of-pocket costs per approved new drug can be obtained by dividing the expected costs per investigational drug noted in the previous section by the estimated clinical approval success rates. These figures are shown in Figure 4.

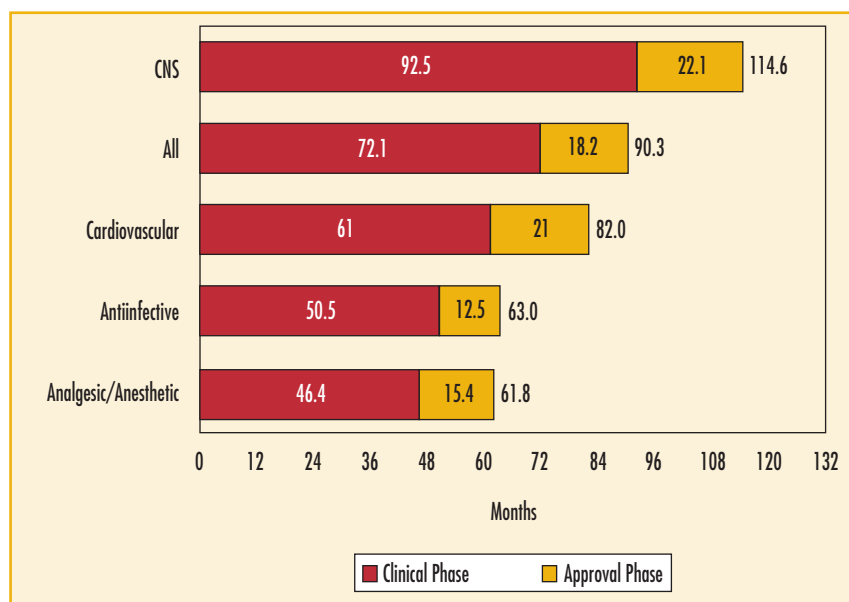
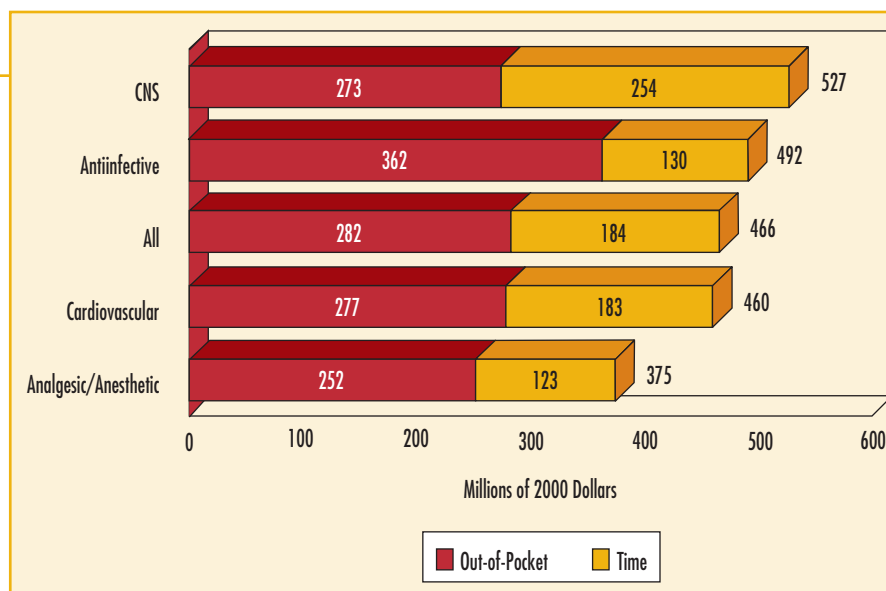


FIGURE 3

Mean clinical development and regulatory approval phase times by therapeutic class.

FIGURE 4

Average clinical period cost per approved new drug by therapeutic class (inclusive of failures).



When both phase attrition rates and clinical approval success rates are factored in, analgesic/anesthetic, cardiovascular, and CNS drugs are seen to have below average out-of-pocket costs per approved drug (11%, 2%, and 3%, respectively). Out-of-pocket cost per approved drug for antiinfective drugs is 28% above average.

Including time costs changes relative costs substantially. As noted from Figure 4, average development plus approval times are slightly below average for cardiovascular drugs, substantially below average for analgesic/anesthetic and antiinfective drugs, and substantially above average for CNS drugs. Consequently, capitalized cost per approved drug for analgesic/anesthetic drugs is even more below average (20%) than is the case for out-of-pocket cost, antiinfective drug capitalized cost per approved drug is much less above average (6%) than is the case for out-of-pocket cost, and capitalized cost per approved drug for CNS drugs is above average (13%) while out-of-pocket cost is below average. Capitalized cost per approved drug for cardiovascular drugs is close to the average for all drugs.

SALES BY CLASS

While the sales profiles for drugs approved in the first half of the 1990s in the United States

for the analgesic/anesthetic, antiinfective, cardiovascular, and CNS therapeutic classes show annual constant dollar sales that rise to a peak and fall (primarily due to generic competition), as is the case for drugs as a whole, their sales profiles differ markedly in terms of absolute levels (Figure 5). The CNS and cardiovascular sales curves are substantially above average, while the analgesic/anesthetic curve is well below average. The classes also differ somewhat in terms of when sales peak. For drugs as a whole, the peak year for the mean drug is the 10th year after launch. Sales for the mean analgesic/anesthetic drug peak at 6 years, the mean antiinfective and CNS drugs have sales that peak at 9 years, and mean cardiovascular drug sales peak at 12 years. Peak year sales for drugs as a whole are \$458 million. In contrast, peak year sales are \$203 million (56% below average) for analgesic/anesthetic drugs; \$389 million (15% below average) for antiinfective drugs; \$746 million (63% above average) for cardiovascular drugs; and \$849 million (85% above average) for CNS drugs.

We can also compare sales over the entire product life cycle by class by computing the net present value (NPV) of annual sales. As was the case for R&D costs, we use an 11% real discount rate to discount sales to the launch year. Table 2 shows statistics for the sales distributions for the therapeutic classes whose R&D costs we

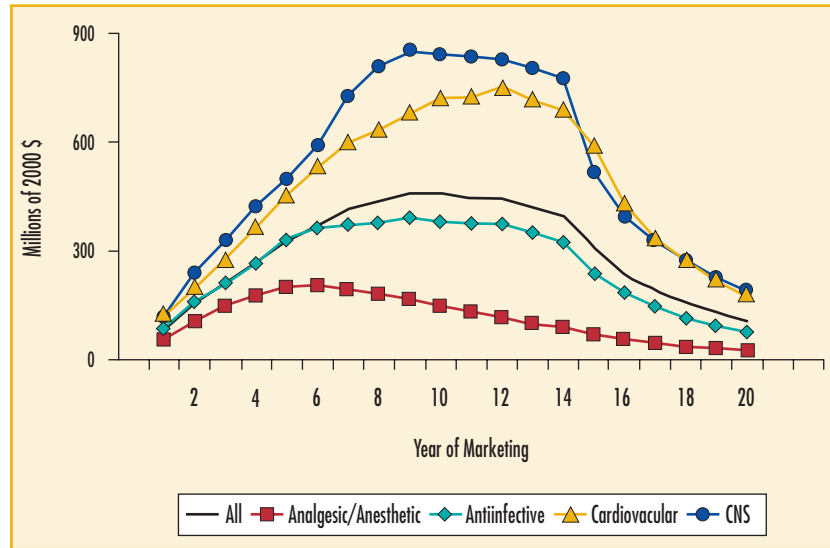


FIGURE 5

Mean annual worldwide sales over the product life cycle by therapeutic class for new drugs approved during 1990 to 1994.

have examined and for some of their major subclasses. Relative mean sales for the broad classes over the entire product life cycle are similar to those for peak year sales. The NPV for life cycle sales for the mean drug is 56% below average for

analgesic/anesthetic drugs, 10% below average for antiinfective drugs, 56% above average for cardiovascular drugs, and 72% above average for CNS drugs.

The differences in mean returns are more pro-

Worldwide Sales Revenues (millions of 2000 dollars) over the Product Life Cycle for New Drugs Approved in the United States during 1990 to 1994 (net present values)

TABLE 2

	Mean	N	25th Percentile	Median	75th Percentile	Coefficient of Variation
All drugs	2434	118	192	797	2863	1.67
Analgesic/Anesthetic drugs	1080	16	93	353	1534	1.45
Anesthetic drugs	556	5	28	297	1059	1.12
NSAIDs	1292	6	242	1486	1760	0.73
Antiinfective drugs	2199	25	229	921	3217	1.23
ARC	1367	5	229	290	340	1.87
HIV	1605	3	677	921	3217	0.87
Antibiotics	2379	11	56	1114	4745	1.23
Cardiovascular	3668	26	447	925	3245	1.78
Beta-blockers	567	3	95	720	887	0.74
ACE-inhibitors	2771	4	2355	2703	3188	0.24
Calcium channel blockers	5399	4	505	1,610	10292	1.61
Statins	15168	3	2,910	15,484	27111	0.80
Central nervous system drugs	4177	15	256	2922	7711	1.02
Hypnotic sedatives	2011	3	109	241	5653	1.58
SSRIs	10692	3	771	11140	13224	0.26

Notes: ARC = drugs to treat AIDS-related complexes. HIV = AIDS antivirals. Sales are discounted at an 11% real rate.

nounced when subclasses are examined. Anesthetic drugs have mean life cycle sales that are 77% below average, while NSAIDs have sales that are 47% below the overall drug average (but 20% above the class average). With respect to the antiinfective class, antibiotic mean sales are close to the overall drug average, but drugs to treat AIDS-related complexes (ARCs) are 44% below average and AIDS antivirals are 34% below average. The cardiovascular subclasses exhibit enormous variability in average life cycle sales. Mean sales for the cardiovascular drugs approved in the study period are: 77% below the overall drug average for beta-blockers, 14% below average for ACE-inhibitors, 122% above average for calcium channel blockers (CCBs), and 523% above average for statins. The two CNS subclasses differ by a factor of approximately five in terms of mean sales. Life cycle average sales are 17% below the overall drug average for hypnotic sedatives, while selective serotonin receptor inhibitors (SSRIs) have mean sales that are 339% above average.

As is the case for all drugs, the sales distributions for the major classes analyzed here are highly positively skewed. The ratio of mean to median sales for all drugs is 3.05. As measured by this ratio, the sales distributions for two of the four major therapeutic classes analyzed are less skewed than the distribution for drugs as a whole. The cardiovascular class has a distribution that is slightly more skewed (3.97) than for all drugs, and the distribution for the analgesic/anesthetic class is essentially equally skewed (3.06). The mean to median ratio for the subclasses are, for the most part, much less skewed than for drugs as a whole and for their respective broader classes. Although the sample sizes are small, the sales distributions for NSAIDs, beta-blockers, ACE-inhibitors, statins, and SSRIs are close to symmetric or slightly negatively skewed.

As was the case for the R&D phase cost distributions, the data suggest that some of the variability in drug sales can be explained by therapeutic category. Of the four major therapeutic classes analyzed, only cardiovascular drugs had a coefficient of variation that is larger (slightly)

than that for drugs as a whole. It is also the case that, for the most part, variability in drug sales is lower when the therapeutic groupings are more narrowly defined. With the exception of drugs for ARCs (a heterogeneous group in terms of mechanism of action and indication), variability is lower for each subclass considered in relation to drugs as a whole. In comparison to the broader therapeutic class, only the ARC drugs and the hypnotic sedatives have more variable sales distributions.

CONCLUSIONS

We found differences in mean out-of-pocket clinical period development costs by phase for new drugs in various therapeutic categories. These differences in phase costs were generally mitigated by variation in development times, clinical approval success rates, and phase attrition rates. In comparison to the results in our previous study on therapeutic category costs (6), we found that the fully-loaded capitalized cost per approved new drug is somewhat less variable across therapeutic categories for the more recent period. We also found some reversals in clinical costs relative to the overall drug average for the current study period. While capitalized cost per approved drug for antiinfective drugs was 25% below the overall drug average in the previous study, here antiinfective cost is 6% above average. Similarly, capitalized cost per approved drug for cardiovascular drugs was 5% above average in our previous study, but 1.3% below average for the current study.

Average sales for new drugs varied even more substantially by therapeutic class. The net present values of mean life cycle worldwide sales for new drugs approved in the first half of the 1990s for cardiovascular and CNS drugs are considerably above the average for all drugs. In contrast, mean life cycle sales are well below average for analgesic/anesthetic drugs and modestly below average for antiinfective drugs. Recent data on worldwide sales confirm that sales for cardiovascular and CNS drugs are high not only on a per drug basis, but also in terms of total sales. These two classes accounted for 37% of all worldwide retail pharmacy sales in 2002 (9). Variability in

average life cycle sales is even greater for subclasses within the broad therapeutic areas than it is across the broad classes.

The data examined here are mixed in terms of a correlation between sales and R&D costs by broad therapeutic class. Analgesic/anesthetic drugs have below average capitalized R&D costs and below average life cycle discounted sales. At the other extreme, CNS drugs have above average capitalized costs and above average life cycle discounted sales. However, average capitalized cost for cardiovascular drugs is slightly below average, while mean life cycle sales are well above average. In addition, antiinfective capitalized cost is modestly above average, but mean antiinfective sales are modestly below average.

Grabowski et al. (3) estimated the rate of return to new drug development as a whole using these and other data. The results of that and previous similar studies do not support the hypothesis that there have been significant sustained excess profits for the industry as a whole. The estimated internal rates of return are relatively close to the estimated industry costs of capital. Estimates for advertising and promotion, manufacturing, and distribution costs were obtained for those studies for drug development as a whole. A complete rate of return analysis would include such values. However, we do not have such estimates by therapeutic class. Thus, our results on R&D costs and life cycle sales make inferring differences in the profitability of drug development by therapeutic class problematic.

There is some evidence that at least some of the class differences in sales relative to R&D costs may be offset by larger costs in other areas. With the exception of biological products, manufacturing and distribution costs may not vary much by drug. However, advertising and promotion costs are significant and these costs likely vary strongly with market size. For example, a recent audit of physician meetings and events found that the two classes with the most events in the United States in the year 2000 were the SSRI and statin classes (10). Of the therapeutic subclasses whose life cycle sales we analyzed,

these are the two with far and away the largest NPV of mean sales.

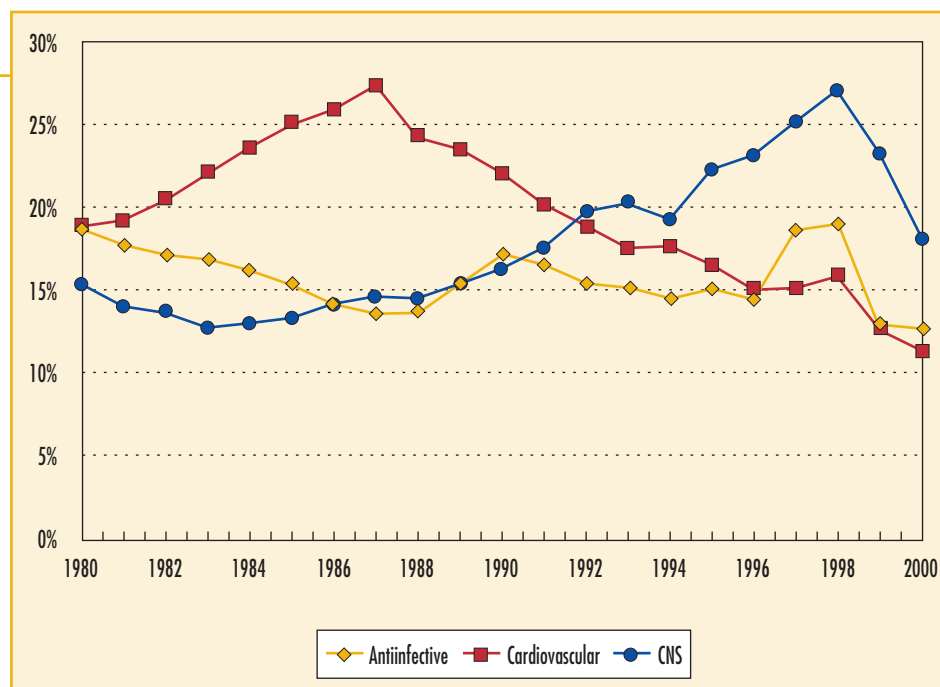
A further difficulty in assessing relative profitability is that the R&D cost and sales periods may not match especially well for some therapeutic subclasses. This may be particularly true for areas where subclass development of new chemical types has proceeded briskly. As noted above, the higher than average costs for antiinfectives in the sample were mostly driven by the development costs of the AIDS drugs in the sample. However, the drugs in this group were all approved in the late 1990s. The life cycle sales data that we have are for approvals in the first half of the 1990s. The AIDS drugs in the sales sample are all nucleoside reverse transcriptase inhibitors (NRTIs). The drugs in the cost sample include the NRTI class, but they also include drugs from the newer protease inhibitor class. It is not possible to examine trends in development costs for AIDS drugs, though, because the study period for our earlier R&D cost study (1), which was based on when drugs first entered clinical testing anywhere in the world, predates AIDS drug development.

The above interpretative problems notwithstanding, the differences in sales relative to costs suggest the possibility that, while there may not be substantial long-run positive economic profits for drug development as a whole, for some periods positive economic profits may exist in some therapeutic areas with negative economic profits in other areas. We would not expect this to persist indefinitely, though, as capital should flow from the unprofitable therapeutic areas to the profitable ones. Scherer (11), for example, has presented evidence to strongly suggest that R&D expenditure levels move in relation to profit margins for the pharmaceutical sector as a whole.

The extent and rate at which capital adjustments are made for various therapeutic areas are interesting questions to analyze. Descriptive data can provide some sense for trends, but they are far from conclusive. For example, Figure 6 shows annual R&D expenditure shares for the antiinfective, cardiovascular, and CNS therapeutic classes based on data published by the

FIGURE 6

Share of annual total PhRMA member firm pharmaceutical R&D expenditures for antiinfective, cardiovascular, and central nervous system (CNS) drugs.



Pharmaceutical Researchers and Manufacturers of America, the United States pharmaceutical industry trade association.

We found average life cycle CNS sales to be substantially above average for the approval period analyzed. The data in Figure 6 show a clear upward trend in the share of R&D expenditures devoted to CNS drugs for most of the 1980s and 1990s. We found both antiinfective costs and sales to be relatively close to industry averages. The antiinfective aggregate R&D expenditure share remained fairly stable throughout the 1980s and the 1990s.

However, the cardiovascular share of R&D expenditures rose to a peak in 1987 and generally fell thereafter. The cardiovascular share of new drug approvals has also declined over time. The percentage of therapeutic new molecular entities approved by the FDA in the cardiovascular area fell from 27% for 1981 to 1987 to 24% for 1988 to 1994, and then to 20% for 1995 to 2001. We found mean life cycle sales for cardiovascular drugs to be significantly above average, but most of the R&D for the approvals whose sales we analyzed would have been spent in the period where the cardiovascular aggregate R&D expenditure share was rising. It is possible that the markets for many cardiovascular indications be-

came sufficiently crowded that relative interest in this area dampened. It would be very instructive to gather more detailed information on non-R&D costs by therapeutic area so as to fully analyze rates of return by therapeutic class and correlate with subsequent shifts in relative R&D efforts in those therapeutic areas.

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