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Returns on Research and Development for 1990s New Drug Introductions

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Abstract

Background: Previously published research by the authors found that returns on research and development (R&D) for drugs introduced into the US market in the 1970s and 1980s were highly skewed and that the top decile of new drugs accounted for close to half the overall market value. In the 1990s, however, the R&D environment for new medicines underwent a number of changes including the following: the rapid growth of managed-care organisations; indications that R&D costs were rising at a rate faster than that of overall inflation; new market strategies of major firms aimed at simultaneous launches across world markets; and the increased attention focused on the pharmaceutical industry in the political arena.

Objective: The aim of this study was to examine the worldwide returns on R&D for drugs introduced into the US market in the first half of the 1990s, given that there have been significant changes to the R&D environment for new medicines over the past decade or so.

Results: Analysis of new drugs entering the market from 1990 to 1994 resulted in findings similar to those of the earlier research – pharmaceutical R&D is characterised by a highly skewed distribution of returns and a mean industry internal rate of return modestly in excess of the cost of capital.

Conclusions: Although the distribution of returns on R&D for new drugs continues to be highly skewed, the analysis reveals that a number of dynamic forces are currently at work in the industry. In particular, R&D costs as well as new drug introductions, sales and contribution margins increased significantly compared with their 1980s values.

Competition in the research-based pharmaceutical industry centres on the introduction of new drug therapies. In this paper, we examine the returns on research and development (R&D) for new drug entities introduced into the US market in the first half of the 1990s. This research work builds directly on earlier analyses of returns on R&D for the 1970s and 1980s introductions performed by Grabowski and Vernon.[1,2]

Our prior analyses indicate that this industry has exhibited very skewed distributions of returns. In this regard, several significant new classes of drug therapies have been introduced since the late 1970s. Early movers in these classes have obtained the highest returns on R&D. We found that the top decile of new drugs accounted for close to half of the overall market value associated with all the new drug introductions in our 1970s and 1980s' samples.

The results of our prior analysis are also consistent with an economic model of rivalrous R&D competition. In particular, the promise of above-average expected returns produces rapid increases in industry R&D expenditures, as firms compete to exploit these opportunities until the returns become unattractive. From an industry perspective, our results indicate that mean returns on R&D are relatively close in value to the risk-adjusted cost of capital for drug industry investments. This rent-seeking model is also supported by a recent empirical analysis by Scherer, who finds a strong relationship between industry R&D outlays and profits over the period 1962 to 1996.[3]

An investigation into the drug returns in the 1990s is timely on a number of grounds. First, this decade has been characterised by the rapid growth of managed-care organisations on the demand side of the market for pharmaceuticals.[4] This has led to greater access to and utilisation of pharmaceuticals, but also greater generic competition in the post-patent period. Second, a new study of R&D costs by DiMasi and colleagues indicates that the R&D costs for new drugs have continued to rise much faster than the rate of general inflation.[5] This reflects, among other factors, the increased size of clinical trials compared with those for earlier new drug introductions. Third, many firms are changing their market strategies and attempting to launch their products simultaneously across world markets, reflecting the higher R&D investment costs and more intensive competition from new molecules in the same product class.

In addition to these economic developments, the industry continues to be the subject of considerable attention by policy makers. Recent policy initiatives in the US include a Medicare prescription drug benefit, the parallel importation of drugs from Canada and Mexico, and various state programmes affecting drug costs and utilisation by the poor and elderly populations. The potential effects of these policy initiatives on R&D returns remain an important issue for research. Our past work on R&D returns has provided a framework for the Congressional Budget Office and other groups to consider the effects on R&D of the proposed Clinton Health Care Reform Act and the Waxman-Hatch Act of 1984.[6,7]

In the next section of this paper, we describe the data samples and methodology for our analysis of the returns to 1990 to 1994 new chemical entities (NCEs). 'Empirical Results' presents the empirical findings on the distribution of returns and a sensitivity analysis involving the main economic parameters. 'Drug Innovation and Industry Evolution Since 1970' provides a discussion of the results and comparisons with the historical findings from our prior work, which is based on the same methodology. The final section provides a brief summary and conclusions.

Methodology and Data Inputs

Overview

This section explains the methodology and key data inputs used in estimating the returns to 1990 to 1994 NCEs. Our sample includes 'large-molecule' biologics, in addition to traditional 'small molecule' chemical drugs. A detailed discussion of the general methodology is provided in our earlier papers on R&D returns.[1,2] Our focus here is on the similarities and differences of the 1990s sample compared with our analysis of prior NCE cohorts.

The basic sample comprises 118 NCEs introduced into the US between 1990 and 1994. This is a comprehensive sample of the NCEs originating from and developed by the pharmaceutical industry that were introduced into the US in the 1990 to 1994 time period. However, three drugs were omitted from our sample because they failed to appear in any year in the IMS sales data audits. These drugs were distributed outside of normal sales channels and were likely to have nonrepresentative R&D costs because of their special indications.

The number of NCE introductions increased significantly in the early 1990s compared with the 1980s. The corresponding 1980 to 1984 sample was 64 NCEs. This increase in NCEs reflects the increased R&D expenditures for new entities by the traditional pharmaceutical industry as well as the growth of the independent biopharmaceutical

industry.[8] The latter industry was in its infancy in the early 1980s, but by the early 1990s it had become a significant source of new drug introductions. There is also a significant increase in the number of new drugs approved for orphan drug indications. As we have discussed elsewhere, there is a high degree of overlap between the biopharmaceutical and orphan drug sub-samples.[8]

Our basic procedure is as follows: for each new drug in our sample, worldwide sales profiles are constructed over the drug's product life cycle. These sales values are converted to after-tax profits and cash-flow values using industry data on profit margins and other economic parameters. These data are combined with R&D investment information, based on the recent analysis by DiMasi et al.[5] Mean net present values (NPVs) and internal rate of return (IRRs) are then computed for this portfolio of new drug introductions. The distribution of returns is another major focus of our analysis.

Cost of Capital

In our earlier analysis of 1980 NCEs, we utilised a 10.5% real cost of capital for the pharmaceutical firms. This was based on an analysis of the industry using the capital asset pricing model (CAPM) that was performed by Myers and Shyum-Sunder.[9] Their study was commissioned by the Office of Technology Assessment as part of a larger study on R&D costs, risk and rewards.[10] They found that the real after-tax cost of capital on equity plus debt varied between 10 and 11% during the 1980s.

For our sample of 1990 to 1994 introductions, the relevant investment period spans the mid-1980s through the late 1990s. In their original article, Myers and Shyum-Sunder provided estimates of the cost of capital for 1985 and 1990. Myers and Howe have subsequently provided a related analysis for 1994.[11] We also performed a comparable CAPM for analysis for January 2000. The results of these CAPM-based studies are summarised in DiMasi et al.[5]

Using these four CAPM-based analyses, occurring at roughly 5-year intervals, we found that the mean cost of capital for pharmaceuticals over this period was just over 11%. Consequently, 11% was selected as the baseline value for the cost of capital in this analysis of 1990 NCEs. This represents a small increase from the 10.5% cost of capital utilised for the 1980 NCEs.

As Myers and Shyum-Sunder indicated in their original article, the CAPM approach provides somewhat conservative cost-of-capital values with respect to investment in new prescription drugs. One reason is that the equity market data on which the CAPM analysis is based pertain to all the different functional areas and commercial activities of drug firms (which can include over-the-counter drugs, animal health, basic chemicals, etc.). Another reason why the cost of capital may be understated is the fact that many pharmaceutical firms carry significant cash balances. Indeed, Myers and Shyum-Sunder found that many pharmaceutical firms have large positive cash balances and are actually net lenders rather than net borrowers. Consequently, these firms have a negative debt ratio. Myers and Shyum-Sunder did a sensitivity analysis to gauge how this factor would affect their 1990 value and they found it causes the nominal (and real cost) of capital to increase by almost a full percentage point.[9]

Several surveys have been performed of the hurdle rates used by US companies. A general finding is that hurdle rates are typically greater than the weighted cost of capital computed by a CAPM analysis.[12] One of the authors undertook an informal survey of six pharmaceutical firms in mid-2001 with respect to the hurdle rates that drug firms utilise in their R&D investment decisions. The survey of these firms yielded (nominal) hurdle rates from 13.5% to over 20%. If one takes 3% as the long-run expected rate of inflation, then an 11% real rate of return corresponds to a nominal rate of 14%. This 14% rate is within the range of hurdle rates utilised by the drug firms in their R&D investment decisions, but it is at the lower end of the range. This is consistent with the view that a CAPM analysis provides conservative estimates on the industry's cost of capital.

Myers and Howe further indicate that the R&D decision process can be modelled as a compound option pricing model.[11] Under this model, at any point in the R&D decision-making process, future R&D serves as a form of leverage, or debt, assuming the firm decides to undertake further development and marketing. Since this 'debt' or leverage declines over the subsequent stages of the R&D process, so will the firm's cost of capital. Implementation of this model requires unobservable informational inputs compared with the standard CAPM approach using a weighted cost of capital. DiMasi et al.[5] performed a sensitivity analysis using this option value approach, and showed that for reasonable values of the forward looking discount rates, the CAPM and option value models yield comparable results.

Research and Development (R&D) Investment Expenditures

To obtain representative R&D investment expenditures for the new drug entities in our sample, we relied on the recently completed study by DiMasi et al.[5] This study obtained R&D cost data for a randomly constructed sample of 68 drugs first tested clinically between 1983 and 1994. The DiMasi study is designed to measure the average cost of a new drug introduction and includes discovery costs as well as the costs associated with failed candidates.

The mean introduction of our sample NCEs is 1992 while the mean introduction of drug candidates analysed in the DiMasi study is 1997. DiMasi and colleagues had previously undertaken an analysis of the costs of 1980s introductions using the same methodology employed in their new study.[13] That study was centred on 1984. Given the availability of these two R&D cost studies centred around 1984 and 1997, we can utilise a linear extrapolation procedure to estimate the mean R&D costs for our sample cohort.[1]

Using this extrapolation procedure, we estimated the mean out-of-pocket R&D expenditures for the drugs in our sample to be $US308.4 million. This is approximately double the estimated R&D expenditures (in $US, 2000 values) for the 1980 to 1984 samples of NCEs. DiMasi also estimated a representative investment period of 12 years from initial drug synthesis to Food and Drug Administration (FDA) approval. We were able to allocate the out-of-pocket R&D costs over this 12-year period using weights derived from the DiMasi et al. study.[5] Capitalising these costs to the date of marketing, at a real cost of capital of 11%, yields $US613 million as the average (pre-tax) capitalised R&D investment per 1990 to 1994 NCE introduction.

Our analysis is performed on an after-tax basis. For the time period under study, we estimated a 30% average effective tax rate for the pharmaceutical industry (see 'Effective Tax Rates'). Since R&D expenditures can be expensed for tax purposes, we multiplied the pre-tax values by 0.7 to get an after-tax value. This is shown in the first row of table I. Utilising the 30% effective tax rate, $US613 million pre-tax capitalised corresponds to an after-tax value of $US429 million.

In addition to these pre-launch R&D expenditures, firms also undertake R&D outlays in the post-approval period for product extensions such as new indications, formulations and dosage levels. Since these activities can be viewed as spillovers from the original NCE introduction, these ongoing R&D investment expenditures, as well as any extra revenues that they generate, are appropriately incorporated into the analysis. On the basis of the DiMasi et al. study,[5] we estimated

Table I. Capitalised research and development (R&D) costs for the mean new chemical entity in the 1990 to 1994 sample

R&D costs ($US millions; 2000 values)[a,b]	Pre-tax	After tax
Discovery and development	$613	$429
Product extensions after launch	$73	$51
Total	**$686**	**$480**

a R&D costs include expenditures on product failures as well as successes.

b R&D costs are capitalised to the first year of marketing using an 11% cost of capital.

1 Since our sample is centred around 1992, we utilise the following linear extrapolation equation to derive R&D costs: $R\&D_{92} = R\&D_{84} + (8/13)\ R\&D_{97}$.

the average post-approval R&D costs per NCE in our sample period to be $US107 million (before tax).[2] We allocated these costs equally over the first 8 years of an NCE's market life, using a discount rate of 11% from the date of marketing. This yields a present value of $US73 million (before tax) and $US51 million dollars (after tax).

When the after-tax values (see column two of table I) are added, the mean capitalised value for both pre- and post-approval R&D for the drugs in our sample is estimated to be $US480 million. This is the baseline value that we compare with the present value of net revenues for the mean NCE in our sample.

Global Sales

In our prior analysis, we obtained US sales data on each NCE in the sample. We then estimated worldwide sales for these compounds using a worldwide sales multiplier common to all NCEs. One limitation of this approach is that the ratio of worldwide sales to domestic sales varies significantly, both over time and across drugs in our sample.

In the current analysis, our approach was to obtain worldwide sales data directly on as large a group of the drugs as possible. We were generally successful in this endeavour, in that we were able to obtain worldwide sales data for a majority of the NCEs in our sample (66 NCEs) using several complementary data sources. These 66 drugs accounted for more than 90% of total US sales realised by our sample of NCEs and presumably a similar, or even larger, share of its realised worldwide sales. With respect to the latter point, there is evidence that the larger selling US drugs diffuse across more countries and have larger sales globally than US compounds with smaller domestic sales.[14]

To obtain worldwide sales data, we collected sales data that firms provide in their annual reports, in the reports of financial analysts, and in publications such as *MedAdNews*. The last-mentioned source has compiled an annual survey of worldwide drug sales, by product, since 1990 on an expanding basis over time. The compilation for 2000 includes information on the 500 top-selling prescription drugs worldwide.[15]

A complementary source of data that we also relied on was IMS data on worldwide sales, which is based on audit data sources from a large number of countries. The IMS data source was available to us (from a prior project) for a sub-sample of drugs consisting of the largest selling global drugs in our sample. It provided a check on the sales information provided by the company sources. In most cases, the IMS sales values were less than the company values. This reflected the fact that the IMS does not capture all the sales channels available across countries, while the company data do include every channel.

In about 25% of the overlapping observations, however, the IMS sales were greater than the company-reported values. An analysis into why this was the case revealed that the sub-sample of drugs with higher IMS sales was marketed internationally under multiple names and by several different companies. Consequently, sources such as *MedAdNews* didn't capture all of the sales that were licensed to different companies for a particular molecule. For the sub-sample of drugs for which this was an issue, we utilised the larger IMS worldwide sales values because they better captured the worldwide market.

Using this approach and these complementary data sources, we assembled worldwide sales data for 66 of the NCEs over the period of 1990 to 2000. For the remaining (very small selling) drugs in our sample, we multiplied their US sales values by a representative global sales multiplier to obtain estimates of their worldwide sales. The value of the global sales multiplier was 2.19. As discussed, this

2 DiMasi et al.[5] obtained data from all the firms participating in his survey on pre-approval and post-approval R&D expenditures. On the basis of an analysis of these data, they estimated that out-of-pocket R&D expenditures for product extensions in the post-approval period were 34.8% of pre-approval R&D expenditures. Applying this percentage to our estimate of $US308.4 million for pre-approval R&D yields an estimate of $US107 million (in $US, 2000 values) as the R&D cost for post-launch product improvements.

latter sub-sample of drugs accounts for a very small share of overall sales for the full sample.

Life-Cycle Sales Profiles

Since data were available for the years 1990 to 2000, 7 to 11 years of worldwide sales values for the NCEs in our sample were provided, depending on their date of introduction into the US market. The next task was to estimate future sales over the complete market life of these products. Twenty years was chosen as the expected market life. This is the same assumption that we utilised for 1980s new drug introductions. We believe this to be a reasonable time horizon for an IRR analysis. Any sales remaining after 20 years of market life are likely to be very small, given the sales erosion experienced by most products from generic competition and product obsolescence. Furthermore, these sales will also be severely discounted by the cost of capital in an IRR analysis.

We utilised a two-step procedure to project future sales values. These steps involve forecasting sales to the point of US patent expiry and then projecting sales in the post-patent period. The two-step approach is illustrated in figure 1 for one of the products in our sample. This product was introduced into the US market in 1992. There are 9 years of sales information and its US patent expires in year 12. By year 9, this product was in the mature portion of its product life cycle. By using a reference life-cycle curve, the product was projected to have relatively stable sales (in constant dollar terms) until year 12. A significant decline is then projected in the period after US patent expiry because of the entry of generic competitors and related economic factors.

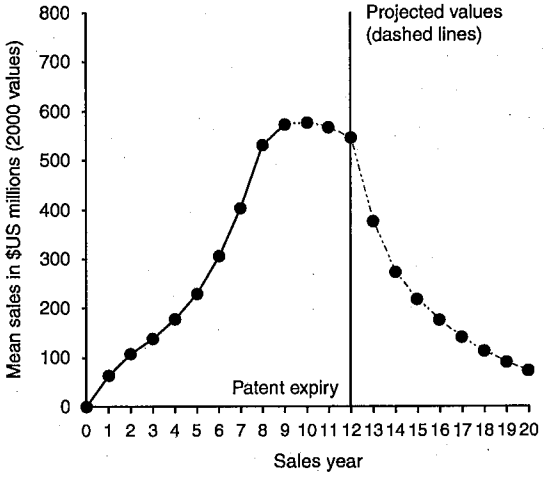

Fig. 1. Actual and projected worldwide sales values for a representative sample product.

The estimated sales decline after patent expiry is based on the experience of major commercial products coming off patent in the 1994 to 1997 period. In particular, we examined worldwide sales losses for a sample of NCEs for a 4-year period following their US patent expiry. The average percentage declines observed were 31, 28, 20 and 20%, respectively. We utilised these percentages to project sales in the first 4 years after patent expiry and, thereafter, a 20% decline until the product's market life is completed in year 20. In our prior work, we found that generic competition is focused on products with significant sales at the time of US patent expiry. Consequently, for the drugs concentrated in the bottom four deciles of our sample (with worldwide sales of less than $US40 million in year 10 of their market life), we assume that the probability of generic competition is very low. For these drugs we assume that sales losses in the mature phase of cycle will proceed at a more moderately declining rate based on the reference curve used for the pre-patent expiry period.

We should note that the percentage declines in sales from generic competition in the US market observed in prior studies are much greater than the worldwide losses in sales for major commercial products observed here.[16] Hence, the decline in worldwide sales in the post-patent period is ameliorated by the lower incidence of generic competition and sales losses outside the US. This may change by the time this cohort actually reaches patent expiry during the current decade, because reference pricing and generic competition are on the rise in many European countries.[17]

Figure 2 provides a plot of the sales life-cycle profile (in $US, 2000 values) for the top two dec-

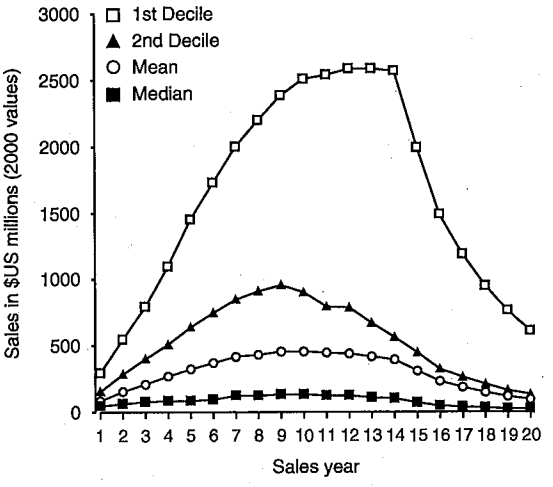

Fig. 2. Worldwide sales profiles of 1990 to 1994 new drug introductions.

iles as well as the mean and median drug compounds in our 1990 to 1994 sample. The sales curves illustrate the highly skewed distribution of sales in pharmaceuticals that was observed for early cohorts. The peak sales of the top decile compounds are several times the peak sales of the second decile compounds. The mean sales curve is also significantly above the median.

Figure 3 provides a plot of mean worldwide sales for the 1990s sample compared with that for the 1980s cohort (in $US, 2000 values). Mean sales have increased significantly in real terms, with peak sales increasing from $US345 million for the 1980s cohort to $US458 million for the 1990s cohort. There is also the suggestion that sales curves have become somewhat steeper in the ascending sales growth stages of the life cycle, with a longer plateau before generic competition and product obsolescence take hold.

Figure 4 shows a corresponding plot of the mean worldwide sales for the top decile compounds in the 1990 to 1994 and 1980 to 1984 periods. This is instructive, given that the prospective returns for top decile compounds are primary drivers of R&D investment activities in pharmaceuticals. For the 1990s cohort, the top decile compounds reached peak sales of more than $US2.5 billion. This may be compared with peak sales of near $US1.8 billion for the 1980s cohort. The peak sales for the 1990s cohort also occur later than for the 1980s cohort.

Pre-Tax Contributions and Other Economic Parameters

The next step in the analysis was to obtain revenues net of production and distribution costs (often categorised in the economic literature as 'quasi-rents'). For this purpose, we analysed pre-tax contribution margins in pharmaceuticals during the 1990s. As in prior work, we utilised data derived from the income statements of the pharmaceutical divisions of a number of major multinational drug companies to obtain representative values on contribution margins over time.[1,2]

Our analysis of the data on these firms indicated that average contribution margins gradually increased from 42% in the early part of the 1980s to approximately 45% at the end of the decade. On the basis of these data, we constructed a linear contribution margin schedule over time. In particular, the contribution margin is 42% in the first year of the product life and grows by increments of 0.3%

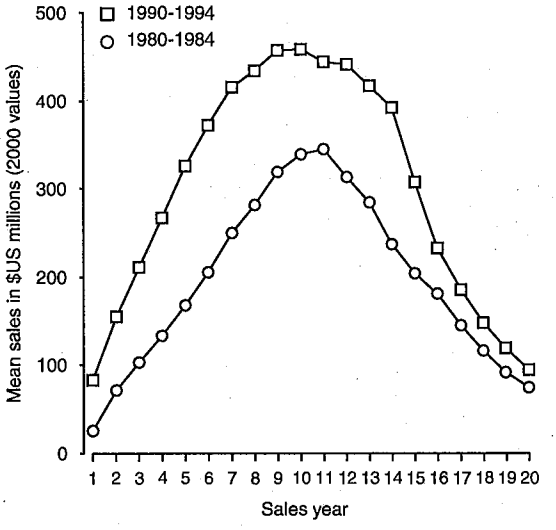

Fig. 3. Comparison of mean worldwide sales curves for new drug introductions in the 1990 to 1994 and 1980 to 1984 samples.

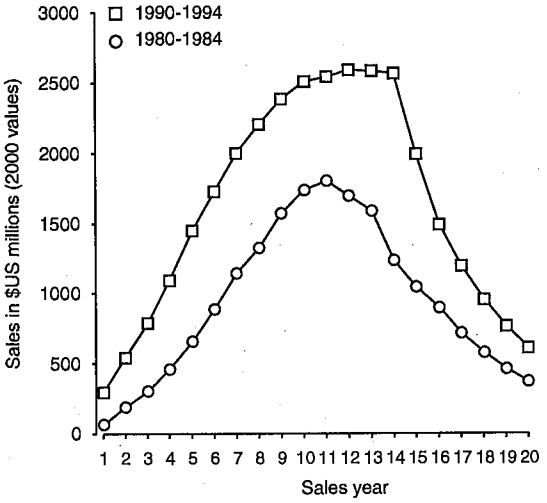

Fig. 4. Comparison of mean worldwide sales curves for top decile drugs in the 1990 to 1994 and 1980 to 1984 samples.

per year. We also assume that contribution margins will continue to rise at this same rate during the current decade. Hence, over the full 20-year life cycle, target contribution margins are expected to rise from 42% in year one, to 48% by year 20, with a mean contribution margin of 45% over the full life cycle.

While we constrained margins to average 45% over the life cycle, we also recognise, as in our earlier analyses, that promotion and marketing expenditures are concentrated in the launch phases of the life cycle. In our prior analysis, we developed the following allocation rule based on a regression analysis of promotional and marketing outlays: promotion and marketing is equal to sales in year 1, declines to 50% in year 2, and falls to 25% in year 3. We retained this assumed pattern on marketing outlays in the present analysis. Interviews with industry participants indicated that the initial post-launch years continue to be the primary focus of marketing and promotion activities.

An analysis performed by Rosenthal et al.[18] indicates that the drug industry's marketing expenses to sales ratios have remained relatively stable around 14% in the 1996 to 2000 period. However, there were some important compositional shifts over this period. The direct-to-consumer advertising to sales ratio increased from 1.2% to 2.2% between 1996 and 2000, at the expense of physician detailing and hospital medical journal advertising.[18]

For the current analysis, we did make one relatively minor change in the allocation and timing of marketing expenditures related to launch. In particular, we estimated pre-marketing launch expenditures in the order of 5 and 10% of first year sales in the 2 years immediately prior to launch. These marketing expenditures are for activities such as pre-launch meetings and symposiums, pricing and focus group studies, and sales force training. Our assumptions concerning the size and timing of these expenditures were guided by a recent survey report on pre-launch marketing expenditures by industry consultants as well as interviews with some of the participating companies.[19]

As indicated above, our model is structured so that margins average 45% over the full product life cycle. Given the assumed pattern of launch expenditures, contribution margins for each product are below representative industry values in the first 3 years of marketing. However, as a product matures, both promotional and administrative costs decline in relative terms, and contribution margins increase over average industry values in the later years of the life cycle.

The model is also structured to provide for capital expenditures on plant and equipment (P&E). As in our model for the 1980s cohort, we assumed overall capital expenditures for P&E to be equal to 40% of tenth year sales. Half of these outlays are assumed to occur in the first 2 years before marketing and the other half during the initial 10 years of the product's market life. These assumptions imply an average capital investment to sales ratio of 3.3% over the full product life cycle. This is generally consistent with data from pharmaceutical industry income statements.

In particular, we checked the reasonableness of our assumptions by comparing this implied 3.3% capital investment to sales ratio with the corresponding ratios observed on industry income state-

ments during the 1990s. We found that the drug industry capital investment to sales ratio averaged about 7.0% during the 1990s. However, the latter value includes investment for R&D as well as production, marketing and administrative facilities. In our model, provisions for capital investment in R&D facilities are included in the cost estimates provided by DiMasi et al.[5] Accordingly, we asked some industry members involved with strategic planning for information on what percentage of their P&E expenditures was devoted to R&D, versus other firm activities. We obtained a range of 40 to 50% of total capital expenditures devoted to R&D. Given this range, the capital investments to sales ratio for non-R&D activities implied by our model is consistent with the observed data from company income statements.

For working capital, it was assumed that accounts receivables are equal to 2 months of annual sales and inventories are 5 months of sales (valued at manufacturing cost). These are also based on the analysis of balance sheet data of major pharmaceutical firms. Working capital is recovered at the end of the final year of product life.

Effective Tax Rates

Our analysis of returns is conducted on an after-tax basis. In our prior studies of returns, we computed average effective tax rates based on analysis of income statement data from eight major pharmaceutical firms. The average effective rate was 35% for the 1970s cohort and 33% for the 1980s cohort. A comparable analysis for the 1990s cohort yielded an effective tax rate of 30%. This is the rate used in our baseline case. The difference between the nominal corporate tax rate (34%) and the average effective tax rate of 30% reflects various credits and deferrals such as the R&D tax credit and manufacturing tax credits for plants in Puerto Rico.[2]

After-tax cash flows are also influenced by the tax treatment of depreciation. In our analysis, cash flow in each year is equal to after-tax profits, plus depreciation charges. Accelerated depreciation, as specified in the US tax code, results in tax deferrals and positive cash flow in the early years of a product's market life. This reverses in the latter years of a product's life.

Summary of Economic Values

Table II provides a summary of the key economic inputs to IRR and NPV analysis for the 1990 to 1994 NCEs cohort compared with the corresponding values for the 1980 to 1984 cohort. R&D investment levels have roughly doubled in real terms, in both uncapitalised as well as capitalised dollar terms. On the revenue side of the equation, sales-life curves have shifted upward significantly. This is reflected in higher peak sales for the 1990 to 1994 cohorts ($US458 million compared with $US345 million for 1980 to 1984 NCEs). While sales have not grown at the same rate as R&D costs, contribution margins have increased in the 1990s, implying higher operational profits from a given level of sales. How all these factors balance out from a returns-on-investment standpoint is a major issue addressed in the analysis that follows. The industry's cost of capital, effective tax rate, and capital investment-to-sales ratio have changed only marginally for the current cohort compared with the 1980s sample.

Table II suggests that R&D investment expenditures are growing over time relative to sales revenues and the other activities of pharmaceutical

Table II. Key economic values for internal rate of return analysis for the 1990 to 1994 versus 1980 to 1984 new chemical entities (NCEs)

Economic parameter	1990 to 1994	1980 to 1984
Average R&D costs[a]		
pre-tax uncapitalised	$US416 mil	$US196 mil
after tax capitalised	$US480 mil	$US251 mil
Peak sales for mean NCE[a]	$US458 mil	$US345 mil
Contribution margin[b]	45%	40%
Cost of capital	11%	10.5%
Effective tax rate	30%	33%
Capital-to-investment sales ratio	3.3%	3.4%

a R&D costs and sales are all expressed in 2000 values.

b Average contribution margins over the full product life cycle; launch costs are concentrated in early phases of life cycle, so margins are lower in initial years and higher in later years.

mil = millions; **R&D** = research and development.

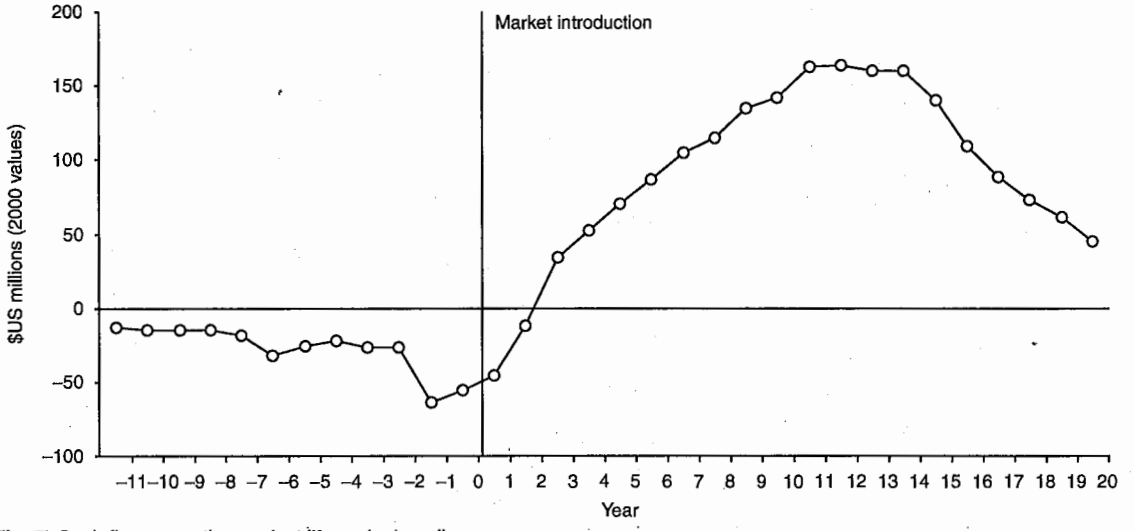

Fig. 5. Cash flows over the product life cycle: baseline case.

firms. This issue is discussed further in 'Drug Innovation and Industry Evolution Since 1970'. This increase in industry research intensity can be interpreted both as a response to increasing profit opportunities from new drug research as well as an equilibrating factor bringing returns in line with the industry cost of capital. This makes the question of industry returns on new drug introduction in the 1990s a particularly interesting question to analyse at the present time.

Empirical Results

The Baseline Case

Using the data and assumptions described above, we constructed the pattern of cash flows for the mean of our sample of 118 NCEs shown in figure 5. The R&D phase lasts for 12 years and results in a stream of negative cash flows. The first years of marketing, years 1 and 2, are also characterised by negative cash flows. This is because of heavy promotion and advertising expenditures during the product launch period. Cash flows rise to a peak in year 12 and then begin to decline. The decline becomes steeper as patent expiry and generic competition begin.

The baseline case results are shown in the first row of table III. The IRR is 11.5% and can be compared with our real cost-of-capital estimate of 11%. Hence, the industry mean performance is positive but only by a small amount. The present value of net revenues at the date of marketing is $US525 million and can be compared with the present value of R&D costs at the same point in time, or $US480 million. This leads to an NPV of $US45 million.

The results for the baseline case for the 1990 to 1994 NCEs are roughly the same as for our earlier 1980 to 1984 sample. In the 1980 to 1984 baseline case, the IRR was 11.1% compared with a cost of capital of 10.5%. The 1990 to 1994 IRR is similarly about a half percentage point above the cost-of-capital estimate.

Sensitivity Analysis

Given the uncertainty surrounding many of the key parameters that affect the IRR and NPV, we have performed a sensitivity analysis for a number of the parameters. These results are reported in table III.

An important parameter is the contribution margin. As discussed earlier, we examined data for a number of firms during the 1990s and found that

the average margin increased from 42 to 45%. We then projected a continuing increase in the margin until year 20, i.e. we assumed an increase from 42 to 48% by year 20, yielding an average of 45%. Hence, for the sensitivity analysis, we calculated the IRR and NPV for average margins of 40 and 50% – in both cases the upward trend of the base case was maintained. For example, for the lower margin case we assumed that the margin increased from 37 to 43% by year 20.

The IRR varied significantly from 10.6 to 12.4% as the average margin varied from 40 to 50%. Similarly, the NPV ranged from a negative $US31 million to $US120 million. It should be noted that for the first 10 years or so of product life the margin is based on real data – it is the last 10 years that are more uncertain and difficult to predict. Hence, the range of change in outcomes is perhaps overstated.

The next parameter that we examine in table III is the tax rate. The base case is 30% and we calculate the effect of tax rates of 25% and 35%. Clearly, changing the tax rate results in quite small changes in the IRR and NPV.At 25% the IRR is 11.6% and at 35% it is 11.4% – compared with the base IRR of 11.5%. This relative insensitivity of the IRR to the tax rate reflects the fact that this rate affects the R&D cost and revenue sides of the equation in a parallel fashion.

The effect of generic competition in eroding pioneer brand sales after patent expiry has tended to become greater over time. In the US, generic market shares in terms of pills sold increased from 35% one year after generic entry in the period immediately following the 1984 Hatch-Waxman Act to 64% in the mid-1990s.[6] Europe is also experiencing a rising trend in generic competition.[17] As a result, it is difficult to predict the degree of sales loss in the future. To examine this problem, we assumed two alternative scenarios: that the sales losses of the pioneer brands after patent expiry were 25 and 50% greater than what was assumed in the base case. Figure 6 shows these alternative sales erosion patterns.

Given that the effect of these sales losses occurs in the later stages of the product life cycle, the effect is made smaller when measured in present value terms. The IRR falls modestly from 11.5% in the base case to 11.4% and 11.3% in the 25% and 50% greater erosion cases, respectively. Similarly, the NPV falls from $US45 million in the base case to $US33 million and $US20 million.

Varying the cost-of-capital results in significant changes in the NPVs. A 10% cost of capital would result in an NPV of $US131 million, considerably larger than the base case using the 11% cost of capital of $US45 million. A 12% cost of capital, on the other hand, leads to a negative NPV of

Table III. Returns to 1990 to 1994 new chemical entities

Case	Present value cash flows (after-tax)[a]	Present value R&D costs (after tax)[a]	NPV[a,b]	IRR (%)
Baseline[c]	525.2	480.3	45.0	11.5
At 40% margin	449.8	480.3	(30.5)	10.6
At 50% margin	600.7	480.3	120.4	12.4
At 25% tax rate	571.3	514.6	56.7	11.6
At 35% tax rate	479.2	446.0	33.2	11.4
At 25% greater sales decline after patent life	512.9	480.3	32.7	11.4
At 50% greater sales decline after patent life	500.7	480.3	20.4	11.3
At 10% cost of capital	586.8	455.7	131.1	
At 12% cost of capital	470.0	506.7	(36.8)	
At 1-year reduction in regulatory review time	525.2	437.7	87.5	12.2

a Present value cash flows, present value R&D costs and NPV are shown in $US millions (2000 values).

b Parentheses indicate negative values.

c Baseline case assumes 11% cost of capital, tax rate of 0.30 and margin of 0.45.

IRR = internal rate of return; **NPV** = net present value; **R&D** = research and development.

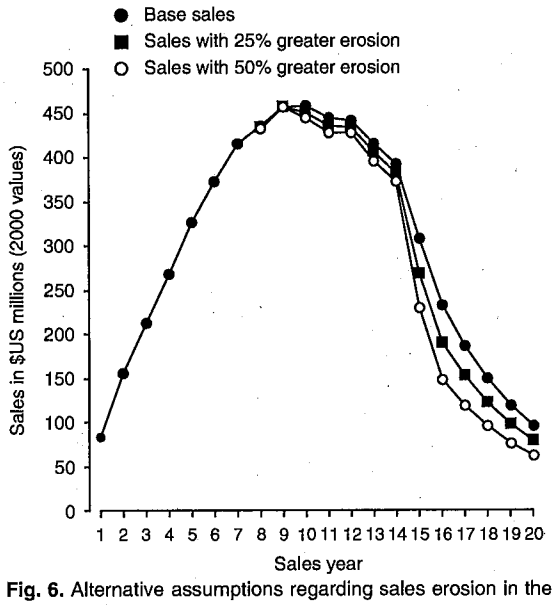

Fig. 6. Alternative assumptions regarding sales erosion in the post-patent period.

$US37 million. These changes are comparable in magnitude to those observed for changes in the contribution margin.

The final sensitivity analysis in table III is the effect of reducing regulatory review time by 1 year. This involves a change in the average regulatory review time from 18 months to 6 months. Our approach is to simply shorten the R&D period by 1 year and compute the lower capitalised value of R&D at the date of marketing. This reduces R&D from $US480 million to $US438 million; hence, the base NPV rises from $US45 million to $US88 million. The IRR increases from 11.5% to 12.2%. These are clearly significant effects.

This sensitivity analysis captures only the direct effects of shorter FDA review times on the capitalised value of R&D costs. We abstracted from any potential benefits associated with a longer effective patent life. As we have explained elsewhere, under the 1984 Hatch-Waxman Act most drugs are eligible for compensatory increases in effective patent life equal to any time lost in regulatory review. Consequently, it is only for a smaller subset of drugs where the patent restoration time is constrained where shorter regulatory review times would increase effective patent life (for example, because there is a maximum of 5 years on the patent life restored under the Act). We abstracted from these potential secondary benefits in the above sensitivity analysis

Distribution of Returns

In figure 7, we show the decile distribution of present values of returns for the 1990 to 1994 samples of NCEs. These returns are gross R&D costs. The deciles are constructed on the basis of the ranking of the 118 NCEs in terms of their individual present values of returns. The average sales of the top decile of NCEs are then used to calculate the present value of returns for the top decile, and so forth.

The graph shows that the distribution is highly skewed. For example, the top decile has an estimated present value of $US2.7 billion. This is almost 6 times the present value of average R&D costs ($US480 million). The top decile alone accounts for about 52% of the total present value generated by all ten deciles. This is comparable to the value of 46% that we found in our 1980 to 1984 study.

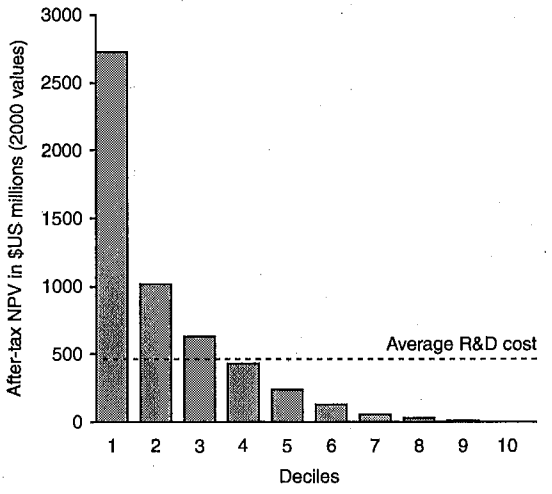

Fig. 7. Present values by decile for 1990 to 1994 new drug introductions. **NPV** = net present value; **R&D** = research and development.

It is also true that the second and third deciles have present values that exceed average R&D costs, or $US1 billion and $US0.6 billion, respectively. However, the fourth decile's present value is only $US433 million in comparison with average R&D costs of $US480 million. A detailed analysis of the present value for the individual NCEs shows that 34% or about one-third of the NCEs have present values in excess of the average R&D cost. By the time one gets to the median drug, present values are significantly below R&D costs.

A further illustration of the importance of top-ranked NCEs to industry returns can be demonstrated by removing the very top-ranked drug from the analysis. That is, we will eliminate Zocor®[3] (simvastatin), thereby reducing the sample from 118 to 117, and re-calculate the mean present value of returns. The result is that the present value falls from $US525 million to $US479 million, and the NPV falls from $US45 million to a negative $US1 million. Hence, if it were not for this one 'blockbuster' drug, the average NCE of the 1990 to 1994 cohort would essentially just break even in terms of an NPV analysis.

We should observe that the fact that most drugs in our sample have present values substantially below the fully allocated R&D cost does not mean that these drugs are not economically important. Since the average R&D cost includes an allocation for drugs that drop out during the development process, an 'unprofitable' drug that more than covers variable costs going forward contributes positively to the firm's bottom line. Many of the uncertainties that exist for a new product (i.e. its clinical profile in terms of risks and benefits, the introduction of substitute products, the size of market demand, etc.), are usually not resolved until late in the R&D process. At this point, most of the R&D costs are sunk. Therefore, it is still worth getting the incremental revenues of these smaller selling drugs, if they can cover their expected variable costs going forward. Over the long run, however, a firm must have its share of products in the top few deciles to have a viable R&D programme.

Figure 8 provides a comparison of the distribution of returns for all four sample cohorts that we have examined to date: 1970 to1974, 1975 to 1979, 1980 to 1984 and 1990 to 1994. The vertical axis in this graph shows the percentage of overall returns that each decile accounts for in its sample cohort. The drug industry has exhibited a high degree of skewness over all four sample cohorts spanning this 25-year period. In this regard, the top decile has accounted for between 46 and 54% of the overall returns over the four sample cohorts that we have analysed. Scherer and colleagues have shown that a high degree of skewness is typical of several different populations of technological innovations, including the outcomes of venture backed start-ups, university licensed patents and venture backed companies in the initial period after their initial public offerings.[20]

Drug Innovation and Industry Evolution Since 1970

As discussed in the introductory section, this is the third study of the industry returns on R&D that we have performed. The three studies employ the same general methodology. Consequently, they provide a convenient window to view the industry's development over the critical period from 1970 through the 1990s.

Trends in Industry Returns and R&D Expenditures

In table IV, we provide a summary of the mean internal return observed for our sample beginning with the 1970 to 1974 cohort and ending with the 1990 to 1994 period. The first column in table IV shows that the IRR has increased steadily from 7% for the 1970 to 1974 sample to 11.5% for 1990 to 1994 introductions. The biggest incremental change occurred during the second half of the 1970s and the first half of the 1980s. Over this time period, the mean return increased from 7.0% to 9.7% and then to 11.1%, respectively.

3 Tradenames are used for identification purposes only and do not imply product endorsement.

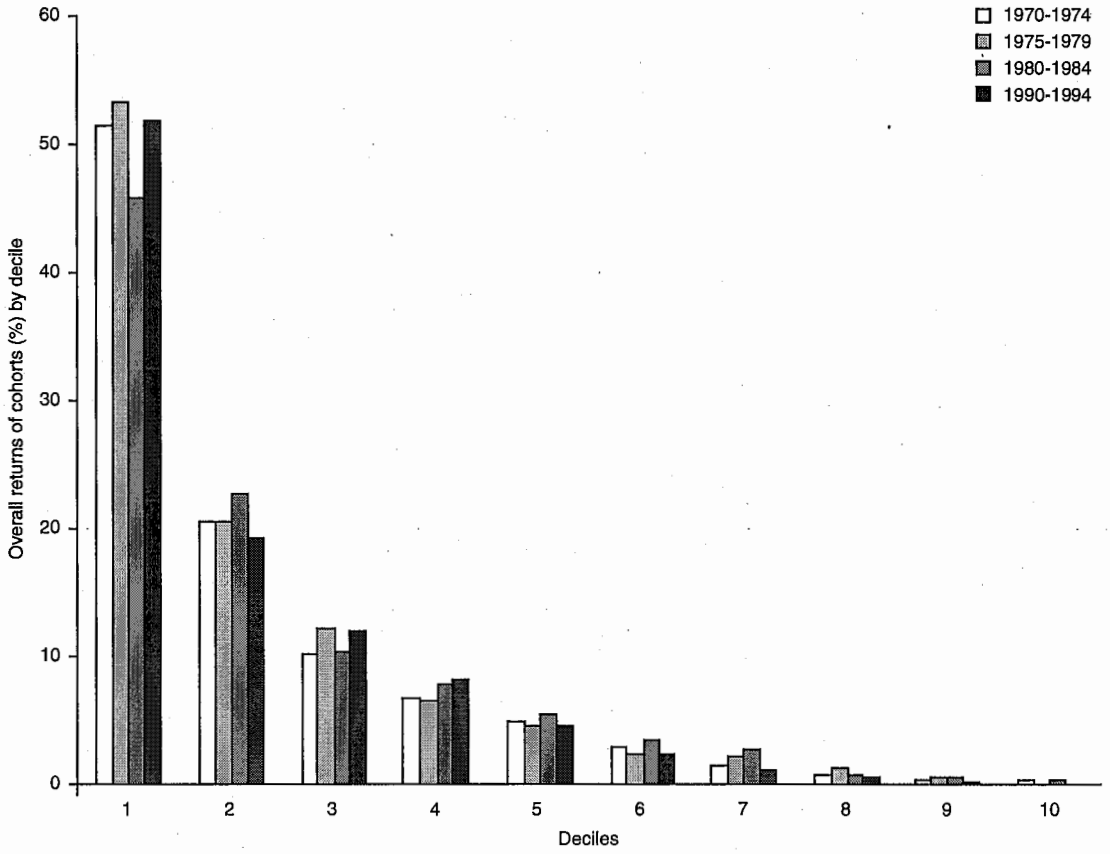

Fig. 8. Present values of four sample cohorts of new drug introductions accounted for by decile.

It is instructive to compare the mean estimated industry return in each period with the corresponding cost of capital for the pharmaceutical industry over that same period. For the 1970 to 1974 cohort, the mean industry return of 7.0% was significantly less than the industry's cost of capital of 9%. This relationship reversed in the second half of the 1970s (with a 9.7% IRR versus a 9% cost of capital). While the industry cost of capital increased in the 1980s and 1990s, so did the mean returns. Returns have remained modestly above the cost of capital for these cohorts.

Table IV. Mean industry returns and cost of capital for different time cohorts of new chemical entities (NCEs)

NCE cohort	Mean IRR	Cost of capital
1970 to 1974	7.0%	9.0%
1975 to 1979	9.7%	9.0%
1980 to 1984	11.1%	10.5%
1990 to 1994	11.5%	11.0%

IRR = internal rate of return.

It is also useful to examine the trends in industry R&D expenditures during these periods. Figure 9 shows the aggregate R&D-to-sales ratios for seven major drug firms that have reported R&D consistently over the complete period 1962 to 1994.[21] This graph shows that the R&D-to-sales ratios for these firms declined in the period 1962 to 1974, stabilised in the second half of the 1970s, and then began a steep increase from 1980 to 1994. The R&D-to-sales ratios for these firms grew from 7% in 1980 to 13% in 1994.

Scherer has recently examined long-term trends in industry R&D expenditures and profit margins for the period 1962 to 1996.[3] He finds a 0.96 rank

correlation in the deviations from trends in this industry's expenditures and profit margins over this 35-year period. His results also indicate that R&D expenditures and profit margins in the pharmaceutical industry generally grew at a slower rate relative to the long-run trend until the late 1970s, when they began a steep upward track.

These findings suggest that a beneficial competitive cycle may be at work in the pharmaceutical industry. In particular, R&D investment has not only led to innovation and profits in the form of the highly skewed distribution of returns observed here, but profits, or the expectation of profits, has produced expanding R&D investment. In this latter regard, Grabowski and Vernon also find that industry profit expectations on R&D, as well as internal cash flows, are highly significant explanatory variables of R&D investment outlays.[21] This type of competitive feedback cycle can be viewed as socially beneficial given the extensive literature on the high social returns from pharmaceutical R&D.[22,23]

Scherer has characterised the strong relationship between industry R&D investment and profitability, in conjunction with the fact that mean industry returns are only modestly above the industry cost of capital, as evidence of a 'virtuous rent seeking model'.[3] If this is a correct interpretation of the industry's competitive behaviour, the data on long-term trends suggest that the late 1970s represented a key turning point in terms of both industry returns and the growth in R&D expenditures. This issue is explored further in the next section.

The Pattern of Drug Innovation Since 1970

A number of pharmaceutical industry studies found diminishing returns to R&D characterised the 1960s and 1970s compared with the earlier post-war period.[24,25] The earlier period had witnessed a wave of important drug introductions. This involved many new antibiotic drugs, hydrocortisone and several other corticosteroids, the thiazide diuretics and β-blocker drugs for hypertension, new classes of anxiolytics and antidepressants, and the initial birth control drugs. However, by the early 1970s, the industry was experiencing diminishing returns in many of the drug classes that had seen major advances in the 1950s and 1960s. A number of hypotheses were investigated, including the effects of more stringent FDA regulations, diminishing technological opportunities and increased product liability. Some scholars saw the industry entering a prolonged period of technological maturity.[26]

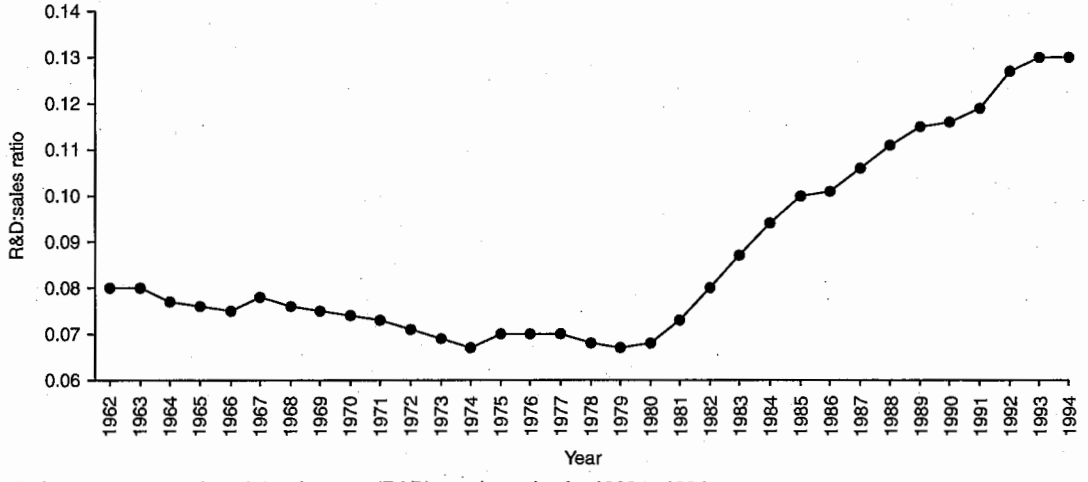

Fig. 9. Aggregate research and development (R&D) to sales ratios for 1962 to 1994.

Finding new drugs that were advances over established drugs had clearly become increasingly costly and more problematical by the early 1970s. Many of the leading firms began to focus their R&D activities on new therapeutic targets and approaches. One important concept that took root during this period was the 'rational drug-design' approach to R&D. This involved the use of x-ray crystallography and other techniques to design specific compounds that could block particular receptor sites and thereby create desired therapeutic responses. The primary approach to discovering new drug therapies prior to this time involved the random screening of compounds against a small number of known targets.

An important milestone for the industry occurred in 1978 with the introduction of Tagamet® (cimetidine) by SmithKline. This drug was not only a significant advance in the treatment of ulcers, but also provided validation of the 'rational drug design' approach to R&D. Tagamet was the first of the histamine H_2 receptor inhibitors. It was specifically designed to block H_2 histamine receptors, which were known to affect the process of acid secretion. Within a few years, it had become the largest selling drug worldwide. This drug by itself had a disproportionate effect on the returns for the full portfolio of 1970s new drug introductions. Indeed, when this one drug was removed from the portfolio of 1970 to 1979 drugs, the average present value for the remaining compounds declined by 14%.[2] Tagamet was eventually replaced by another H_2 blocker, Zantac® (ranitidine), as the largest selling drug worldwide. Zantac® became the top selling drug in our 1980 to 1984 cohort of NCEs.[1]

The 2.5 decades that have elapsed since the introduction of Tagamet® in 1978 have witnessed an impressive renaissance in drug innovation that is reflected in the trends toward higher returns and R&D intensities over this period. Table V provides a list of several important new chemical classes of drugs that were first introduced between 1978 and 1994. These classes all represent a new approach to, or mode of action in, treating particular diseases or indications. The pioneering drugs in these classes are concentrated in the very top deciles of the sample cohorts for which we have analysed returns. Many of these drugs have been the subject of specific cost-benefit and pharmacoeconomic studies.

Table V also provides information on the various indications and disease categories to which these new drug classes are targeted. There are many diseases listed that previously had few or inadequate drug treatments (i.e. herpes, AIDS, ovarian cancer, migraine, schizophrenia, etc.). The list also includes several novel biotech drugs such as erythropoietin (used to treat anaemia in patients undergoing kidney dialysis, and in those with AIDS or cancer) and the α- and β-interferons used in the treatment of cancer and multiple sclerosis. Several of the new classes of drugs listed in table V provide medical and economic benefits in the form of better patient tolerability and adverse-effect profiles in the treatment of widespread medical problems (i.e. hypertension, cholesterol reduction, depression, etc.).

Looking forward, the drug industry is currently confronted with a new wave of technological opportunities. The mapping of the genome and related advances in fields such as bioinformatics have led to an abundance of potential new targets for disease intervention. These advances could have profound effects on the discovery process itself, the size of clinical trials and the nature of demand for pharmaceutical products.[27] However, it remains unclear how quickly these new technologies will result in important new drug therapies and how they will influence industry returns. In this regard, a recent report by Lehman Brothers foresees a negative impact on returns until at least the latter part of this decade, when the substantial required buildup in R&D investments should begin to bear fruit.[28] If this is so, the industry could be facing another crossroads in the immediate future as the transition to new R&D paradigms compounds already existing economic pressures from the healthcare sector, financial markets, and government officials.

Table V. Important new drug classes 1978 to 1994

Year	Class	Early entrants	Indication
1978	H_2 receptor antagonists	Tagamet® (cimetidine), Zantac® (ranitidine)	Ulcers
1981	ACE inhibitors	Capoten® (captopril), Vasotec® (enalapril)	Hypertension
1982	Calcium channel blockers	Procardia® (nifedipine), Calan® (verapamil)	Hypertension
1982	Nucleosides	Zovirax® (acyclovir), Famvir® (famciclovir)	Herpes virus
1983	Interleukin-2 inhibitors	Sandimmune® (cyclosporin A)	Transplantation
1985	Human growth hormones	Protropin®, Humatrope®	Human growth hormone deficiency
1986	Quinolones	Noroxin® (norfloxacin), Cipro® (ciprofloxacin)	Antibiotic
1986	Interferon alphas	Intron A® (interferon α-2b), Roferon A® (interferon α-2a)	Cancer
1987	Statins	Mevacor® (lovastatin), Pravachol® (pravastatin)	Cholesterol reduction
1987	Nucleoside reverse transcriptase inhibitors	Retrovir® (zidovudine), Videx® (didanosine)	AIDS
1988	Serotonin reuptake inhibitors	Prozac® (fluoxetine), Zoloft® (sertraline)	Depression
1989	Proton pump inhibitors	Prilosec® (omeprazole), Prevacid® (lansoprazole)	Ulcers
1990	Erythropoietin	Epogen® (epoetin-α), Procrit® (epoetin-α)	Anaemia
1990	Macrolides (semi-synthetic)	Biaxin® (clarithromycin), Zithromax® (azithromycin)	Antibiotic
1990	Bis-triazoles	Diflucan® (fluconazole)	Antifungal
1991	Serotonin 5-HT_3 antagonists	Zofran® (ondansetron), Kytril® (granisetron)	Antiemetic
1992	Granulocyte colony stimulating factors	Neupogen® (filgrastim)	Cancer adjunct
1993	Taxoids	Taxol® (paclitaxel), Taxotere® (docetaxel)	Ovarian cancer
1993	Interferon-betas	Betaseron® (interferon β-1b), Avonex® (interferon β-1a)	Multiple sclerosis
1993	Serotonin 5-HT_1 antagonists	Imitrex® (sumatriptan), Zomig® (zolmitriptan)	Migraine
1994	D_2/5HT_2 antagonists	Risperdal® (risperidone)	Schizophrenia

a Tradenames are used for identification purposes only and do not imply product endorsement.

Summary and Conclusions

Consistent with our prior studies, a primary finding of the current analysis is that the distribution of returns for 1990 to 1994 new drug introductions is highly skewed. In this regard, only one-third of the new drug introductions had present values in excess of average R&D costs. The top decile of compounds by itself accounted for more than 50% of the present value of post-launch returns generated by the full sample of introductions.

From an industry perspective, the estimated mean return for the 118 new drug introductions in the 1990 to 1994 period was 11.5%. This compares with a real cost of capital of 11% for this sample cohort. At this cost of capital, the mean introduction earned an NPV of $US45 million ($US, 2000 values). A sensitivity analysis showed that returns are robust to changes in the economic parameters and assumptions. Changes in contribution margins and R&D times had the most impact on returns.

The principal results are, therefore, similar in nature to our study of 1980 to 1984 new drug introductions – namely, that R&D in pharmaceuticals is characterised by a highly skewed distribution of returns and a mean industry IRR modestly in excess of the cost of capital. However, the pattern of change on the inputs into our analysis shows a number of dynamic forces at work in this industry. In particular, R&D investments per new drug introduction approximately doubled compared with the 1980 to 1984 period. At the same time, the number of new introductions, the average sales per introduction and industry contribution

margins increased significantly in the 1990s compared with the 1980s.

Our studies of industry returns provide support for what has been labelled a 'virtuous rent seeking model' of R&D competition in the pharmaceutical industry. Since the end of the 1970s, the industry has experienced rapid growth in R&D outlays and the introduction of many important new therapeutic classes and blockbuster compounds. At the same time, mean industry returns on R&D over this period have only modestly exceeded the industry's cost of capital. Whether this beneficial cycle of increasing R&D intensities and innovative new product introductions will continue into the future remains to be seen. There are currently a number of promising new developments in the pharmaceutical R&D process, but the benefits from these technologies have an uncertain time horizon and it is likely they will require substantial increases in industry R&D investments. How quickly these evolving new technologies will lead to important new medicines will depend not only on scientific and economic factors, but also on the course of public policy actions.

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