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]

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

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.

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 glob-

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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.

ally 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

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