RETURNS ON R&D FOR

1990s NEW DRUG INTRODUCTIONS

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ABSTRACT

Previously published research by two of the authors found that returns on R&D for drugs introduced into the 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, there have been significant changes to the R&D environment for new medicines: the rapid growth of managed care organizations; indications that R&D costs are rising at a rate faster than overall inflation; new market strategies of major pharma firms; increased alliances with the emerging biotech sector; and, the increased attention focused on the pharmaceutical industry in the political arena. Nevertheless, analysis of new drugs entering the market from 1990-1994 resulted in findings similar to the earlier research—pharmaceutical R&D is characterized by a highly skewed distribution of returns and a mean industry internal rate of return modestly in excess of the cost-of-capital. These findings provide support for a model of intensive R&D competition by pharmaceutical firms to gain economic advantage through product innovation and differentiation.

I. INTRODUCTION

Competition in the research based pharmaceutical industry centers around the introduction of new drug therapies. In this paper, we examine the returns on R&D for new drug entities introduced into the U.S. 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 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 of 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 characterized by the rapid growth of managed care organizations on the demand side of the market for pharmaceuticals[4]. This has led to greater access to and utilization of pharmaceuticals, but also greater generic competition in the post-patent period. Second, a new study of R&D costs by DiMasi, et al. 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 to 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 include a Medicare prescription drug benefit, the parallel importation of drugs from Canada and Mexico, and various state programs affecting drug costs and utilization of 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].

The plan of the paper is the following. In the next section, we describe the data samples and methodology for our analysis of the returns to 1990-94 new molecular entities (NMEs). Section III presents the empirical findings on the distribution of returns and a sensitivity analysis involving the main economic parameters. Section IV 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 conclusion.

II. METHODOLOGY AND DATA INPUTS

A. Overview

This section explains the methodology and key data inputs used in estimating the returns to 1990-94 new chemical entities (NCEs)..(1) A detailed discussion of the general methodology is provided in our earlier papers on R&D return[1, 2]. Our focus here is on the similarities and differences of the 1990s sample from our analysis of prior NCE cohorts.

The basic sample is 118 NCEs introduced into the United States 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 United States in the 1990-94 time period.(2) The number of NCE introductions has increased significantly in the early 1990s compared to the 1980s. The corresponding 1980-84 NCE 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.(3)

Our basic procedure is as follows: for each new drug in our sample, worldwide sales profiles are constructed over the drug's complete 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 NPVs and IRRs are then computed for this portfolio of new drug introductions. The distribution of returns is another major focus of our analysis.

B. Cost-of-Capital

In our earlier analysis of 1980 NCEs, we utilized 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 1990-94 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 summarized in DiMasi et al.[5]

Using these four CAPM based analyses, occurring at roughly five 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 utilized 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 the equity market data on which the CAPM analysis is based pertains 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 that the cost-of-capital may be understated is the fact that many pharmaceutical firms carry significant cash balances.**(4)**

One of the authors undertook an informal survey of six pharmaceutical firms in mid-2001 with respect to the hurdle rates that drug firms utilize 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 utilized 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 analyses provides conservative estimates on the industry's cost-of-capital.**(6)**

C. R&D Investment Expenditures

To obtain representative R&D investment expenditures for the new drug entities in our sample, we rely on the recently completed study by Di Masi et al.[5] This study obtained R&D cost data for a randomly constructed sample of 68 drugs that were 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 analyzed 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 centered around 1984. Given the availability of these two R&D cost studies centered around 1984 and 1997, we can utilize a linear extrapolation procedure to estimate the mean R&D costs for our sample cohort .**(7)**

Using this extrapolation procedure, we estimated the mean out-of-pocket R&D expenditures for the drugs in our sample to be $308.4 million. This is approximately double the estimated R&D expenditures (in 2000 dollars) for the 1980-84 samples of NCEs. DiMasi also estimated a representative investment period of 12 years from initial drug synthesis to 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 study. Capitalizing these costs to the date of marketing, at a real cost-of-capital of 11%, yields $613 million as the average (pre-tax) capitalized R&D investment per '90-'94 NCE introduction.

Our analysis is performed on an after-tax basis. For the time period under study, we estimate a 30% average effective tax rate for the pharmaceutical industry (see Section II-G). 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 1. Utilizing the 30% effective tax rate, 613 million pre-tax capitalized corresponds to an after-tax value of $429 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. Based on the DiMasi et al study, we estimated the average post-approval R&D costs per NCE in our sample period to be $107 million (before tax).[(8)] We allocated these costs equally over the first eight years of a NCEs market life, using a discount rate of 11% from the date of marketing. This yields a present value of $73 million (before-tax) and $51 million dollars (after-tax).

Adding the after-tax values (Col. 2 of Table 1), the mean capitalized value for both pre and post approval R&D for the drugs in our sample is estimated to be $480 million. This is the baseline value that we compare to the present value of net revenues for the mean NCE in our sample.

D. Global Sales

In our prior analysis, we obtained U.S. sales data on each NCE in the sample. We then estimated worldwide sales for these compounds using a worldwide sales multiplier that was 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 endeavor, in the sense 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 over 90% of total U.S. sales realized by our sample of NCEs and presumably a similar, or even larger share, of their realized worldwide sales. With respect to the latter point, there is evidence that the larger selling U.S. drugs diffuse across more countries and have larger sales globally than U.S. 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 Med Ad News. The latter 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 top 500 selling prescription drugs worldwide.[15]

A complementary source of data that we also relied on is 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 very 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 figures. This reflected the fact that IMS does not capture all the sales channels available across countries, while the company data does 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 Med Ad News 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 utilized 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. We used a global multiplier approach for the remaining (very small selling) drugs in our sample. In particular, for these drugs, we multiplied their U.S. sales values times a representative global sales multiplier to obtain estimates of their worldwide sales.[(9)] As discussed, this latter sub-sample of drugs accounts for a very small share of overall sales for the full sample.

E. Life Cycle Sales Profiles

Given that the data were available for the years 1990 to 2000, this provided seven to eleven years of worldwide sales values for the NCEs in our sample, depending on their date of introduction into the U.S. 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 utilized for 1980s new drug introductions. We believe this is 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 utilized a two step procedure to project future sales values. These steps involve forecasting sales to the point of U.S. 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 U.S. market in 1992. There is nine years of sales information and its U.S. patent expiration occurs in year 12. By year 9, this product was in the mature portion of its product life cycle. Using a reference life cycle curve, the product is projected to have relatively stable sales (in constant dollar terms) until year 12.[(10)] A significant decline is then projected in the period after U.S. patent expiration due to the entry of generic competitors and related economic factors.

The estimated sales decline after patent expiry is based on the experience of major commercial products coming off patent in the 1994-97 period. In particular, we examined worldwide sales losses for a sample of NCEs for a four year period following their U.S. patent expiration. The average percentage decline observed were 31%, 28%, 20% and 20% respectively. We utilize these percentages to project sales in the first four years after patent expiration and thereafter, use a 20% percentage decline until the products market life is completed in year 20.**(11)**

We should note that the percentage declines in sales from generic competition in the U.S. market observed in prior studies are much greater than the worldwide losses in sales 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 United States. This may change by the time this cohort actually reaches patent expiration 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 2000 dollars) for top two deciles as well as the mean and median drug compounds in our 1990-94 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 to that for the 1980s cohort (expressed in 2000 dollars). Mean sales have increased significantly in real terms, with peak sales increasing from $345 mil for the 1980s cohort to $458 mil 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 takes hold.

Figure 4 shows a corresponding plot of the sales for the top decile compounds in the 1990-94 to 1980-84 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 over $2.5 billion. This may be compared to peak sales of near $1.8 billion for the 1980s cohort. The peak sales also occur later in time compared to the 1980s cohort.

F. Pre-Tax Contributions and Other Economic Parameters

The next step in the analysis is to obtain revenues net of production and distribution costs (often categorized in the economic literature as "quasi-rents"). For this purpose, we did an analysis of pre-tax contribution margins in pharmaceuticals during the 1990s. As in prior work we utilize data derived from the income statements of the pharmaceutical divisions of a number of major multinational drugs firms 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. Based on 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% 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 constrain margins to average 45% over the life cycle, we also recognize, 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 an allocation rule based on a regression analysis of promotional and marketing outlays. This rule was: promotion and marketing is equal to sales in year one, declines to 50% in year two, and falls to 25% in year three. 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] further indicates that the drug industry's marketing expenses to sales ratios have remained relatively stable in the 1996 to 2001 period.(12)

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 that pre-marketing launch expenditures will occur on the order of 5% and 10% of first year sales in the two 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 done by industry consultants as well as interviews with some of the participating companies.(13)

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 three 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 two years before marketing and the other half during the initial ten 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.(14)

For working capital, it was assumed that accounts receivables are equal to two months of annual sales and inventories are five 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.

G. 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 that is 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 U.S. 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.

H. Summary of Economic Values

Table 2 provides a summary of the key economic inputs to IRR and NPV analysis for the 1990-94 NCEs cohort compared with the corresponding values for the 1980-84 cohort. R&D investment levels have roughly doubled in real terms, in both uncapitalized as well as capitalized 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 1990-94 cohorts ($458 million compared to $345 million for 1980-84 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 which 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 to the 1980s sample.

Table 2 suggests that R&D investment expenditures are growing over time relative to sales revenues and the other activities of pharmaceutical firms. This issue is discussed further in Section IV. 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 analyze at the present time.

III. Empirical Results

A. 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 twelve years and results in a stream of negative cash flows. The first years of marketing, years 1 and 2, are also characterized 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 twelve and then begin to decline. The decline becomes steeper as patent expiration and generic competition begin.

The baseline case results are shown in the first row of Table 3. The IRR is 11.5% and can be compared to our real Cost-of-Capital (COC) 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 $525 million and can be compared to the present value of R&D costs at the same point in time, or $480 million. This leads to a Net Present Value (NPV) of $45 million.

The results for the baseline case for the 1990-94 NCEs are roughly the same as for our earlier 1980-84 sample. In the 1980-84 baseline case, the IRR was 11.1% compared to a COC of 10.5%. The 1990-94 IRR is similarly about a half percentage point above the COC estimate.

B. 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 3.

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. That is, we assumed that the margin increased 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 $32 million to $120 million. It should be noted that for the first ten years or so of product life the margin is based on real data—it is the last ten years that is more uncertain

and difficult to predict. Hence, the range of change in outcomes in perhaps overstated.

The next parameter that we examine in Table 3 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 to 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 expiration has tended to become greater over time. In the U.S., 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 pioneers after patent expiration 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 $45 million in the base case to $33 million and $20 million.

Varying the COC results in significant changes in the NPVs. A 10% COC would result in a NPV of $131 million, considerably larger than the base case using the 11% COC of $45 million. A 12% COC, on the other hand, leads to a negative NPV of $37 million. These changes are comparable in magnitude to those observed for changes in the contribution margin.

The final sensitivity analysis in Table 3 is the effect of reducing regulatory review time by one 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 one year and compute the lower capitalized value of R&D at the date of marketing. This reduces R&D from $480.3 million to $437.7 million; hence, the base NPV rises from $45 million to $87.5 million. The IRR increases from 11.5% to 12.2%. These are clearly significant effects.[15]

C. Distribution of Returns

In figure 7, we show the decile distribution of present values of returns for the 1990-94 samples of NCEs. These returns are gross of R&D costs. The deciles are constructed based upon 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 figure shows that the distribution is highly skewed. For example, the top decile has an estimated present value of $2.7 billion. This is almost six times the present value of average R&D costs ($480 million). The top decile alone accounts for about 52% of the total present value generated by all ten deciles. This compares to the value of 46% that we found in our 1980-84 study.

It is also true that the second and third deciles have present values that exceed average R&D costs, or $1 billion and $0.6 billion respectively. However, the fourth decile's present value is only $433 million in comparison to average R&D costs of $480 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, 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 $525 million to $479 million, and the NPV falls from $45

million to a negative $1 million. Hence, if it were not for this one "blockbuster" drug, the average NCE of the 1990-94 cohort would essentially just break even in terms of an NPV analysis.

We should observe that the fact that the majority of the 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 it share of products in the top few deciles to have a viable R&D program.

Figure 8 provides a comparison of the distribution of returns for all four sample cohorts that we have examined to date: 1970-74, 1975-79, 1980-84 and 1990-94. 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 4 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 4 sample cohort that we have analyzed. 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 startups, university licensed patents and venture backed companies in the initial period after their IPOs.[20]

IV. Drug Innovation and Industry Evolution Since 1970

As discussed in the Introduction, this is the third study that we have performed of the industry returns on R&D. 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.

A. Trends in Industry Returns and R&D Expenditures

In Table 4, we provide a summary of the mean internal return observed for our sample beginning with the 1970-74 cohort and ending with the 1990-94 period. The first column in Table 1 shows that the IRR has increased steadily from 7% for the 1970-74 sample to 11.5% for 1990-94 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% respectively.

It is instructive to compare the mean estimated industry return in each period to the corresponding cost-of-capital (COC) for the pharmaceutical industry over that same period. For the 1970-74 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% COC). While the industry cost-of-capital increased in the 1980s and 1990s, so has mean returns. Returns have remained modestly above the cost-of-capital for these cohorts.

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 figure shows that the R&D-to-sales ratios for these firms declined in the period 1962 to 1974, stabilized 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 grow from 7% in 1980 to 13% in 1994.

Mike Scherer has recently examined long term trends in industry R&D expenditures and profit margins for the period 1962 to 1996.[2] 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 grow out 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 characterized 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." If this is a correct interpretation of the industry's competitive behavior, the data on long term trends suggests 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.

B. The Pattern of Drug Innovation Since 1970

A number of pharmaceutical industry studies found diminishing returns to R&D characterized the 1960s and 1970s compared to 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 cortocoids, the thiazide diuretic and beta blocker drugs for hypertension, new classes of tranquilizers and anti-depressants, 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]

Finding new drugs that were advances over established drugs had clearly become increasingly costly and more problematic 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 1970-79 drugs, the average present value for the remaining compounds declined by 14%.[2] Tagamet was eventually replaced by another H_2 blocker, Zantac, as

the largest selling drug worldwide. Zantac became the top selling drug in our 1980-84 cohort of NCEs.[1]

The two and one-half 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 5 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 or mode of action to 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 analyzed returns. Many of these drugs have been the subject of specific cost benefit and pharmcoeconomic studies.

Table 5 also provides information on the various indications and disease categories to which these new drug classes are targeted. There are many diseases listed which previously had few or inadequate drug treatments (i.e., herpes, AIDS, ovarian cancer, migraine, schizophrenia, etc.). The list also includes several novel biotech drugs like Erythropoletin (used to treat anemia for patients undergoing treatment for kidney dialysis, AIDS and cancer) and the alpha and beta interferons used in the treatment of cancer and multiple sclerosis. Several of the new classes of drugs listed in Table 5 provide medical and economic benefits in the form of better patient tolerability and side 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 like bioinformatics, has 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 fast these new technologies will result in important new drug therapies and how they will impact industry returns. In this regard, a recent report by McKinsey and 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 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 health care sector, financial markets, and government officials.

V. Summary and Conclusions

Consistent with our prior studies, a primary finding of the current analysis is that the distribution of returns for 1990-94 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 over 50% of the present value of post-launch returns generated by the full sample of introductions.

From an industry prospective, the estimated mean return for the 118 new drug introductions in the 1990-94 period was 11.5%. This compares to a real cost-of-capital of 11% for this sample cohort. At this cost-of-capital, the mean introduction earned an NPV of $45 million dollars (2000 dollars). 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 1980-84 new drug introductions – namely R&D in pharmaceuticals is characterized by a highly skewed distribution of returns and a mean industry IRR modestly in excess of the cost-of-capital. However, a look at 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 to the 1980-84 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 to the 1980s.

Our studies of industry returns provide support for what has been labeled as 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 they will likely 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.

FOOTNOTES

1. We are using a broad definition of NCE here. Our sample includes "large-molecule" biologics, in addition to traditional "small molecule" chemical drugs.

2. Three drugs were omitted from our sample because they failed to appear in any year in the IMS sales data audits. These three drugs involved an antiprotozal agent for sleeping sickness, an agent for opiate dependence, and one for nephropathic cystinosis, a rare inherited disorder affecting functioning of the liver. These products are apparently distributed outside of normal sales channels. In addition, given their special indications and characteristics, they are also likely to have non-representative R&D costs.

3. Another related fact is the passage of the Orphan Drug Act by Congress in 1983. This provided economic incentives, especially 7 years of market exclusivity, for the development of drugs targeted to indications involving less than 200,000 patients (or for which the manufacturer could demonstrate that development would be unprofitable). As we have discussed elsewhere, there is a high degree of overlap between the biopharmaceutical and orphan drug sub-samples.[8] This reflects the fact that many of the initial recombinant biotech drugs had indications for small patient populations and, in addition, biopharmaceutical firms sought out the market exclusivity protection of the Orphan Drug Act, given the uncertainties surrounding many biopharmaceutical patents.

4. 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 do a sensitivity analysis to gauge how this factor

would affect their 1990 value and they find it causes the nominal (and real cost-of-capital) to increase by almost a full percentage point.[9]

5 Several surveys have been performed of the hurdle rates used by U.S. companies. A general finding is that hurdle rates are typically greater than the weighted cost-of-capital computed by a CAPM analysis. For example, Poterba and Summers received responses from 228 companies, of the Fortune 1000, and found an average hurdle rate of 12.2% in real terms in the early 1990s.[12] They also found that hurdle rates can vary substantially across a company's functional areas and specific projects. The average difference between the highest and lowest hurdle rate within companies was 11.2%.

6. Myers and Howe further indicate that the R&D decision process can be modeled 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 to the standard CAPM approach using a weighted cost-of-capital. DiMasi et al, perform a sensitivity analysis using this option value approach, and show that for reasonable values of the forward looking discount rates, the CAPM and option value models yield comparable results.

7. Since our sample is centered around 1992, we utilize the following linear extrapolation equation to derive R&D costs:

$$R\&D_{92} = R\&D_{84} + (8/13)\ R\&D_{97}$$

8. DiMasi et al. obtained data from all the firms participating in his survey on pre-approval and post-approval R&D expenditures. Based on 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 $308.4 million for pre-approval R&D yields an estimate of $107 million (in 2000 dollars) as the R&D cost for post-launch product improvements.

9. For these purposes, we utilized a global sales multiplier of 2.19 that was derived from actual worldwide sales and U.S. sales for the other drugs in our sample. This multiplier may overstate worldwide sales for drugs to which it is applied since, as noted, these drugs may well not have diffused globally as extensively as the drugs for which we had worldwide sales data.

10. The reference life cycle curve is based on observed sales for drug products introduced into the market in the immediately prior period. We used this as the basic template for most of the NCEs. However, we also make adjustments to these values using the sales projections of security analysts to allow for changing market conditions and competitive developments in particular therapeutic classes.

11. In our prior work on generic competition, we found that generic competition is focused on products with significant sales at the time of U.S. patent expiration. Consequently, for the drugs concentrated in the bottom four decile of our sample (with worldwide sales of less than 40 million dollars in year 10 of their market life), we assume that the probability of generic competition is very low. For these drugs we assume 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 expiration period.

12. Although the aggregate marketing to sales ratio in the U.S. pharmaceutical industry was stable around 14% between 1996 and 2000, there were some important compositional shifts over this period. 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. The growth in direct-to-consumer advertising was stimulated, in part, by a change in the FDA regulations involving television ads for prescription drugs in 1997.[18]

13. Best Practices LLC, a Chapel Hill, NC management consulting firm, conducted interviews with and obtained data from 11 pharmaceutical firms on global marketing launch expenditures in 1998. In particular, they focused on 12 market launches in depth and obtained detailed marketing data relating to these launches. We talked with several of the participants in this study to get further perspective on how these budgeted expenditures generally related to first year sales. We used this information to develop the representative percentages used in the model.

14. In particular, we checked the reasonableness of our assumptions by comparing this implied 3.3% capital investment to sales ratio to the corresponding ratios observed on industry income statements 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. Accordingly, we asked some industry members involved with strategic planning for information on what percentage of their plant and capital equipment expenditures were 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.

15. This sensitivity analysis captures only the direct effects of shorter FDA review times on the capitalized value of R&D costs. We abstract 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 lost time 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 five years on the patent life restored under the Act). We abstract from these potential secondary benefits in the above sensitivity analysis.

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TABLE 1

Capitalized R&D Costs for Mean NCE in the 1990-94 Sample

R&D Costs (mils 2000$)	Pre-Tax	After-Tax
Discovery and Development	$613	$429
Product Extensions After Launch	73	51
Total	$686	$480

NOTES

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

2. R&D costs are capitalized to the first year of marketing using an 11% cost-of-capital.

TABLE 2

Key Economic Values for IRR Analysis
1990-94 vs. 1980-84 NCEs

Average R&D Costs:	**1990-94**	**1980-84**
Pre-Tax Uncapitalized	$416 mil	$196 mil
After-tax Capitalized	$480 mil	$251 mil
Peak Sales for Mean NCE	$458 mil	$345 mil
Contribution Margin	45%	40%
Cost-of-Capital	11%	10.5%
Effective Tax Rate	30%	33%
Capital to Investment Sales Ratio	3.3%	3.4%

NOTES

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

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.

TABLE 3

Returns to 1990-94 NCEs

Case	Present Value Cash Flows (after-tax)	Present Value R&D Costs (after-tax)	NPV	IRR
Baseline	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 0.25 tax rate	571.3	514.6	56.7	11.6
at 0.35 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

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

TABLE 4

Mean Industry Returns and Cost-of-Capital for Diffect Time Cohorts of NCES

NCE Cohort	Mean IRR	Cost-of-Capital
1970-74	7.0%	9.0%
1975-79	9.7%	9.0%
1980-84	11.1%	10.5%
1990-94	11.6%	11.0%

TABLE 5

Important New Drug Classes
1978 – 94

Year	Class	Early Entrants	Indication
1978	H_2 receptor antagonists	Tagamet, Zantac	Ulcers
1981	ACE inhibitors	Capoten, Vasotec	Hypertension
1982	Calcium Channel Blockers	Procardia, Calan	Hypertension
1982	Nucleosides	Zovirax, Famvir	Herpes Virus
1983	Interleukin-2 inhibitors	Sandimmune	Transplantation
1985	Human Growth Hormones	Protropin, Humatrope	HGH Deficiency
1986	Quinolones	Noroxin, Cipro	Antibiotic
1986	Interferon Alphas	Intron A, Roferon A	Cancer
1987	Statins	Mevacor, Pravachol	Cholesterol Reduction
1987	Nucleoside/RT inhibitors	Retrovir, Videx	AIDS
1988	Serotonin Reuptake Inhibitors	Prozac, Zoloft	Depression
1989	Proton pump inhibitors	Prilosec, Prevacid	Ulcers
1990	Erythropoietin	Epogen, Procrit	Anemia
1990	Macrolides (semi-synthetic)	Biaxin, Zitromax	Antibiotic
1990	Bis-Triazoles	Diflucan	Antifungal
1991	5-HT_3 antagonists	Zofran, Kytril	Antiemetic
1992	Granulocyte (G-CSFs)	Neupogen	Cancer Adjunct
1993	Taxoids	Taxol, Taxoterre	Ovarian Cancer
1993	Interferon-betas	Betaseron, Avonex	Multiple Sclerosis
1993	5-HT_1 antagonists	Imitrex, Zomig	Migrane
1994	D_2/5HT_2 antagonists	Risperidal	Schizophrenia

FIGURE LEGENDS

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

Figure 2 Worldwide sales profiles of 1990-94 new drug introductions.

Figure 3 Comparison of sales curves for the mean drug in 1990-94 and 1980-84 samples.

Figure 4 Comparison of sales curves for top decile drugs in 1990-94 and 1980-84 samples.

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

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

Figure 7 Present values by decile for 1994 new drug introductions.

Figure 8 Present values by deciles for four samples of new drug introductions.

Figure 9 Aggregate R&D to Sales Ratios 1962-1994.