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THE COSTS AND RETURNS TO PHARMACEUTICAL RESEARCH AND DEVELOPMENT

ABSTRACT

The paper presents an empirical analysis of the innovative performance and structure of the pharmaceutical industry. The first section presents a discussion of R&D costs and returns on an industry-wide basis for new chemical entities (NCEs) introduced in the United States in the 1980s. Section II gives the primary results and includes a comparison of returns in the 1980s and in the 1970s. Real R&D costs have increased greatly over the period as has the range of present net values of revenues. This suggests that the optimal size of R&D budgets has increased and indeed, a number of major mergers have occurred in the industry.

A recent cover story in «Fortune» begins by observing that the US pharmaceutical industry has consistently had returns on equity far above the average for manufacturing industries — it notes that this figure was 26% in 1990, «double the “Fortune 500” median». The article attributes these results partially to highly successful innovation and partially to the fact that during the 1980s «the average cost per prescription for established drugs climbed at double the rate of inflation». Furthermore, it is pointed out that «Congressmen and Senators leap before the TV cameras to decry outrageous profiteering» and «Senator David Pryor... ominously notes that the US is the only major country that regulates neither drug prices nor drug profits».

A somewhat different perspective is provided by the wave of mergers and strategic alliances that have recently taken place in the industry. The often cited reason for these mergers is the high threshold costs of R&D and the skewed distribution of sales emerging from the pharmaceutical innovation process. As the Chairman of the combined Bristol Myers Squibb Corporation was recently quoted in the «Wall Street Journal», «there is a lot of opportunity, but you need a lot of money to seize it. I don't know if Bristol Myers or Squibb would have been able to do it going alone». The US pharmaceutical executives surveyed in this article overwhelmingly agreed that more industry consolidation would occur and predicted that all remaining mid-sized firms would be subject to mergers or a major joint venture in the near future.

Given the interest at the present time in the economic performance of the pharmaceutical industry, this paper presents an empirical analysis of the innovative performance and structure of the industry. Our primary focus is on the return to R&D costs and returns on an industry-wide basis for new chemical

entities (NCEs) introduced in the United States in the 1980s. We also review and update findings from a similar study that we did of NCEs introduced in the 1970s (Grabowski-Vernon, 1990). We are interested not only in the mean return earned by the industry, but also the distribution around the mean given the recent movement toward industry consolidation.

A particular advantage to analyzing returns to recent NCE introductions is that it is arguably the most relevant measure of current industry profitability. In a dynamic industry like pharmaceuticals, there are many changes occurring over time in the factors influencing both R&D costs and returns. Analyses of the returns on recent NCE introductions can better capture these changes, both directly and in sensitivity analyses, compared to analyses of static measures such as the total industry returns on stockholder equity.

The return to equity measure is an accounting ratio of current period total returns to total equity. Fisher and McGowan (1983) have argued in a widely-cited article that it is a poor proxy for the underlying internal rate of return (IRR) of a firm or industry. The basic reasons are problems of bias due to both timing and aggregation. The most fundamental problem is that this performance measure ignores future returns which will be forthcoming due to current equity investment¹.

The return on equity measure of profitability is also less suitable for pharmaceutical firms than for other firms because of the problem of unusually high intangible capital investments in pharmaceuticals. Since accountants do not include investments like R&D in a firm's assets, the return to equity measure is distorted. The consensus is that the return to equity for pharmaceuticals is overstated at least 20 to 25% for this reason (Clarkson, 1977; Grabowski-Mueller, 1978; Megna-Mueller, 1991).

Our focus on the mean returns for the industry's portfolio of new drug introductions is broadly consistent with the Fisher and McGowan approach. Their view is that a firm or industry can be viewed as a collection of investment projects and the correct returns measure is a weighted averaged of the IRRs resulting from this portfolio. We explicitly set out to estimate the cash flows forthcoming over the life of each NCE and compare the present value of these flows with the capitalized value of mean R&D costs. We also calculate the IRR for the mean NCE in each time period.

Of course, our approach also has limitations. We must make forecasts of future sales revenues that are necessarily somewhat uncertain. It is also true that

¹ Baber and Kang (1991) in a recent paper have shown how the internal rate of return can be derived from an accounting approach (*i.e.*, the cash flow recovery return) under very special assumptions. They have applied this approach to the pharmaceutical industry. However, it remains to be seen how sensitive their findings are to the special assumptions that are employed in this analysis. In addition, in contrast to our approach based on individual innovations, their analysis uses aggregate corporate level data which includes non-pharmaceutical businesses.

the returns estimates that we obtain apply only to NCEs and not to profits resulting from existing, older products. Nevertheless, it would seem to us that estimating the returns to 1980-1984 NCEs is the best empirical approach for shedding light on whether excess returns exist on recent new drug introductions and if so, whether they are likely to persist in the future.

The paper is organized as follows. In the next section, we present a discussion of R&D costs to 1980 introductions. The primary results are given in Section II, which includes a comparison of returns in the 1980s with our prior findings on returns to 1970s introduction.

I - R&D COSTS

In this section, findings are presented from a new study of R&D costs published in the «Journal of Health Economics» (Di Masi *et Al.*, 1991). The analysis was performed under the sponsorship of the Center for the Study of Drug Development. The lead author of the study is Joe DiMasi and I am a co-author along with Ron Hansen and Lou Lasagna.

The R&D cost study investigates a random sample of 93 self-originated drugs first tested in humans between 1970 and 1982. The R&D cost data were obtained from a questionnaire survey of twelve US firms. Each firm provided information on a sample of drug entities that were randomly selected by us from the full universe of their clinically tested compounds. The surveyed firms account for approximately 40 percent of US industry R&D expenditures. They include a number of the largest firms in the US pharmaceutical industry as well as some very small ones in terms of annual sales.

The major objective of our study was to estimate the average R&D cost, including the opportunity costs, of discovering and developing a new drug for the US market. Accordingly, the R&D costs of unsuccessful drug candidates are incorporated into the costs of the new drugs approvals. R&D expenditures are also capitalized to the date of marketing using a 9 percent rate. This discount rate, which is a real rate after adjusting for inflation, reflects the opportunity cost of investment in pharmaceutical R&D. It is based on a financial analysis of returns earned by investments of comparable riskiness to pharmaceutical R&D (Grabowski-Vernon, 1990).

The estimated mean R&D cost per approved NCE from our study is 231 million dollars measured in 1987 dollars. This is the average R&D cost of a new introduction in the mid 1980s. Out of pocket costs account for 114 million dollars of the 231 million dollar estimate. The other 117 million dollars are the time costs arising from capitalizing the out-of-pocket outlays at the 9 percent real rate. The details of our R&D cost analysis and some of the other important findings are presented below.

1.1. Phase Times and Attrition Rates

The pre-clinical phase from synthesis to first testing in humans was estimated to be 42.6 months. Long term animal testing and the clinical development phases together take another 68.6 months (that is after adjusting for gaps and overlaps in phases). The NDA phase takes an average of 30.3 months. This adds up to a 11.8 year total gestation period for a new NCE in our sample. This long R&D investment period is what causes the time cost component to be such a significant part of the total R&D costs per approved NCE.

We also analyzed the average attrition rate of a representative new drug compound in our sample as it goes through each development phase toward FDA approval. Of the full cohort of drugs beginning clinical testing, 75 percent enter Phase II and 36 percent survive to Phase III. Furthermore, 23 percent of the clinically tested compounds for our sample firms eventually obtain FDA approval. While this success rate has been increasing over time, 4 to 5 compounds must still be taken into man for each one that obtains approval. This is an important factor which causes R&D costs in pharmaceuticals to multiply in value as one proceeds through the different testing phases.

1.2. Out-of-Pocket and Capitalized Costs

In Figure 1, time costs are added to out-of-pocket costs to obtain our baseline estimate of 231 million dollars per NCE. This figure shows that pre-clinical R&D expenditures per approved NCE account for 156 million dollars of the 231 million dollar baseline cost estimate. Clinical expenditures comprise the other 75 million dollars.

Time costs equal 90 million dollars of the 156 million preclinical costs per approved NCE. Time costs are disproportionately larger at the pre-clinical stage because these expenditures occur early in the investment process and are subject to much greater compound interest effects. By contrast, time costs account for only 27 million dollars at the clinical stage.

1.3. Effects of Reduced NDA Review Time

In our study, we simulated the effect on total R&D costs of a one year reduction in regulatory approval time. The regulatory approval phase in the United States has averaged approximately 2 1/2 years over the past decade. If this could be reduced by one year, we estimate that it would decrease R&D costs by 19 million dollars. This is roughly 8 percent of our overall estimate.

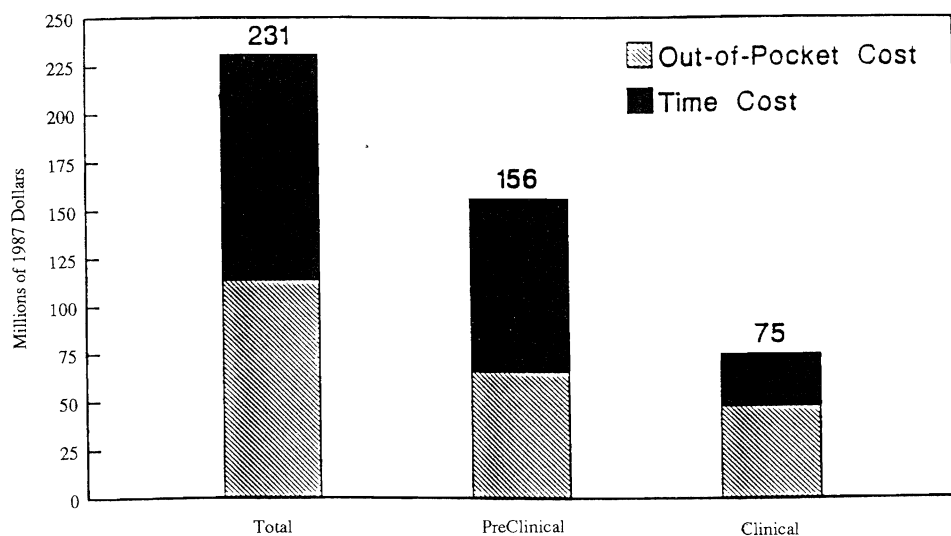


FIG. 1 - Capitalized Costs per Approved NCE (NCEs First Tested in Humans 1970-1982).

A reduction in regulatory review time, of course, may require more resources at the FDA. However, the aggregate R&D cost saving for the industry of a one year reduction in review times would be substantial. In particular, a saving of 19 million dollars per approved NCE, multiplied by an average of 19 approved NCEs per year, yields an aggregate annual potential savings in industry R&D costs of 361 million dollars. To put this in perspective, this is roughly half the FDA's total annual budget in recent fiscal years. Furthermore, it significantly exceeds the annual budget for the new drug division of FDA. Hence, there are strong potential benefits to be obtained from a faster and more efficient FDA review process.

1.4. Compared to Prior Estimates of R&D Costs

It is useful to compare the capitalized R&D cost per approved NCE from our study to an earlier one by Ron Hansen (1979). His study of R&D costs utilizes a similar methodology and a sample of drugs first entering man between 1963-1975. The R&D cost estimates for both studies are expressed in 1987 dollars, so differences in real dollar expenditures can be compared for the two studies. Hansen's overall R&D cost estimate values in 1987 dollars is 100.7 million. Our R&D cost estimate of 231 million dollars is therefore 2.3 times higher in real terms. This is a very rapid increase given the periods of time covered by the two studies, which are a little less than a decade apart.

1.5 Implications and Issues for Future Research

In summary, our new study clearly shows that pharmaceutical R&D costs are escalating very rapidly in real terms. An analysis of aggregate industry expenditures and NCE introductions was also performed in our study as a check on our findings. It provides strong confirmation of our baseline estimate on R&D costs of over 200 million dollars for new drug introductions during the mid 1980s.

Research into the factors underlying the rapid escalation in real R&D costs is an important area for continuing study. It is useful to list some of the hypotheses that warrant further attention.

1.5.1. Increased Discovery Research

This has been mentioned as one of the factors causing R&D costs to grow significantly in real terms at the pre-clinical level. This hypothesis is consistent with the higher success rates observed in the clinical phase compared to earlier analyses.

1.5.2. Increased Emphasis on Chronic Disease Categories

Another factor apparently tied to higher real costs is the increasing emphasis in pharmaceutical R&D on chronic diseases like cardiovascular illness and cancer. Chronic diseases generally require more testing and greater overall resource investments prior to introduction. We plan to look at R&D costs across therapeutic classes in a subsequent paper.

1.5.3. Expanded Patient Trials

There is also some case study evidence which suggests that NCEs now entail much larger scale patient trials and higher out-of-pocket costs to execute these trials than in the past. The extent to which this is driven by regulatory requirements is an important issue for future work.

Another related issue for future research concerns the question of economies to scale in pharmaceutical R&D. Given the recent trends toward mergers and industry concentration in the pharmaceutical industry, it would be interesting to examine the role of R&D costs and whether there are economies of scale in pharmaceutical R&D. This is another issue we plan to investigate in future research.

II - RETURNS TO PHARMACEUTICAL R&D

John Vernon and I have been engaged in an on-going long term study of the returns to US new drug introductions. We have completed our analysis of the returns on new drugs introduced during the 1970s (Grabowski-Vernon, 1990). We are currently analyzing the returns to the new drug introduction of the 1980s utilizing a comparable methodology. This section discusses the nature of the analysis and some of the major findings from this ongoing work.

A key question which we address in this work is whether the average US NCE earns a rate of return on R&D investment that is commensurate with the pharmaceutical industry's cost of capital. We also examine the distribution of returns and the break-even time for the average NCE to cover its R&D costs. Our analysis is based on a comprehensive sample of US NCE introductions and is performed on a real after-tax basis.

2.1. *R&D Costs and Sales Profiles*

The R&D investment costs for 1970s NCE introductions are based on Hansen's earlier study adjusted to the particular time periods of our analysis. For 1980s introductions, we based our R&D cost values on the R&D cost study discussed in the previous section.

The first step in the analysis of sales revenues is to construct life cycle profiles for each introduction. In particular, for each NCE in our sample, we obtained US sales data over the product's lifetime to date from audit data sources. We then estimated sales over the future years of the product life cycle by utilizing information on each NCE's patent expiration date and other relevant economic information. Sales are projected to worldwide levels utilizing international sales multipliers.

Figure 2 illustrates the aggregated sales profiles for the US market for 1970-1979 introductions. In particular, it shows annual sales estimates for the mean, median and top few deciles of our sample. These curves exhibit the classical life cycle pattern of rapid sales growth, maturity, and sales decline.

Two points of interest can be noted from this figure. First, it illustrates the highly skewed nature of the sale distribution for new drug introductions. The sales peak of the top decile drugs are several times greater than the sales peak for the second decile. Furthermore, the mean sales curve is much higher than the median one. This skewed distribution of sales is also observed for 1980 introductions.

Another interesting point concerns the longevity of sales curves for 1970s introductions. In this regard, sales in year 17 (the nominal US patent life) for the top decile are still approximately 80 percent of the sales peak. This is not ex-

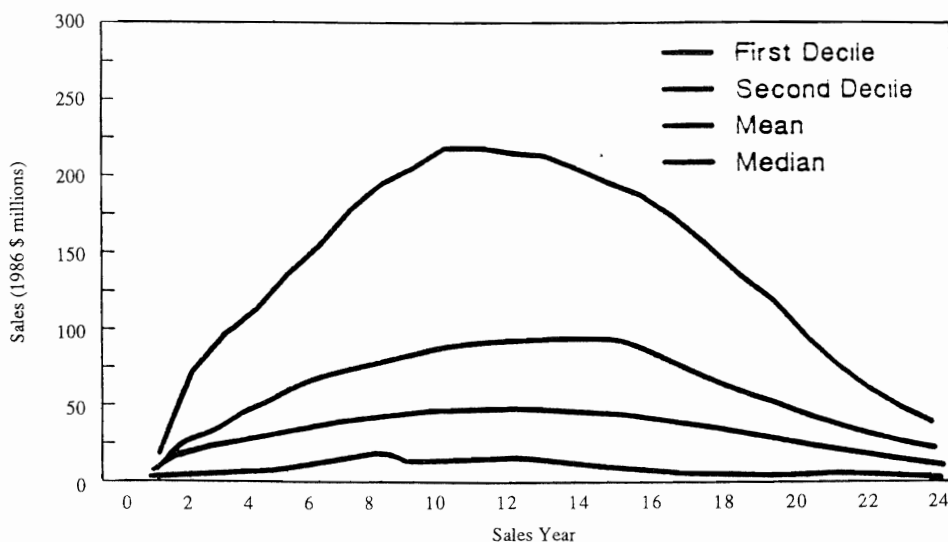


FIG. 2 - Sales Profile of 1970-1979 Compounds.

pected to be the case for more recent new product introductions. In particular, there is a tendency for more rapid erosion of sales due to increased generic entry during the 1980s after the effective patent life expires (Grabowski-Vernon, 1992). Effective patent life in the United States now averages between 10 and 12 years for the typical new drug introduction.

In our analysis, cash flows after product launch are derived from sales values by applying drug industry profit margins on sales. During the 1980s, pre-tax profit margins on sales for pharmaceuticals increased in value and were estimated to be in the neighborhood of 40 percent². Both cash flows from sales and R&D input costs are transformed to after tax values in our study using an average tax rate of 35 percent for the pharmaceutical industry.

2.2. Estimates of Mean Returns

Rates of return are estimated from the series of annual net cash flows starting at the beginning of the R&D investment period and going to the end of the product's life cycle. Cash flows are negative over the pre-clinical and clinical R&D period and become increasingly so in the years prior to initial marketing due to the addition of heavy launch and capital investment outlays. By year 3

² These margins are derived from aggregate income and sales information from the pharmaceutical divisions of twelve major US health firms.

after product launch, cash flows generally become positive. They then escalate rapidly, reach a peak in the period around 10 to 15 years after marketing and then begin a period of gradual decline. We assumed 25 years as the expected product lifetime for our sample cohorts.

The economic rate of return computed in our analysis is the compound interest rate which equates the present value of positive cash inflows to the present value of cash outflows. Table I shows the estimated mean rates of return for US NCE introductions grouped in five year cohorts beginning in 1970. One significant result is that the average return has increased over time. Our mean estimated return for the 1970-1974 period was 7 percent, it rose to 9.7 percent in the 1975-1979 period and is between 10 and 11 percent in our preliminary results for the 1980-1984 cohort. This pattern of increasing returns over time reflects, among other things, the introduction of several products of major therapeutic and commercial importance beginning in the late 1970s. By contrast, the early 1970s is generally perceived as a depressed period for new drug introductions. This is reflected in the relatively low rate of return of 7 percent in this period.

While pharmaceutical industry returns increased beginning in the mid 70's, the mean returns have generally remained within the range of estimates for the industry's opportunity cost of capital. This is shown in the last column to range from 8 to 10 percent in the 1970s and 10 to 12 percent in the 1980s. The general consensus of experts in finance is that real interest rates for all investments have increased in the 1980s. The recent estimates for the pharmaceutical industry opportunity cost of capital reflect this upward trend (Meyers-Shyam-Sunder, 1990).

2.3. *The Distribution of Returns*

While mean returns have been in line with the cost of capital, the distribution of income across NCE introductions is highly skewed. Figure 3 gives the

TABLE I
Comparison of Internal Rates of Returns
(In 1970s and 1980s)*

NCE Cohort	IRR	Opportunity Cost of Capital
1970-1974	7.0%	8-10%
1975-1979	9.7%	9-10%
1980-1984	10-11%	10-12%

* Preliminary Result.

distribution of present values of after tax cash flows by decile for the sample of all 1970s introductions. These cash flows are gross of R&D investment but net of all other expenditures. The top decile has an estimated after tax present value which is several times the average after tax R&D investment³. Furthermore, the after-tax cash flows exceed average R&D investments only for the top three deciles.

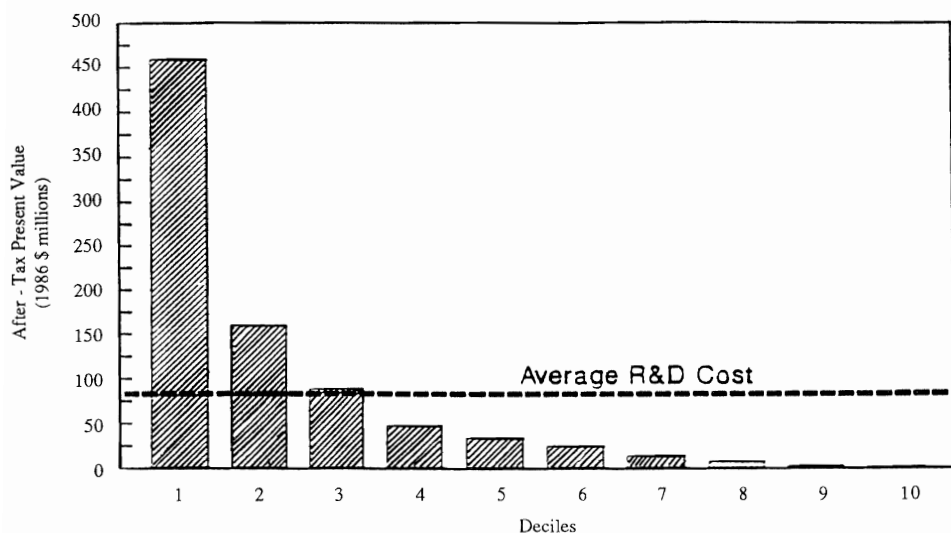


FIG. 3 - Present Values by Decile 1970-1979 NCEs.

In interpreting the findings, it would be wrong, even with the benefit of hindsight, to conclude that the industry made a mistake in developing the bottom ranked 70 percent of the NCE introductions. Many of these products are useful therapies in the physician's arsenal. Furthermore, a great many of these products also contribute to the firm economically in terms of covering their direct R&D investment expenditures. However, the products below the third decile will not typically cover all the indirect costs or opportunity costs of research. Hence, a firm must occasionally obtain a drug in the top few deciles, if it is to earn positive long run returns on its total portfolio of projects. Furthermore, our preliminary work on 1980s introductions suggests that the distribution of returns is highly skewed in this period of time.

³ A 9 percent discount rate is used to capitalize both series to the date of marketing.

III- SUMMARY AND CONCLUSIONS

The estimated mean return on pharmaceutical industry NCE introductions has been increasing over time, but has remained generally in line with the estimated (real) cost of capital. Furthermore, the distribution of present values for new drug introductions is highly skewed, with the top few deciles accounting for over 90 percent of the total present values.

HENRY G. GRABOWSKI

*Department of Economics
Duke University, Durham (N.C.)*

JOHN M. VERNON

*Department of Economics
Duke University, Durham (N.C.)*