ORIGINAL RESEARCH ARTICLE

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The Distribution of Sales Revenues from Pharmaceutical Innovation

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Abstract

Objective: This report updates our earlier work on the returns to pharmaceutical research and development (R&D) in the US (1980 to 1984), which showed that the returns distributions are highly skewed. It evaluates a more recent cohort of new drug introductions in the US (1988 to 1992) and examines how the returns distribution is emerging for drugs with life cycles concentrated in the 1990s versus the 1980s.

Design and setting: Methods were described in detail in our earlier reports. The current sample included 110 new drug entities (including 28 orphan drugs), and sales data were obtained for the period 1988 to 1998, which represented between 7 and 11 years of sales for the drugs included. 20 years was chosen as the expected market life for this cohort, and a 2-step procedure was used to project future sales for the drugs – during the period until patent expiry and then beyond patent expiry until the 20-year time-horizon was completed. Thus, the values in the first half of the life cycle are essentially based on realised sales, while those in the second half are projected using information on patent expiry and other inputs.

Main outcome measures and results: Peak annual sales for the top decile of drugs introduced between 1988 and 1992 in the US amounted to almost $US1.1 billion compared with peak sales of less than $US175 million (1992 values) for the mean compound. In particular, the top decile accounted for 56% of overall sales revenue. Although the sales distributions were skewed in both our earlier and current analysis, the top decile in the later time-period exhibited more rapid rates of growth after launch, a peak that was more than 50% greater in real terms than for the 1980 to 1984 cohort, and a faster rate of expected decline in sales after patent expiry. One factor contributing to the distribution of sales revenues becoming more skewed over time is the orphan drug phenomenon (i.e. most of the orphan drugs are concentrated at the bottom of the distribution).

Conclusion: The distribution of sales revenues for new drug compounds is highly skewed in nature. In this regard, the top decile of new drugs accounts for more than half of the total sales generated by the 1988 to 1992 cohort analysed. Furthermore, the distribution of sales revenues for this cohort is more skewed than that of the 1980 to 1984 cohort we analysed in previous research.

In this study, we examine the distribution of sales revenues for a comprehensive sample of new drugs introduced into the US during the period 1988 to 1992. In earlier research, we examined the returns to research and development (R&D) on US new drug introductions during the 1970s and early 1980s.[1,2] One of the key findings was that the top decile of new drugs accounted for a large share of the total market value generated by these entities. In this regard, the returns to R&D projects in pharmaceuticals have properties similar to those of venture capital investments. This has important implications for both private and public decision- makers.

A new analysis of this issue is warranted by a number of important changes on both the demand and supply sides of the market for new drugs. In particular, there has been significant new entry and industry restructuring since our last analysis of the returns to R&D. In addition, managed care has grown dramatically during the 1990s, and now accounts for a dominant proportion of drug prescriptions. These factors can significantly affect the life cycles of sales and the distribution of revenues across new drug introductions.

Background

The 1980 to 1984 Cohort of New Drug Introductions

In this section, we summarise some of the core findings from our previous work on pharmaceuticals and relate them to recent work on the returns for venture capital investment. Our last analysis focused on a comprehensive sample of 64 new chemical entities (NCEs) introduced into the US market between 1980 and 1984.[1] In this regard, figure 1 shows the sales profiles over the marketing life cycle for the top 2 deciles of NCEs (ranked by tenth-year US sales) and the mean and median compound. The figure indicates that there is a high degree of variability in the sales performance of NCEs. In particular, the peak annual US sales were more than $US700 million for the top decile compounds, approximately $US300 million for the second decile compounds, $US150 million for the mean compound, and only $US50 million for the median compound (1990 values). In our analysis, we also estimated the 'quasi-profits' for each entity – the surplus of global sales revenues over production and distribution costs – and discounted them to the date of market launch. The top decile, the most profitable 10% of the compounds, contributed 48% of the quasi-profits realised by the full sample of NCE introductions during this period. By contrast, the bottom half of the distribution (deciles 6 through 10, encompassing the entities with peak sales below $US50 million) accounted in total for only 8% of the quasi-profits.

Returns for Venture Capital Investments and Initial Public Offerings (IPOs)

Recent work by Scherer et al.[3,4] has shown that many other innovational activities are characterised by skewed outcome distributions. Of particular interest are 2 of their data samples involving a large number of investments by US venture capital firms in start-up companies between 1969 and 1988. The first sample was compiled by Venture Economics Incorporated and involved a portfolio of investments in 383 start-up companies made by 13 venture capital firms. The second sample involved a similar data set assembled by Horsley-Keough Associates of 670 distinct investments made by 16 venture capital companies.

Scherer's analysis indicates that investment returns from venture-financed start-ups are highly skewed. As shown in table I, a relatively small number of start-up firms generate a large share of the total investment value, as measured by the capital appreciation or loss at the time of investor exit from each investment. In the case of the Venture Economics sample, the most profitable decile of projects accounted for 62% of the total value generated by all 383 investments. For the Horsley-Keough sample, 59% of the overall value was attributed to the top decile of start-up company investments. This can be compared with our samples of 1980 to 1984 NCEs, where the top decile of NCEs accounted for 48% of the quasi-profits.

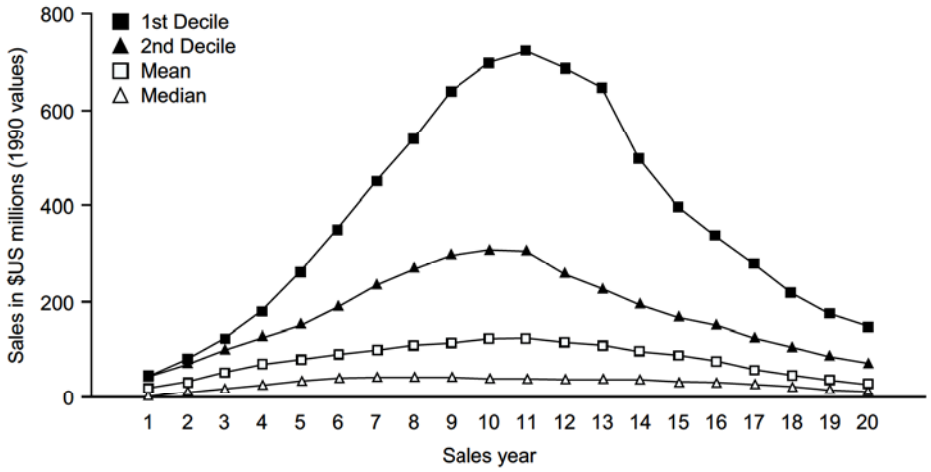

Fig. 1. US sales profiles for 1980 to 1984 new chemical entities.[1]

Scherer et al.[3] also examined the stock market performance of a comprehensive sample of 110 venture-funded high-technology companies that had their IPOs between 1983 and 1986. A decade later, he examined the returns from an equal dollar investment in each of these companies at the time of their IPO. An investment in a full bundle of these IPO companies would have slightly outperformed a comparable dollar investment in the NASDAQ index over the same period.[1] However, the market performance of these IPO firms also exhibited the same tendency toward extreme values as the samples involving venture-financed start-up investments discussed earlier in this section. As shown in table I, the 11 firms that constituted the most profitable decile of these IPO companies accounted for 62% of the overall market value in 1995. Correspondingly, the other 99 high-technology firms in this sample accounted for the remaining 38%.

Implications for R&D Investments

The data shown in table I indicate that R&D investments in pharmaceuticals have much in common with private investments by venture capital firms in start-up companies as well as public market investments in high-technology IPO companies. All of these innovative investment activities are characterised by a high degree of risk. This results from the fact that a few extreme values account for a large share of the cumulative realised returns. As Scherer and others have observed,[4] the law of large numbers doesn't work very well when the probability distribution of outcomes is highly skewed. One important consequence for pharmaceutical R&D is that considerable variability in portfolio outcomes can be expected, even for those pharmaceutical companies with large diversified portfolios of R&D pipeline drugs.

In the case of pharmaceuticals, the blockbuster compounds, which constitute the top decile of NCEs in figure 1, generally represent significant therapeutic advances in treating a particular dis-

Table I. Distribution of returns for selective innovative samples

Data set	Percent of value in top decile
Venture Economics (383 start-up investments) [Scherer et al.[3]]	62
Horsley-Keough (670 start-up investments) [Scherer et al.[3]]	59
Scherer et al.[3] (1983-1986 IPOs: market value in 1995)	62
Grabowski and Vernon[1] (1980-1984 NCEs)	48

IPOs = initial public offerings; **NCEs** = new chemical entities.

1 Returns were based on the market values of these companies approximately 1 decade later (December 31, 1995). This analysis takes account of the market values of the surviving IPO companies, those that merged with other firms, and those deleted because of bankruptcies and failure to meet NASDAQ financial criteria.

ease, usually one with significant market size. In most instances, these therapies are the first or second introductions in a new chemical class of compounds, and offer a novel approach to treating a particular disease.[5] The pharmaceutical industry has also been characterised historically by significant first-mover advantages.[6,7] Other things being equal, later market entrants tend to capture substantially lower market shares.

The most novel compounds face the greatest risks – from a scientific, regulatory and commercial perspective. In this regard, the therapeutic profiles of these compounds are the most difficult to predict on the basis of preclinical screens and leads. In addition, the long lag time and R&D activities of competitors magnify these scientific and technical risks. Accordingly, unforeseen clinical outcomes, the introduction of rival products and other changes in the market, and regulatory problems and lag times can dramatically affect a new drug's economic prospects during the development process.

These factors help to explain why so many of the compounds in figure 1 are marketed despite very small peak sales revenues and quasi-profits that are a small fraction of mean R&D costs.[2] If significant uncertainties surrounding a compound's economic prospects are not resolved until clinical development is largely complete, most of the R&D costs are then sunk. At this point, as long as a compound's expected revenues cover the incremental or variable costs on a prospective basis, it is rational to market or license out the compound, even if this doesn't cover any of the compound's large fixed R&D costs. Of course, in the long run, the firm also must have its share of winners for its R&D programme to be profitable and remain viable.

Recent Market Developments

The basic sample to be investigated comprises 110 new drug entities developed for the US market, approved by the FDA, and introduced into the US market between 1988 and 1992. This is a comprehensive sample of the new drug entities introduced into the US market during this period. In this paper, we focus on the US sales performance of these entities. In future papers, we will examine the returns on R&D of these entities and integrate global sales and costs into the analysis.

In our past work, we have found that differences in sales revenues constitute the major driving force underlying the skewed distribution of quasi-profits across NCEs.[1,2] An analysis of sales performance in the US is therefore interesting in its own right. In this regard, the US is also the largest market for pharmaceuticals, accounting for roughly half of the sales relating to new drug introductions studied in past samples. We also found that sales of these new drugs in other major markets (Europe and Japan) were significantly positively correlated with their US sales revenues.

Managed Care and Demand Side Changes

As noted in the introduction, the demand side of the market for new pharmaceuticals has been undergoing substantial change during the past decade. Pharmacy benefit management firms (PBMs) have emerged as the main overseers of the prescription drug plans of employers and managed-care institutions.[9,10] PBMs have implemented drug formularies to encourage more price competition and incentive programmes for generic drug usage when brand products come off patent. At the same time, managed-care institutions have broadened insurance coverage for prescription drugs, and unit sales have grown as drug therapies and compliance have been encouraged as a way of avoiding more expensive medical treatments.

2 We did not have R&D costs on an individual NCE basis. Another factor could be that R&D costs are also lower for drug entities with smaller sales and quasi-profits. While this may be the case, an analysis of R&D costs for a representative sample of NCEs at different stages of the R&D process by DiMasi et al.[8] indicated that there is much less variability in R&D costs than in revenues across NCEs. This is plausible, given the fact that all FDA approved drugs must meet stringent regulatory requirements. Approved drugs also share in common pre-project discovery costs and the costs of failures. These components account for more than 50% of the mean estimated R&D cost of $US202 million in the mid-1980s.

PBMs and health maintenance organisations (HMOs) can have differing effects on the sales revenue for a new drug introduction over the marketing life cycle. New drugs that represent novel therapeutic interventions for particular diseases and conditions have generally received broad coverage and speedy approvals for inclusion on drug formularies. However, as follow-on drugs are introduced into the same class, price discounting and competition usually occur in order to obtain formulary access. The growth of managed care has also been an important factor contributing to a more rapid erosion of sales when drugs come off patent. Therefore, as a new drug proceeds through its marketing life cycle, and as competition develops in a given therapeutic class, the influence of the PBMs of managed-care providers on sales revenues is subject to important shifts over time.

Biopharmaceuticals, Orphan Drugs and Supply Side Changes

There have also been important changes in the supply side of the market. In this regard, the number of new drug entities introduced onto the US market during the 1988 to 1992 period is significantly larger than during the earlier 1980 to 1984 period. This reflects some important industry developments. First, the current sample includes new biopharmaceutical entities as well as NCEs. The biotechnology industry was essentially in its infancy in the early 1980s. However, by the early 1990s, it had become a significant source of new therapeutic entities.

Another important event was the passage of the Orphan Drug Act by Congress in 1983. This provided incentives in the form of tax credits, market exclusivity, and regulatory assistance for the development of drugs targeted to diseases and conditions involving small patient populations.[11] In particular, a drug is eligible for orphan drug status under the law if it is approved for an indication involving a population of <200 000 patients. Roughly one-quarter of the drugs in our current sample were granted orphan drug status for at least one approved indication.

In our sample, there is also a high degree of overlap between the biopharmaceutical and orphan drug sets. This phenomenon has been discussed elsewhere and is the result of several factors.[11] First, many of the initial biotechnology drugs were recombinant versions of natural hormones with approved indications for small patient populations. In addition, many biopharmaceutical firms sought the market exclusivity protection of orphan drug status, given the initial uncertainties surrounding biopharmaceutical patents.

It is important to point out that there is wide variability in the sales revenues realised by orphan drugs in our sample. In particular, some of the novel biotechnology drugs granted orphan drug status were able to achieve blockbuster status by obtaining relatively large reimbursements per drug treatment. In addition, some of these drugs received orphan drug status for some indications as well as approval for other non-orphan indications. Conversely, many of the orphan drug approvals in the 1988 to 1992 period were for very rare conditions and, by historical standards, these drugs had very small sales (i.e. annual sales of only a few million dollars). Hence, the group of orphan drug compounds is very heterogeneous in nature.

Data Samples and Methodology

Annual drugstore and hospital sales in the US were obtained from IMS America for each of the 110 new drug entities in our sample. The sales data covered the period 1988 to 1998. This provided between 7 and 11 years of sales data for the drugs in our sample cohort, depending on a drug's year of introduction.

20 years was chosen as the expected market life for this cohort. We felt this was a reasonable value, since virtually all of the drugs in our sample had patent lifetimes of significantly less than 20 years, and products with substantial market sales would be expected to face strong generic competition and sales losses after patent expiry. While some products may have positive sales after year 20, these sales would be expected to be small and to have

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