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The Distribution of Sales Revenues from Pharmaceutical Innovation

Henry G. Grabowski and *John Vernon*

Department of Economics, Duke University, Durham, North Carolina, USA

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.

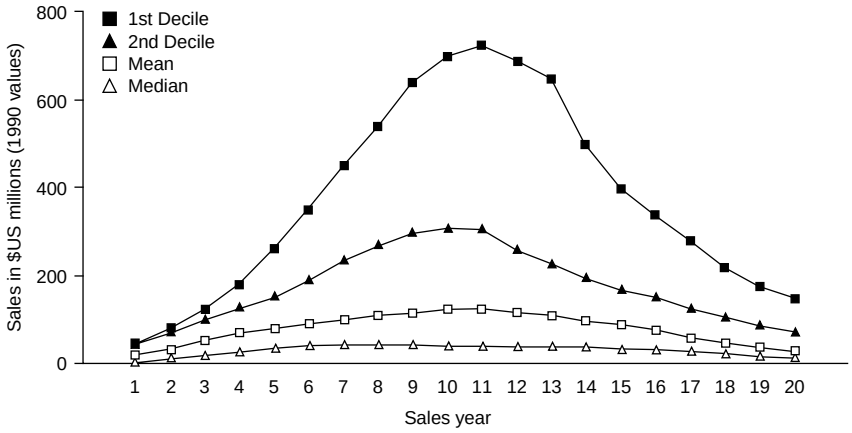

Fig. 1. US sales profiles for 1980 to 1984 new chemical entities.[1]

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

very low weights in any type of discounted present value analysis.

We used a 2-step procedure to project future sales values for the products in this sample. A key time-point in the life cycle of sales is the year of patent expiry. This is clustered between years 10 and 14 for the current sample. In our approach, the first step involved projection to the year of patent expiry and the second step projection of the post-patent expiry values.

To project sales to the point of patent expiry, we utilised an approach similar to our past analyses.[1,2] In particular, we constructed a reference life cycle curve based on the sales of products introduced in the mid-1980s (i.e. the new drug cohort immediately preceding the current one). We used this as the basic framework to project sales values for most of the NCEs. However, to take account of recent market and competitive developments affecting demand for the leading compounds and therapeutic groups, we also utilised the sales forecasts from a group of security analysts to make adjustments when there was a significant deviation from the reference case.

The estimated sales for the period after patent expiry were based on an analysis of generic competition in the mid-1990s.[12,13] When this analysis was used, the percentage decline in average sales during the first 2 years after patent expiry for products with annual sales of $US50 million or more at the time of patent expiry were computed to be 43 and 42%, respectively.[3] Thereafter, a 10% annual decline was utilised over the remaining years of market life. In our analysis of generic competition since the passage of the 1984 Waxman-Hatch Act, we have observed a strong trend over time toward an increased erosion of sales after patent expiry.[13] Since most of the products in our sample will experience patent expiry in the early part of this decade, the rates of erosion of sales after patent expiry for these drugs will tend to be understated if current trends persist into the future.

Empirical Results

Sales of Orphan versus Non-Orphan Drugs

The first issue we examined was the sales performance of the orphan versus non-orphan drugs in our sample. Figure 2 shows a plot of the life cycle of sales profiles for the mean compound in these 2 subsamples of drugs. As discussed in the previous section, Data Samples and Methodology, 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.[4]

The non-orphan drugs exhibit the general characteristics observed in prior work: rapid growth after launch, maturation about 10 to 11 years into the life cycle, and then a rapid decline in sales after patent expiry and generic entry. By contrast, the orphan compounds exhibit more moderate growth rates after launch, a much lower expected peak sales level, but also slower expected rates of declines in sales in the later stages of the life cycle. The last-mentioned phenomenon is due to longer average patent protection periods as well as less generic exposure for the orphan drug population, given their smaller average sales levels.

As discussed in the section entitled Biopharmaceuticals, Orphan Drugs and Supply Side Changes, there are different economic incentives in terms of the R&D and regulatory process for orphan drugs compared with non-orphan drugs. In future work, we plan to investigate their economic returns in a separate study. Nevertheless, the 28 orphan drugs in our current sample are very heterogeneous and include some of the leading biopharmaceutical products such as epoetin-α (erythropoietin) and

3 The probability of generic competition is low for drugs with annual sales at the time of patent expiry that are below $US50 million. Accordingly, we assumed no generic competition would occur in the case of these smaller selling drugs.

4 Since our sample involves a basket of new drugs introduced between 1988 and 1992, years 8 to 11 of the life cycle are a blend of actual and forecasted sales. For example, year 8 involves the first year of forecasted sales for the 1992 cohort and actual sales for the 1988 to 1991 cohorts. Similarly, year 11 involves actual sales for the 1988 cohort and projected sales for the other cohorts.

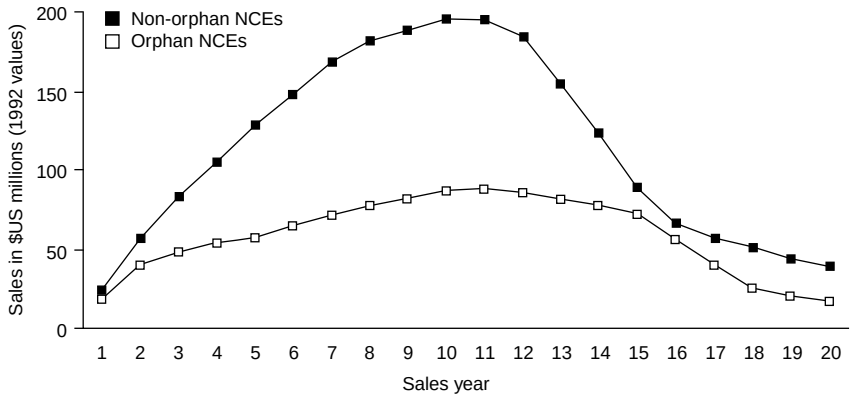

Fig. 2. Mean US sales for 1988 to 1992 new chemical entities (NCEs). Orphan versus non-orphan drugs.

human growth hormone. Because of this, we have chosen not only to retain these orphan drugs in our sample but also to analyse the distribution of sales with and without these drugs present. The results do not change in a qualitative manner.

Distribution of Sales for 1988 to 1992 Introductions

Figure 3 provides a plot of the expected sales profiles for the full sample of new drugs for the 1988 to 1992 period. This provides an exact counterpart of figure 1, and shows the life cycle of sales patterns for the top 2 deciles and the median and mean drug compounds. The main observed difference between figures 1 and 3 is associated with the top decile of drugs. In particular, the 'mountain' type profile of the top decile in figure 3 has grown taller and steeper compared with the other profiles displayed in these figures. In this respect, the top decile in the later time-period exhibits more rapid rates of growth after launch, a peak 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.

The definite impression from figure 3 is that the distribution of revenue has become more skewed over time. One factor contributing to this trend is the orphan drug phenomenon. Most of the orphan drugs are concentrated at the bottom of the distribution, with a few blockbuster drugs in the top decile. This tends to make the overall distribution more skewed. However, the basic findings are not altered in a qualitative manner when the orphan drugs are omitted from the sample.

The movement toward more skewness over time, as indicated in figure 3, was confirmed by a more detailed analysis that we performed. This is

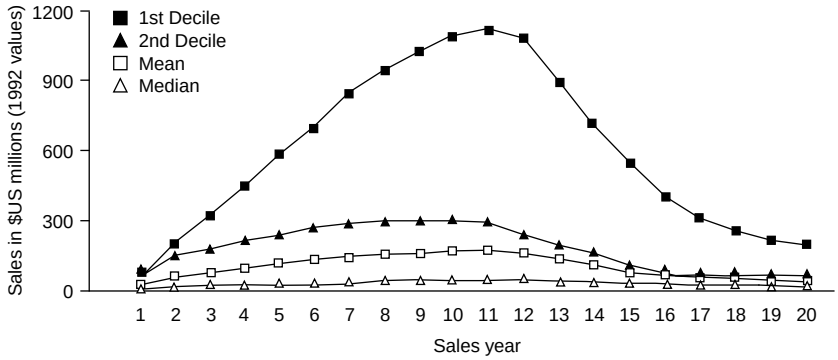

Fig. 3. US sales profiles of 1988 to 1992 new chemical entities.

presented in figure 4. In this figure, we plot the full distribution of sales by decile for the 1980 to 1984 and the 1988 to 1992 cohorts. Here sales data are based on the seventh year after launch, so that this analysis is based completely on actual sales values. In particular, the top decile of new drugs for the 1988 to 1992 period accounts for 56% of the overall sales revenue for the full sample of 110 drugs. If we omit the 28 orphan drugs, the top decile accounts for 52% of the sales revenue. By contrast, the top decile of NCEs for the 1980 to 1984 period accounted for 48% of overall sales (and the same percentage of quasi-profits).

The top decile in figures 3 and 4 is dominated by new drug introductions that are pioneers or early entrants in a new therapeutic class of compounds. In particular, this group includes the world's largest selling drug in 1998, Prilosec® (omeprazole), the first drug in the proton pump inhibitor class, which is used to treat ulcers. It also includes the first 2 selective serotonin re-uptake inhibitors, Prozac® (fluoxetine) and Zoloft® (sertraline), used to treat depression. Also in the top decile of drugs are the 2 largest selling biopharmaceutical therapies – Epogen® (epoetin-α), which is used for treating anaemia, and Neupogen® (filgrastim), which is used as an adjunctive chemotherapeutic agent. In addition, the top-selling decile includes the following: Taxol® (paclitaxel), the leading chemotherapeutic drug for ovarian cancer; Norvasc® (amlodipine), a new kind of calcium antagonist for treating hypertension; Biaxin® (clarithromycin) and Zithromax® (azithromycin), 2 semi-synthetic macrolide anti-infective agents; and Pravachol® (pravastatin) and Zocor® (simvastatin), 2 leading statin drugs for cholesterol reduction.

Changes in Mean Sales over Time

In the case of skewed distributions, the revenue performance of the mean compound is disproportionately affected by the realised values in the upper tail of the distribution. Accordingly, we would expect the mean sales to be significantly greater in the 1988 to 1992 cohort, compared with the earlier 1980 to 1984 cohort. In order to see how sales of the mean compound have changed over time, we plot the mean curves for the 2 time cohorts on a separate graph in figure 5. This graph is based on the entire sample of 1988 to 1992 drugs, including the orphan compounds. The case with the orphan drugs excluded is shown in figure 6.

In both cases, there is a significant upward shift in the mean sales curves through the period of product maturity. However, the faster rate of generic competition expected for the later time cohorts causes a projected convergence of the 2 curves after year 15 of the life cycle. Nevertheless, the expected present value of sales revenues will be higher for the more recent time cohort, given the

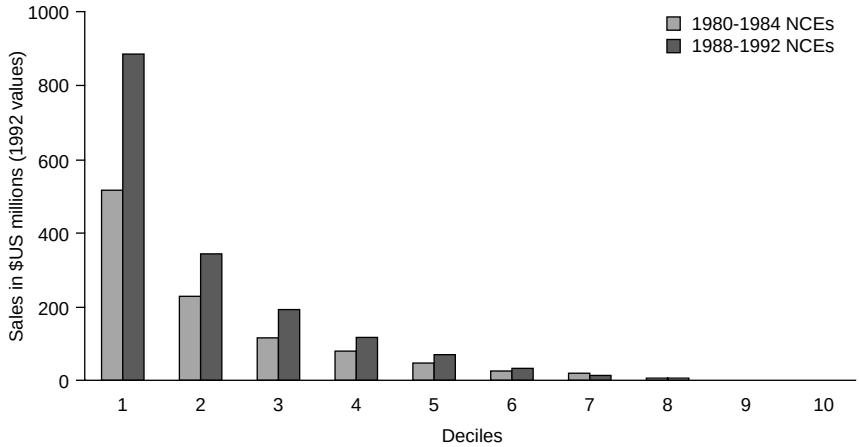

Fig. 4. Distribution of US sales by decile. Data reflect actual sales in the seventh year after marketing. **NCEs** = new chemical entities.

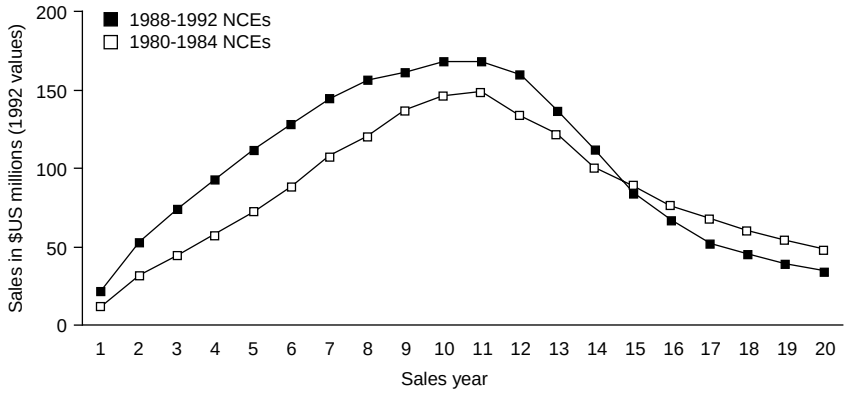

Fig. 5. Comparison of mean US sales for the different new chemical entity (NCE) cohorts, with orphan drugs included in the 1988 to1992 cohort.

positive differences in the earlier years of the life cycle. As noted, this is driven in large part by the sales performance of the top decile products.

Sales of New Drug Introductions versus R&D Outlays by Company

As discussed earlier, one important consequence of a skewed distribution is that even firms with sizeable portfolios of R&D projects can expect considerable variability in portfolio outcomes. In order to gain some further insights into this issue, we aggregated each company's sales (in the seventh year of market life) for all of its new drug introductions during the 1988 to 1992 period. We then plotted these portfolio outcomes against the company's pharmaceutical R&D expenditures in the 1983 to 1985 period. We utilised an average lag time of 6 years between R&D expenditures and new drug introductions to reflect the long gestation period in pharmaceutical R&D.[8]

Figure 7 shows the resulting plot of new drug sales versus R&D expenditures for a total of 18 firms for which R&D expenditure data were available. There is a considerable range in the size of these firms, but all can be characterised as multinational companies that are also vertically integrated across all types of pharmaceutical activities (i.e. R&D, manufacturing and marketing). The annual R&D expenditures of these 18 firms in the mid-1980s was between $US100 million and $US500 million (measured in 1992 dollars).

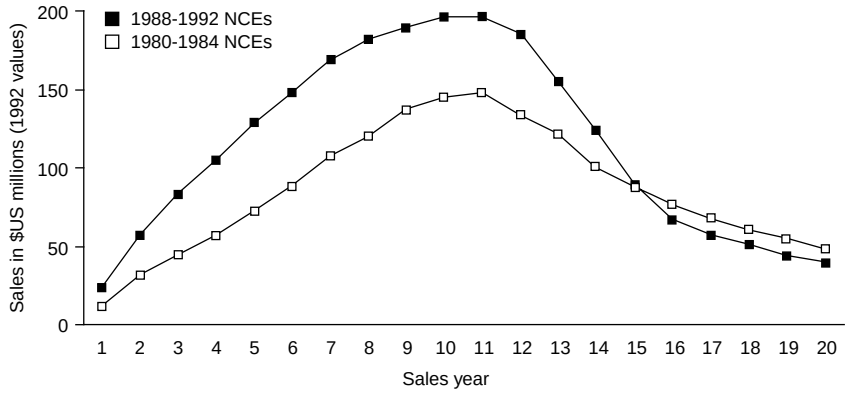

Fig. 6. Comparison of mean US sales for the different new chemical entity (NCE) cohorts, with orphan drugs excluded in the 1988 to 1992 cohort.

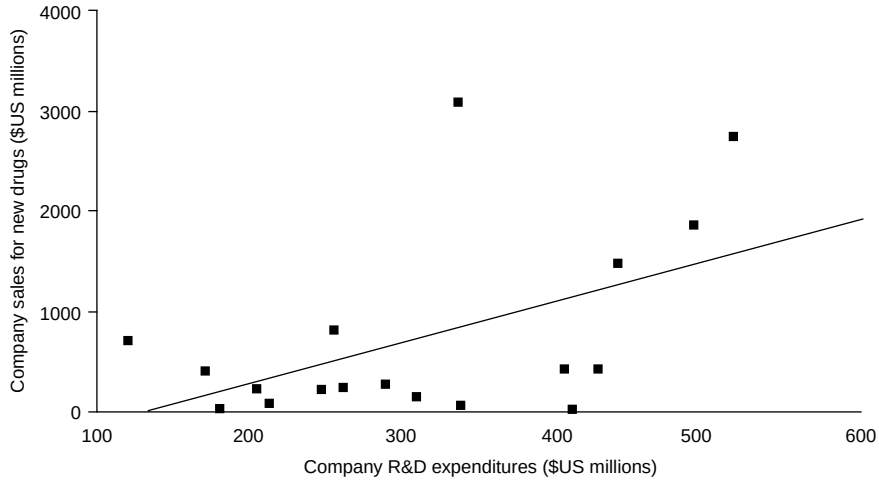

Fig. 7. Sales for 1988 to 1992 new drug introductions (data from the seventh year post-launch) plotted against 1983 to 1985 mean research and development (R&D) expenditures for 18 multinational pharmaceutical companies. Both sales revenue and R&D outlays are expressed in 1992 dollars.

Figure 7 shows that there is a positive relationship between a company's R&D expenditures and its subsequent sales from new drug introductions.[5] However, there is also much variation in the scatter of points around the best fitted least-squares regression line, as shown in figure 7. This is especially true for the group of large firms with R&D outlays between $US300 and $US500 million. The total seventh-year sales for the new drugs portfolios of these 9 firms range from <$US100 million to more than $US3 billion.[6]

In previous work, we examined the temporal pattern of new drug sales outcomes across firms.[14] One of the main findings was that there was a high degree of variability from one period to the next in the performance of new drug sales for individual firms. This result is also consistent with the skewed distribution that we have observed for new drug introduction samples dating back to the early 1970s.

Comparison with Global NCE Introductions

In a recent analysis, William Machtiger of IMS International examined the 1997 worldwide sales levels of 315 drugs that were first introduced onto the worldwide market over the period 1986 to 1992.[15] This provides an interesting benchmark to compare with our sample of US drugs. One would expect a global sample of NCE introductions to exhibit more skewness than a US based sample because many of these global introductions are 'localised' NCEs. In particular, many of these NCEs are introduced in only a few countries with much smaller markets than the US. By contrast, US NCE introductions tend to include a greater percentage of international or 'consensus' NCEs.[16]

In fact, the global sample does exhibit more skewness. In this regard, the drugs were grouped according to their worldwide sales levels. The top group comprised new drug introductions achieving

5 An alternative lag structure of 5 years yielded similar results.

6 We did not include the biotechnology firms in figure 7, because annual R&D expenditures were not available for these firms for the 1983 to 1985 period. However, we do know that these firms were in their formative period and had annual R&D expenditures below $US100 million. Inclusion of these biotechnology firms would have produced much more scatter than shown in figure 7, because most of the biotechnology firms had very small sales from new drug introductions; however, one firm in particular (Amgen) had annual sales in excess of $US1.5 billion in the seventh year of market life from its 2 blockbuster products introduced in the 1988 to 1992 period.

worldwide sales of $US500 million in 1997. Approximately 10% of the 315 global introductions were in this category. This top decile accounted for 66% of the $US60 billion in total sales achieved by this group of 315 drug introductions. At the other end of the distribution were products that achieved <$US50 million in worldwide sales. These products accounted for 57% of the introductions but only 4% of the total sales in 1997. This is a significantly greater degree of skewness than that observed for our sample of US introductions (fig. 4).

Discussion and Conclusions

The analysis presented in this paper indicates that 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 in this paper. Furthermore, the distribution of sales revenues for this cohort is more skewed than for the 1980 to 1984 cohort that we analysed in previous research.[1] This increased skewness can be explained in part by the emergence during the past decade and a half of orphan drug compounds as a result of the incentives provided by the 1983 Orphan Drug Act. However, even when the orphan drug compounds are omitted from the current sample, some tendency toward greater skewness is still observed.

One important implication of this distribution observed in pharmaceuticals is that even very large firms with sizeable portfolios of R&D projects are subject to substantial volatility in the sales performance of their new drug introductions. In this regard, we found that firms spending between $US300 and $US500 million for R&D in the mid-1980s (measured in 1992 dollars) had aggregate sales from their new product introductions in the 1988 to 1992 period ranging from $US100 million to $US3 billion in the seventh year of market life. Moreover, as one would expect in this situation, there is a high degree of volatility across companies in the historical sales performance of new drug cohorts from different time-periods.

Because pharmaceutical firms and venture capital firms confront outcome distributions with similar properties, they face similar strategic issues in managing the extreme risks and rewards that characterise their investment activities. In particular, timing and adaptability are critical elements for both entities. On the one hand, it is important to recognise and accelerate the development of potential winners to get them to the market as quickly as possible. At the same time, it is important to terminate and cut one's losses on unsuccessful projects before large development costs become totally sunk costs. This is a difficult balancing act that is subject to alternative types of errors. Venture capital firms employ external financial controls, including staged finance and milestones as risk-hedging strategies in this regard.[17,18] Pharmaceutical firms employ internal controls that embody some of these same principles.

During recent years, pharmaceutical firms have placed increased emphasis on reducing the development time to market by use of various strategies, including parallel path development of activities that are along the critical path. In addition, firms are incorporating competitive and pharmacoeconomic analysis earlier in the development life cycle, well prior to the go-no-go decision for phase III development. In this regard, many drug firms traditionally placed primary control of their R&D decisions in the hands of scientific and technical personnel until clinical tests were nearly completed. However, DiMasi[19] has recently shown that the main reason new drugs are abandoned in phase III is not concern for safety or efficacy, but for economic reasons. Hence, prioritisation of R&D projects, using economic modelling as well as technical milestones, can increase the probability of economic success and reduce the likelihood of expensive late-stage failures.[20] Many firms appear to be moving in this direction.

From a public decision-making perspective, the winners among new drug introductions with blockbuster sales make a tempting target for price controls and profit constraints. However, as we have shown in prior analyses, expected returns are

highly sensitive to the performance of these top decile drugs.[21] Imposing controls on today's drug winners will have adverse effects for future R&D investments, especially for the very risky projects that involve the most novel approaches to therapeutic advancement.

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Correspondence and offprints: Prof. *Henry G. Grabowski*, Department of Economics, 314 Social Sciences, Box 90097 Duke University, Durham, NC 27708, USA.