CONSOLIDATION AND COMPETITION IN THE PHARMACEUTICAL INDUSTRY

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Chapter 5
Pressures from the Demand Side: Changing Market Dynamics and Industrial Structures

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This paper has three parts. First it recaps the work from a 1994 study that looked at the overall profitability of a sample of products that came to the US and global market place in the early 1980s (Grabowski and Vernon, 1994a). Second, it presents research in progress on the next cohort of drugs which entered the US and global market place in the early 1990s. Finally, it draws out some implications for industry structure.

To give some context for the new study, we first consider some information and findings from our 1994 paper. It focused on a sample of 64 new chemical entities (NCEs) that were introduced between 1980 and 1984 in the US market place. It used sales data for each NCE (obtained from IMS) to estimate the sales profiles. In a second stage, we compared the present value of net revenues with the cost of bringing those products to market using R&D cost estimates from a study by DiMasi et al. (1991). Figure 5.1 shows the worldwide sales profiles for that cohort of 64 NCEs. These are the lifetime sales of products that were introduced in the US market place in the five-year period between 1980 and 1984, expressed in 1990 US dollars. The first decile, the top 10 percent of products ranked in terms of tenth-year sales, obtained at their peak about $1.5 billion in annual sales. The second decile had peak sales of a little over $600 million per annum. The mean peak was around $200 million per annum sales, and the median peak for these products was somewhere below $100 million.

The difference in overall economic performance of the 64 products is highlighted further in Figure 5.2, which compares the after-tax net present value (NPV) for each of the 10 deciles with average R&D costs per introduction. This after-tax NPV is calculated as sales revenue minus production and distribution costs, discounted to the point of launch. This is compared with average R&D costs per product, which are compounded to the year of launch. Average after-tax R&D cost per
Figure 5.1  Worldwide sales profiles of 1980-1984 NCEs

NCE launched for this period, derived from the DiMasi study, is just over $200 million.

The distribution of NPVs is highly skewed. In this regard, the top decile accounts for 48 percent of the overall NPV generated by all of the products. That is, the top 10 percent account for nearly half of all the effective profit generated by these 64 products introduced in the US marketplace during the 1980-84 period.

Although it is not clear from Figure 5.2, the mean product does have a positive overall NPV. That is, its sales less production and distribution costs have a present value that exceeds average R&D costs (Grabowski and Vernon, 1994a). However, the median product does not. The median (32nd-ranked) product has a NPV that is roughly half the compounded value of average R&D costs for this period. The NCEs in deciles 4 to 10 have present values that are generally far less than average R&D costs.
A key question is why did companies bring to market the 70 percent of products that have not covered average R&D costs? We considered two possibilities. One is that these products had lower than average R&D costs. One might expect the big products to be breakthrough products and, by definition, they may require greater research effort, have higher failure rates in development, and so on. In a separate piece of work, DiMasi et al. (1995b) examined differential R&D costs across therapy areas and by types of compound. This study of R&D costs found significant variability but nothing like the variability that is seen across the distribution of NPVs in Figure 5.2. In this respect, all US new product approvals share common discovery costs and have to satisfy similarly stringent FDA regulatory criteria.

We found, when we were looking at the effective patent life of this group of 64 products, that the most successful products tended to have a longer effective patent life (the time from market launch to the
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point of patent expiration). This suggests that companies, to the extent they were able, were fast-tracking the products that they thought were most likely to be commercially successful. One of the ways in which they may fast-track is by spending more money through parallel R&D and related activities. It may be that the more lucrative products do cost more to bring to market. On the other hand, one of the most important elements of R&D costs is time cost. If companies are getting the product to market more quickly, then they are saving the opportunity costs of capital tied up in the innovation process. How these offsetting factors balance out is unclear. This is an issue that we plan to consider in future research.

The second explanation that we explored is that companies often cannot predict how successful a product is going to be until quite late in the process. This is due to unexpected clinical outcomes, regulatory lags, competitive developments of rival products, imperfect marketing forecasts and so forth. The R&D process in pharmaceuticals can be viewed as a sequential decision-making process under uncertainty. At each stage of the process, companies are in effect weighing the extra costs of going to the next stage against the expected revenues. The most likely explanation for bringing small revenue products to market is that, at the margin, by the time companies realize that these products are not going to be large sellers, the costs of carrying on and launching them are often relatively low compared to the money that has already been sunk. Therefore it is worth getting those incremental revenues since they still make a positive contribution to the bottom line.

An interesting point of this NPV analysis is how the degree of skewness in rates of return to NCEs compares with what occurs in venture capital environments. To gain insights on this point, we compared the returns of the top 10 percent of pharmaceutical projects in this study with those from three venture capital studies analysed by Scherer et al. (2000). See Table 5.1.

9 Firms are making stronger efforts to integrate economic modelling into the R&D process to avoid very expensive late-stage failures. See Grabowski (1997) on this issue.
Table 5.1  **Total value realized by the top 10% of innovations for select samples**

<table>
<thead>
<tr>
<th>Data set</th>
<th>Percent of value in top decile</th>
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<tbody>
<tr>
<td>Venture Economics start-ups*</td>
<td>62</td>
</tr>
<tr>
<td>Horsley-Kéough start-ups*</td>
<td>59</td>
</tr>
<tr>
<td>1980s IPOs – 1995 value*</td>
<td>62</td>
</tr>
<tr>
<td>1980-1984 NCEs**</td>
<td>48</td>
</tr>
</tbody>
</table>

*Note: IPO = Initial public offering of shares.
Source: *Scherer et al. (2000)
**Grabowski and Vernon (1994a).

The first two studies in the table looked at venture capital start-ups over a 20-year period. The first one, from Venture Economics, is based on 383 start-up projects commissioned by 13 venture capital companies. The top decile of products in this study account for 62 percent of the total value earned by all of the venture start-ups in the sample. The second study, the Horsley-Kéough start-ups, involved an even larger group of 670 investments by 16 venture capital firms. Again looking at the returns, as measured by capital appreciation or loss at the point at which the venture capital exited, 59 percent of the overall returns from those projects came from the top decile.

The next study shown in Table 5.1 examined 131 high tech initial public offerings (IPOs) taking place in the mid-1980s and at their value 10 years later. In particular, it examined the returns after 10 years from a portfolio that involved an equal dollar investment in each of these IPOs. Scherer et al. found that 62 percent of the appreciation in the overall market value came from the most successful 10 percent of those high tech projects. The other 90 percent of these IPOs contributed only 38 percent of the overall increase in value. Furthermore, several of these IPOs dropped off the NASDAQ or exhibited long-term losses in market value.

Skewed outcome distributions imply high risks for both venture capital and pharmaceutical firm investments. In particular, as Scherer
(1999) and others have observed, the law of large numbers does not work very well in these circumstances. In other areas, if we invest in a large diversified portfolio of projects then, by and large, we expect that returns can be predicted with some confidence. When returns are highly skewed, considerable volatility in outcomes remains even if companies are investing in large numbers of projects as individual companies.

Overall a key implication of our 1994 work is that the returns of research-intensive firms are positive but are highly dependent on a few new blockbuster products. A related conclusion is that it is unwise to focus public policy attention simply on the products that were successful without a clear understanding that underneath there were many products that were making very poor returns or that never got to the market.

Given significant changes in the demand and supply sides of the pharmaceutical industry, we decided to repeat our original study with more up-to-date data. On the demand side, particularly in the US market place, we have seen a dramatic rise of managed care. One important effect has been a significant increase in the extent of insurance coverage for prescription drugs. This has been driven in part by a desire to substitute drugs for more costly medical interventions. Increased coverage for pharmaceuticals has been one of the main factors linked to the increased per capita expenditures on pharmaceuticals in the US in the 1990s (Berndt, 2000; Danzon and Pauly, 2000).

At the same time, the growth of managed care is still evolving and producing offsetting effects on pharmaceuticals. Health maintenance organizations (HMOs) and employers have widely subcontracted the management of their pharmacy benefit to management firms (PBMs). These specialty firms have instituted a variety of programs to reduce drug costs (Grabowski and Mullins, 1997; Schulman et al., 1998). In particular, where there were competing manufacturers in the same therapy area, PBMs have used formularies, multiple-tier co-payments and other mechanisms to try to obtain price discounts from drug companies. PBMs have also instituted strong incentives to encourage increased generic utilization. The degree of generic drug usage has grown significantly during the 1990s. This is a main factor
underlying faster sales erosion after patent expiration in the US market place.

Outside the US, cost containment measures have become more stringent over time (Danzon, 1997). Reference price reimbursement systems have evolved in Denmark, Germany, the Netherlands and New Zealand. In addition, controls on volumes and total expenditures have been superimposed on traditional price and reimbursement controls. In this regard, France has introduced manufacturer-specific budgets, while physician drug budgets have been utilized in Germany and the UK. Furthermore, patient co-payments have been on the rise in many leading European countries.

On the supply side, two critical things have happened. First, molecular biology and the emerging biotech industry have become an important source of new drug entities. By 1992, there were more than 200 biotechnology firms whose primary business involved the development of new pharmaceuticals. They had aggregate R&D expenditures in that year of over $2 billion (Dibner, 1993). The vast majority of the biopharmaceuticals approved before 1993 originated in dedicated biotechnology firms, but many of these products were developed and marketed in collaboration with an established pharmaceutical firm (Grabowski and Vernon, 1994b). In an earlier chapter in this volume, Kettler documents the growing interdependencies that have occurred over time between the pharmaceutical and the biotech industries.

The second supply change in the US, that is also linked to the rise of the biotech industry in part, is the 1983 US Orphan Drug Act (Schulman et al., 1992). It was designed to give incentives to manufacturers to produce products for markets where the patient population is small, less than 200,000 in the case of the US policy. In normal circumstances, a company would not expect a commercial return from such a small patient group, and therefore might not develop the product. Under the Act, however, in exchange for bringing an orphan drug to market, companies earn tax credits and grants on R&D, a seven-year period of market exclusivity from the time of launch and, thirdly, expedited regulatory approval so that they can get an orphan drug to the market more quickly.
Our sample of products from the 1988-1992 period is much larger than the earlier one (110 versus 64), reflecting the increased number of products coming onto the US market in the 1980s and 1990s. This increase reflects in part the growth of biotech and impact of the orphan drug legislation. A quarter of the sample is products classified as orphan drugs for at least one indication. There is also a close overall relationship between orphan drugs and biotech drugs during this period. This reflects the fact that many initial biotech drugs were recombinant versions of natural hormones that were already in the market place with approved indications for small patient populations. Orphan drugs status was also sought because there was uncertainty about patent rights in some areas of biotech and it was a way of obtaining market exclusivity for particular indications.

Rather than deal with orphan drugs separately, we include them in the current analysis. Hence, we have a comprehensive universe of new drug introductions in the 1988–92 period. The US sales profiles of orphan drug products have been examined in another paper (Grabowski and Vernon, 2000). Sales of orphan drugs are also very skewed. In the top decile of products, there are two biotech products, Epogen and Neupogen, that are among the top best-selling products in the overall sample, alongside several other products that were genuine orphan products with extremely small sales.

Figure 5.3 shows the worldwide sales profiles for the 110 NCEs launched between 1988 and 1992, based on IMS sales data extending through to 1999. There were up to 12 years of actual sales data for individual NCEs. In most cases drugs’ patents expire between 10 and 14 years after launch. Sales data were extrapolated to the point of patent expiration by a combination of two methods: first, by using

10 In some cases these products were very successful outside that indication and so were not orphans in the sense that they did not earn much money but were classified as orphan drugs under the terms of the Act. Neupogen is an example of this type of situation.

11 IMS data were obtained on US sales for all 110 NCEs and on worldwide sales for the 40 top-ranked drugs that accounted for over 90 percent of US sales from these NCEs. The latter sub-sample was utilized to construct foreign sales multipliers to estimate worldwide sales from US sales where worldwide sales data were unavailable.
Figure 5.3 Worldwide sales profiles of 1988-1992 NCEs

a reference life cycle sales curve based on new drug product introductions in the mid-1980s (the immediately prior drug cohort); second, by incorporating securities analysts’ sales forecasts for leading compounds and therapeutic classes to take account of recent market developments. The post-patent expiry decline in sales was based primarily on an analysis of US products experiencing initial generic competition during the 1990s (Grabowski and Vernon, 1996; 2000).

Figure 5.3 confirms that blockbuster compounds remain critical to the success of research-intensive firms. The top decile of NCEs for the 1988-1992 period has a sales peak of $3.2 billion (in 1999 dollars). This is roughly a doubling in real terms of the sales peak for 1980-1984 NCEs (Figure 5.1). Furthermore, the top decile has experienced a significantly higher growth rate over the earlier period than the second decile. Hence, it appears from Figure 5.3 that the distribution of sales has become more skewed over time. This issue is examined further below.

The top decile compounds are listed in Table 5.2. The group is
Table 5.2  Top decile compounds from the 1988-1992 sample

<table>
<thead>
<tr>
<th>Prilosec</th>
<th>Zocor</th>
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<tr>
<td>Prozac</td>
<td>Pravachol</td>
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<tr>
<td>Zoloft</td>
<td>Zithromax</td>
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<tr>
<td>Epoogen</td>
<td>Biaxin</td>
</tr>
<tr>
<td>Neupogen</td>
<td>Prinivil/Zestril</td>
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<tr>
<td>Norvasc</td>
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comprised primarily of new drug introductions that are pioneers or early entrants in a new therapeutic class. The largest-selling drug in the top decile, Prilosec, was the first proton pump inhibitor for the treatment of ulcers. It was the world’s largest selling drug in 1999. Neupogen and Epoogen, the two top-selling biotech products, from Amgen, also made the top decile and hence contribute to the skewness in the sub-analysis of biotech and orphan drug products. Also, interestingly, there are some cases of pairs of products being from the same therapeutic classes. Among the SSRIs, Prozac and Zoloft are both in the top decile as are the two leading statins, Zocor and Pravachol. Similarly, Zithromax and Biaxin are the initial entrants and leading products in the macrolide anti-infectives class. Other top-decile compounds include Prinivil/Zestril, the leading ACE-inhibitor for hypertension, and Norvasc, a new type of calcium antagonist for treating hypertension.

Figure 5.4 compares the mean worldwide sales curves for our current cohort of 1988-1992 NCEs with the earlier one for 1980-1984. The newer products produce the top, steeper curve. We can see that the more recent generation of products takes off more quickly and achieves higher peak sales. They are also projected to have a more rapid decline from this peak. This is associated primarily with increased price and generic competition after patent expiration compared to the earlier period.

The degree of skewness also has increased for the new cohort compared to the earlier one. In Figure 5.5, we compare worldwide sales by decile for the 1980-1984 and 1988-1992 cohorts. The sales data are based on the tenth year after launch. The biggest upward shift over time occurs in the top decile. In particular the top decile
Figure 5.4  **Comparison of the mean worldwide sales for two NCE cohorts**

![Graph showing comparison of mean worldwide sales for two NCE cohorts](image)

for the new cohort accounts for 64 percent of total worldwide sales versus 51 percent in the earlier sample. If we omit the 28 orphan drugs, the top decile in 1988-92 accounts for 59 percent of worldwide tenth-year sales, so the orphan drug sample is even more skewed than the full sample of 110 drugs.

The overall conclusions from this stage of the analysis are that sales of the later cohort of 1988-1992 products, achieves higher peak sales, achieves greater sales overall, and exhibits more skewedness than the earlier sample. Given this high degree of skewedness, it is interesting to consider what relationship exists between how much a company spends on R&D and its subsequent sales from its new products. To gain insights

12 As pointed out in Table 5.1, the top decile for 1980-1984 NCEs accounted for 48 percent of the net present value (sales minus distribution and production costs) generated by the full sample. In future work, we plan to do a similar analysis of NPVs for the 1988-1992 cohort and compare the NPVs in each decile to R&D costs.
Figure 5.5  **Comparison of worldwide sales for two cohorts of NCEs by decile**

![Chart showing comparison of worldwide sales for two cohorts of NCEs by decile.](chart.png)

*Note: Data are based on sales in tenth year after marketing.*

into this question, we have plotted worldwide sales for new drugs for the 1988-1992 time period against the R&D expenditure for 18 traditional pharmaceutical companies from the 1983-1987 time period. This effectively assumes an average lag of five years between R&D expenditures and new product sales.\(^{13}\) We excluded biotech firms from this analysis because R&D data were unavailable for many of these firms, and most biotech products were still in the R&D pipeline in 1992.

The best-fitting regression line in Figure 5.6 indicates that there is a positive relationship between company R&D expenditures and sales from new products. There also appears to be a threshold-type relationship. Most of the small and mid-tier drug firms have sales

\(^{13}\) The full gestation period for a new drug introduction in this period is generally 10 years or more, so we took the midpoint of a 10-year stream of R&D expenditures, or five years, in the lagged relationship shown in Figure 5.6. The results are not sensitive to alternative lag structures around this value.
Figure 5.6  Worldwide sales plotted against R&D expenditures (in millions of 1992 dollars)

Note: Company sales are for the tenth year of market life. They are the sum of all NCEs introduced by a firm in the 1988-1992 period. R&D outlays are lagged by five years, so that they correspond to products coming on to the market between 1988-1992.
well below the fitted curve. These firms have few blockbuster products. The larger R&D companies in the $400 million to $600 million range of R&D expenditure range during this period account for most of the blockbusters. However, there is also a great deal of variation across these larger R&D firms. The tenth year's sales of their NCEs vary from practically zero to over $9 billion. This reconfirms the point made earlier about the law of large numbers; even firms with large portfolios of R&D products are subject to substantial volatility in their new product sales.

This paper has focused on the worldwide sales performance of NCEs introduced between 1988-1992. In future work, we will integrate analysis of R&D costs and compare them with the present values of net revenues as in our earlier work. The R&D data will come from a new R&D cost study by DiMasi et al. now in progress. While the new DiMasi R&D cost study is not yet completed, there is evidence from various sources that suggests that R&D costs have increased significantly since our earlier study. In this regard, Kettler (1999) has examined specific data trends for the various components of R&D costs and concluded that, on balance, R&D costs have increased significantly over time.

Rising real costs for R&D are consistent with some of the macro trends from industry data shown in Figure 5.7 for the period 1970-1999. Both R&D spending and NCE approvals have an upward trend, but the R&D spending line has been rising much more steeply. R&D expenditures have increased at a rate of more than 10 percent per annum over this period, while new drug introductions have grown from an average of 13.7 NCEs in the 1970s to 18.5 in the 1980s and to 27.4 in the 1990s (DiMasi, 2001). Hence, NCE outputs have doubled during this period while real R&D expenditures have increased six-fold (see Figure 5.7). Even allowing for qualifications.

14 As discussed, Amgen introduced two of the blockbuster products in this period. The biotech firms were excluded because R&D expenditures generally were not available for 1983 to 1987, and many biotech firms were private firms without Securities and Exchange Commission reporting requirements. Had they been included, however, this would presumably have increased the dispersion in the less than $300 million R&D segment, given the high degree of skewness exhibited for the biotech products in our sample.
Figure 5.7 Pharmaceutical industry inflation-adjusted R&D expenditures and NCE approvals, 1970-1999

Source: PhRMA; Tufts University CSDD.
such as lags and sample composition issues, these industry trends suggest that the R&D costs of bringing an NCE to market have been rising significantly in real terms throughout this period. The forthcoming DiMasi study will provide a detailed microeconomic analysis of R&D costs encompassing the relevant period for our new sample of NCE introductions.

In conclusion, it is appropriate, given the objectives of this volume, for us to consider some implications for industry structure. Over the past two decades, the pharmaceutical industry has been characterized by contrasting structural changes. First, there have been many significant horizontal mergers and increased consolidation among established pharmaceutical firms (Grabowski and Vernon, 1994b). Second, there has been significant entry into the industry by hundreds of newly established biotech firms, especially at the research end of the spectrum. Third, there have been increasing collaborations and interdependencies between these emerging biotech firms and established big pharmaceutical firms.

The economic characteristics of the innovation process have been an important factor shaping these changes in drug industry structure. Our analysis indicates that R&D costs and revenues have increased significantly in real terms, while the distribution of sales revenues has remained highly skewed. We also found that the innovative output of the small- and middle-tier pharmaceutical firms was relatively weak for the NCEs analyzed in our sample, suggesting that many of these firms were either unable or unwilling to assume the increasing risks associated with the pharmaceutical innovation process. Several of these mid-tier firms have now merged into larger entities. The R&D productivity of these firms in the post-merger period remains an interesting issue for further research.

15 For a discussion of these issues see Section 8 of DiMasi et al. (1991) which utilized aggregate data as a check on their micro analysis.
16 In a prior study that we performed with DiMasi, we also found lower R&D productivity for small- to mid-tier firms (DiMasi, Grabowski and Vernon, 1995). That study focused on NCE introductions in the 1980s by the group of 12 firms participating in the original R&D cost study. See also Henderson and Cockburn (1996) on this issue.
In the skewed outcome world, collaborations between big pharmaceutical companies and small biotech firms provide important potential benefits to both sides. They enable the big pharmaceutical companies to leverage their internal R&D and obtain more options for new products. At the same time, they enable the smaller biotech firms to get risk-sharing benefits and gain credibility for their technology. Thus the evidence of skewed returns reinforces points made by other contributors to this book about the nature and importance of the relationship between big pharma and the emerging new players in the biotech sector. Quantifying the economic benefits of these collaborations is another important topic for further research.

REFERENCES


