R&D Costs, Innovative Output and Firm Size in the Pharmaceutical Industry

JOSEPH A. DIMASI, HENRY G. GRABOWSKI and JOHN VERNON

ABSTRACT This study examines the relationships between firm size, R&D costs and output in the pharmaceutical industry. Project-level data from a survey of 12 US-owned pharmaceutical firms on drug development costs, development phase lengths and failure rates are used to determine estimates of the R&D cost of new drug development by firm size. Firms in the sample are grouped into three size categories, according to their pharmaceutical sales at the beginning of the study period. The R&D cost per new drug approved in the US is shown to decrease with firm size, while sales per new drug approved are shown to increase markedly with firm size. Sales distributions are highly skewed and suggest that firms need to search for blockbuster drugs with above-average returns. The results are consistent with substantial economies of scale in pharmaceutical R&D, particularly at the discovery and preclinical development phases.

Keywords: economies of scale; pharmaceutical R&D cost; sales-weighted output.
JEL classifications: L65, 032.

1. Introduction

The questions of whether or not scale economies exist in pharmaceutical R&D and whether or not new drug development is carried out more productively in larger firms have been addressed in a number of published studies (Comanor, 1965; Angilley, 1973; Vernon and Gusen, 1974; Schwartzman, 1976; Jensen, 1987; and Graves and Langowitz, 1993). Each of these studies applied regression models to aggregate pharmaceutical firm data and focused on the relationship between a firm’s new drug output (weighted in some way by sales or a measure of medical importance) and some measure of its R&D input (typically, total R&D expenditures or total R&D employees). However, the conclusions drawn in these studies vary widely.

One of the fundamental problems that has beset industrial organization studies
of R&D scale economies in this and other industries is the highly aggregative character of the underlying data observations (Cohen and Levin, 1989). In particular, the research-intensive pharmaceutical industry is characterized by diversified, multinational firms whose R&D activities span a number of pharmaceutical and non-pharmaceutical areas. Because of this, cross-sectional regressions of a firm's new drug output on its total R&D expenditures, at best, give a cloudy view of issues related to scale economies. Furthermore, there is a long and variable time-span between inputs and outputs in pharmaceutical R&D, which makes the dynamic specification of aggregate firm regression studies vulnerable to significant measurement error. On these grounds alone, it is perhaps not surprising that past analyses have not led to robust conclusions.

To examine the relationships between firm size, R&D costs and output in the pharmaceutical industry, we utilize in this study a disaggregative data set in which R&D costs and other data are collected at the individual project level. In particular, we utilize a representative sample of 93 new drug candidates first tested in humans between 1970 and 1982. These data were obtained from 12 US pharmaceutical firms, which together accounted for 40% of total US industry pharmaceutical R&D expenditure in the early to mid-1980s. The R&D programs in these firms span a spectrum from very small to very large. In prior work, these survey data were utilized to estimate the average R&D cost per self-originated new drug introduced into the US market, and to examine how these R&D costs vary by therapeutic class (DiMasi et al., 1991; 1995a). In this paper, we utilize this dataset to consider the issue of R&D scale economies.

By utilizing project-level data and matching them with corresponding new chemical entity (NCE) output for the survey firms, we are able to consider a number of hypotheses about scale economies that are obscured in more aggregative studies. These points include questions such as the following. Are there economies to scale in both the discovery and development stages of the R&D process? Do larger firms engage in more innovative projects than do smaller firms? How do the R&D outputs of larger firms differ from those of smaller firms? Insights into these and other related questions can only be obtained by utilizing disaggregate data sources.

Economies of scale in pharmaceutical R&D is also currently an interesting issue on policy grounds, given the recent consolidation occurring in this industry. For several decades, there were virtually no major mergers among the research-intensive firms. Since the late 1980s, however, there have been several mergers among the larger established pharmaceutical firms. Furthermore, this trend appears to be accelerating in recent years. Among the reasons cited for this 'merger wave' are the increasing costs of R&D and the need to achieve critical mass in both R&D and marketing activities.

The next section of the paper discusses the R&D process in pharmaceuticals, and potential sources of economies and diseconomies of scale. Section 3 discusses our data sample and methodology. Section 4 presents our empirical analysis of economies of scale in pharmaceutical R&D. The final section presents a brief summary and questions for future research.

2. Drug R&D Process and Sources of Scale Economies

2.1. Discovery and Development Process for New Drugs

Pharmaceutical R&D can be viewed as a sequential decision process of information acquisition under uncertainty. In recent years, basic biomedical knowledge
has played an increasingly important role in the discovery process. As a consequence, the R&D process has moved away from the random screening that was typical of earlier eras, approaching a more structured "discovery by design" approach (Grabowski and Vernon, 1983). Nevertheless, the drug R&D process is still characterized by considerable trial-and-error searching. This is reflected by the significant attrition rates for new drug candidates at both the preclinical and clinical stages. In addition, serendipity continues to be a significant factor in the innovation process (Goodwin, 1991).

At the discovery stage of the R&D process, multidisciplinary teams of biologists, chemists and other scientists are engaged in research to develop concepts and hypotheses concerning new compounds. The objective is to identify promising compounds that can be synthesized and tested for safety and efficacy. For example, scientists may focus on identifying compounds that can bind to a particular cell receptor or enzyme, thereby blocking a hormone or cellular metabolic function relevant to a specific health problem (such as the beta blockers in hypertension). Once a lead compound is identified and chemically synthesized, it is screened first in vitro and then in animals for both pharmacological activity and toxicity. If the drug is still considered to be a promising candidate for testing in humans, the firm files an investigational new drug application (IND) with the Food and Drug Administration (FDA).

Clinical testing typically occurs over three separate phases, which are designed to provide increasing levels of information on the safety and efficacy of a compound. Phase I testing is performed on a small number of (usually healthy) volunteers to obtain data on toxicity and safe dosing in humans. In phase II, the drug is tested on a relatively limited number of patients in controlled studies to obtain a preliminary evaluation of its efficacy, as well as additional data on its safety. Phase III involves large-scale trials on patients to quantify more precisely the therapeutic benefits and side-effects (including infrequent side-effects).

If a new drug candidate makes it through all these phases and a firm believes that it has sufficient evidence for approval, then the firm files a new drug application (NDA) with the FDA. The FDA requires substantial evidence of a drug's safety and efficacy from at least two well-controlled clinical trials before a drug can be marketed. During this stage, the firm also submits information to the FDA with regard to labelling and promotional claims, as well as specifications of its manufacturing process. Marketing for approved indications may begin upon notification of approval from the FDA. Typically, the entire process is very lengthy. The mean time from discovery to US marketing approval for new drugs approved in the US was 14 years for the 1980s and 15 years for the early 1990s (DiMasi et al., 1994).

2.2. Sources of Economies of Scale and Scope

The pharmaceutical R&D process presents several opportunities for traditional economies of scale and scope.¹ The R&D process, in general, and the discovery process, in particular, are characterized by significant fixed costs. In principle, larger firms can spread these fixed costs over more R&D projects and also over a larger expected sales base.
Our earlier study of the R&D costs of self-originated compounds indicated (DiMasi et al., 1991) that drug discovery and preclinical testing account for more than half of total R&D expenditures on an out-of-pocket basis. Moreover, because discovery and preclinical testing precede clinical development by several years, these earlier phases account for a disproportionate share of capitalized R&D costs. Larger firms can benefit from increased specialization of scientific skills and resources in the discovery phase of new drug innovation. This can be an important factor in an era when the underlying science in pharmaceuticals and other biomedical fields has become increasingly complex and dependent on specialized scientific knowledge.

The clinical development process may also be subject to economies of scale, though of a different variety from those in the discovery phase. Specifically, the process requires significant regulatory and legal expertise, which is also subject to spreading of fixed costs and specialization. However, because of the routine and structured character of clinical development, smaller (and larger) firms can utilize outside contract research organizations (CROs) to conduct clinical trials, so offsetting many disadvantages of a smaller size. It should be noted that CROs have experienced a rapid rate of growth in recent years.

There are also opportunities for economies of scope that come from a larger R&D enterprise. In particular, larger R&D programs will be engaged in a number of diverse projects, which increases the possibilities for positive internal spillovers and the ability to exploit serendipitous results in related fields (Henderson and Cockburn, 1994). Many drugs affect multiple body systems and organs, and so can be relevant to several therapeutic areas. As a consequence, researchers working in different areas have the benefit of positive externalities from a firm's advancements in related fields.

An additional Schumpeterian hypothesis that is relevant to the present case involves the risk-pooling ability of larger R&D programs and the advantages to financing these risky R&D programs internally within the firm. Our earlier work indicated that pharmaceutical R&D is indeed a costly and risky affair. The typical self-originated new drug introduction required over US$100 million in out-of-pocket expenditures (DiMasi et al., 1991). Our analysis also indicated that only 23% of the new drug candidates that enter phase I clinical trials will eventually be approved by the FDA. At the preclinical stage, several hundred drugs are screened for every one that is tested on humans.

Another dimension of risk derives from the fact that only a small proportion of new drugs can be termed as commercial successes. Analyses by Grabowski and Vernon (1990, 1994a) of the present values of cash flows for NCEs approved in the 1970s and in the early 1980s, when compared with the average R&D costs per NCE for these periods, indicate a highly skewed distribution of returns. Only drugs in the top few deciles earned premium returns. Drugs in the lower half of the distribution did not contribute much to covering the large fixed cost components of R&D (i.e. common discovery costs and the costs of failed drug candidates). As a consequence, pharmaceutical R&D is increasingly driven by the search for blockbuster drugs with above-average risks and returns.

The ability of larger firms to pool risky R&D projects and fund them through internally generated funds has been cited as a principal factor that underlies the mergers that have occurred among pharmaceutical firms in recent years. Another reason cited by firms is the rationalization of sales and detailing forces. Since
market competition has increased, as a result of managed care and other forces, there has been greater pressure on firms to shorten R&D times and to achieve faster market penetration with innovative products. Efficient utilization of marketing forces also requires a reasonably steady stream of new product launches that is characteristic of larger R&D programs.

The Schumpeterian hypotheses on the advantages of large size for R&D productivity have been criticized by a number of authors. They point to the increasingly bureaucratic character of R&D management as firms become larger, the associated distortion of information flows and the disincentives for individual creativity in hierarchical organizations. These ideas have received resonance in the case of independent biotechnology firms that have arisen in recent years to exploit new technological approaches to pharmaceutical discovery and development originating in university settings (Grabowski and Vernon, 1994b). Biotechnology firms typically have a different management style, with a more collegial, less hierarchical, scientific organisation and management structure than those of larger pharmaceutical firms. It is still too early to evaluate the R&D productivity of these organizations, given that their initial entry into discovering and developing pharmaceuticals occurred only a decade or so ago. Nevertheless, they present a contrasting internal organizational structure to the more traditional drug firms.

In summary, there are a number of potential sources of economies of scale and scope for pharmaceutical R&D, but there also may be countervailing forces at work. For this reason, a more disaggregate empirical analysis of this issue is warranted. In the next section, the data and methodology utilized in the current paper are discussed in further detail.

3. Data and Methodology

Project-level data on the cost and timing of development were obtained from a confidential survey of 12 US-owned pharmaceutical firms. The project-level data consist of a stratified random sample of 93 NCEs first tested in humans during 1970–82. Each NCE was self-originated (i.e. both discovered and developed by the same firm). We restricted our analysis to self-originated drugs, because the R&D costs for licensed or otherwise acquired NCEs are not fully reflected in the R&D expenditures of the firms that acquire them. We also excluded consideration of drugs that involved new formulations or indications of drugs already approved for marketing.

The sample was selected from a larger database of investigational NCEs assembled by the Tufts Center for the Study of Drug Development (CSDD). This database includes information on the development history of all the investigational NCEs of a large number of pharmaceutical firms regularly surveyed by the CSDD. We selected at random a number of NCEs from our survey firms that met inclusion criteria (a self-originated drug first tested in humans from 1970–82). Hence, none of the survey firms could preselect drugs on which to report costs. The sample constituted 19% of all NCEs in the CSDD database that met the survey inclusion criteria.

In our prior work (DiMasi et al., 1991), we utilized the cost data obtained from all 12 firms to estimate the average R&D cost for new drug introductions. For the clinical development period, we utilized our detailed data on costs and attrition rates by phase, to compute estimated expected clinical development costs per new drug tested. We then transformed these estimates into development costs per
approved NCE, utilizing information on clinical development success rates for the survey firms.

For this study, we estimated clinical approval success rates for firms in different size groups. The estimation process is a variant of the approach detailed in our earlier study (DiMasi et al., 1991). We used the portion of the CSDD database of investigational NCEs that contains the development history of all the cost survey firms' investigational NCEs that meet cost survey inclusion criteria. For our purposes, these data are right-censored, since the fate of some of the NCEs is not yet known. This fact makes it necessary that we predict the proportion of still-active NCEs that will eventually be approved.7

To estimate the preclinical costs, we used annual company expenditures on all preclinical and clinical R&D activity. In contrast to clinical testing, firms are not able to allocate all their preclinical expenditures to specific NCEs. Consequently, we used the data on the ratio between a firm's aggregate expenditures for preclinical and clinical testing, together with our estimate of the out-of-pocket average clinical period cost, to estimate the out-of-pocket preclinical cost per approved NCE (DiMasi et al., 1991). In this study, we calculated such ratios for groups of firms in different size categories.

For both the preclinical and clinical phases, we capitalized the out-of-pocket costs to the point of marketing approval, using estimated development and regulatory review phase lengths. For a discount rate, we used an estimate of the real long-term equity cost of capital (9%) for a sample of pharmaceutical firms that was consistent with our period of analysis (DiMasi et al., 1991). Myers and Shyam-Sunder (1995) estimated a slightly higher cost of capital (10%) for a sample of firms in the early 1980s and the Office of Technology Assessment of the US Congress (1993) applied a variable discount rate (10%–14%) to capitalize the out-of-pocket costs reported in our earlier study. However, the main effect of using higher discount rates is to raise the absolute levels of the cost estimates. Since we are concerned here with relative costs for firms in different size groups, we retain the assumption of a 9% discount rate. Our qualitative results are unaffected and the quantitative results are only slightly affected if we use higher rates.

For the current analysis, we divided the 12 survey firms into three separate groups, based on their total US pharmaceutical sales during 1970–74.5 This period pre-dates the time when marketing of the NCEs under analysis could contribute in a substantive way to the firm's pharmaceutical sales base; the first US approval among the survey firm NCEs that met survey inclusion criteria occurred in late 1974. Specifically, we defined small, medium and large firms to be those that had average annual sales (1993 $) during 1970–74 of less than $500 million, $500–600 million and more than $600, million respectively. These cut-off points provided a reasonable basis for combining our survey firms into groups that contained firms with similar sales levels and that also, in aggregate, had a comparable number of NCEs in the sample. Finer divisions, with fewer firms in each group, would yield too few sample observations. Our grouping yielded three large firms (37 NCEs), four medium-sized firms (33 NCEs) and five small firms (23 NCEs). The small, medium and large firms in our sample had mean annual US pharmaceutical sales (1993 $) during 1970–74 of $261 million, $560 million and $894 million respectively.6

In Section 5, we also consider grouping firms on the basis of the number of self-originated NCEs first tested in humans during 1970–82. While the grouping is somewhat different, the qualitative results are the same. An attractive alternative
is to use a direct monetary measure of the size of a firm’s R&D program. In our
cost survey, we requested data on the amount that firms spent in a year on
self-originated NCE R&D during 1970–86. However, our survey data on the
firms’ self-originated NCE R&D expenditures are complete for all firms only for
the period 1981–86. This is not an ideal basis for combining firms into size
categories, since sales from the marketing of NCEs developed early in the study
period could have influenced the level of R&D expenditures in the 1980s.
Grouping firms on the basis of R&D expenditures for 1981–86 differs more with
the sales criterion adopted here than does grouping on the basis of the number of
investigational NCEs, but the qualitative results are similar. In addition, for the
data that we have, the Pearson correlation coefficient between self-originated NCE
R&D expenditures and pharmaceutical sales in a year is very high (0.91).

In the current analysis, we consider NCEs in the three firm size groups to
constitute different samples drawn from distinct populations (see DiMasi et al.
(1991) for a discussion of our methodological approach in this regard). Hence,
each group of firms received different sample stratification weights (defined
according to the rate of an NCE). Furthermore, since we have shown that costs
vary by therapeutic class (DiMasi et al., 1995a), we adjusted the time and cost data
to account for differences in the therapeutic class distributions of the investiga-
tional NCEs of the three groups.10 However, the results when therapeutic class
weights are not applied are similar.

For this study, we also assembled market information on NCE output. In
particular, we assembled market data on all the self-originated NCEs of the sample
firms that first entered clinical testing between 1970 and 1982.11 Hence, we are
able to connect R&D outputs to the R&D costs, using a dynamically correct
linkage. This contrasts with the aggregative studies of R&D scale economies
discussed earlier, which utilize ad hoc dynamic linkages. These are generally based
on a fixed time-lag between a firm’s total R&D expenditures and its NCE outputs.

5. Empirical Results

Our data on the costs of new drug development are rich enough that we can
examine differences by firm size for a number of components of total cost.
Specifically, we generate results on out-of-pocket clinical phase costs per NCE
entering a phase, as well as out-of-pocket phase costs per approved NCE (by
accounting for differences in phase attrition rates and approval success rates). In
addition, to obtain capitalized costs, we develop estimates of the average length of
each development phase.

5.1. Clinical Costs per Investigational New Drug

Figure 1 shows weighted mean clinical period phase development costs per NCE
tested in humans.12 The out-of-pocket costs for the clinical phases tend to increase
with firm size. The expected clinical costs per investigational NCE for the small-, medium-
and large-sized firms, using the category definitions discussed in the
preceding section, are shown in Table 1. The total expected out-of-pocket costs
are estimated by taking the mean cost incurred in each phase of development,
multiplying by the estimated probability that an NCE reaches that phase,
and then summing over all clinical development phases. The capitalized costs per investigational NCE are also shown. The time horizon for capitalization was determined from two sets of estimates: (1) the actual weighted mean phase lengths shown in Table 1, and (2) the average gaps between and overlaps with successive clinical phases, determined by combining the data on actual phase lengths with the results on the time between the start of one phase and the start of the next phase, as shown in Figure 2.

Table 1 reveals a pattern of increasing clinical costs per tested NCE with respect to firm size. The estimated out-of-pocket cost per NCE tested on humans is $16.6 million for the large firms. This is 12% higher than the cost for medium-sized firms and 45% higher than that for small firms. These differences reflect the fact that the smallest firms have the lowest out-of-pocket expected costs for each of the three phases of clinical development. This would suggest a more efficient development process for smaller firms or, alternatively, less ambitious objectives in terms of the innovativeness of their new drug candidates.\textsuperscript{13}

As can be seen from Table 1, when clinical costs are capitalized, the differences in cost per investigational NCE persist but are diminished. The time from the initiation of clinical testing to NDA approval is 8.0 months longer for medium-sized firms and 5.8 months longer for small firms than is the case for large firms (Figure 2). Small firms have shorter clinical phase lengths (Table 1) but their approved NCEs have a much longer than average NDA review time (Figure 2). Consequently, the capitalized clinical period cost per investigational NCE for large firms is only 4% higher than that for medium-sized firms and 27% higher than that for the small firms.

Figure 1. Mean phase costs by firm size for NCEs entering a testing phase
Table 1. Expected out-of-pocket and capitalized clinical period cost* per investigational NCE by firm size** (adjusted for differences in therapeutic class distributions)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>2136</td>
<td>14.0</td>
<td>4174</td>
</tr>
<tr>
<td>Phase II</td>
<td>3454</td>
<td>17.6</td>
<td>6010</td>
</tr>
<tr>
<td>Phase III</td>
<td>3127</td>
<td>28.1</td>
<td>4766</td>
</tr>
<tr>
<td>Animal</td>
<td>2747</td>
<td>44.8</td>
<td>4422</td>
</tr>
<tr>
<td>Total</td>
<td>11,464</td>
<td></td>
<td>19,372</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>2857</td>
<td>18.7</td>
<td>5577</td>
</tr>
<tr>
<td>Phase II</td>
<td>4315</td>
<td>24.5</td>
<td>7220</td>
</tr>
<tr>
<td>Phase III</td>
<td>6042</td>
<td>40.0</td>
<td>8064</td>
</tr>
<tr>
<td>Animal</td>
<td>1651</td>
<td>31.6</td>
<td>2768</td>
</tr>
<tr>
<td>Total</td>
<td>14,865</td>
<td></td>
<td>23,629</td>
</tr>
<tr>
<td>Large</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>2978</td>
<td>13.1</td>
<td>5600</td>
</tr>
<tr>
<td>Phase II</td>
<td>4150</td>
<td>31.1</td>
<td>6604</td>
</tr>
<tr>
<td>Phase III</td>
<td>8167</td>
<td>35.6</td>
<td>10540</td>
</tr>
<tr>
<td>Animal</td>
<td>1335</td>
<td>32.2</td>
<td>1833</td>
</tr>
<tr>
<td>Total</td>
<td>16,630</td>
<td></td>
<td>24,577</td>
</tr>
</tbody>
</table>

*Costs were deflated using the GDP Implicit Price Deflator and capitalized using a 9% real discount rate.  
**Firms were grouped according to their average annual US pharmaceutical sales over the period 1970–74. Small, medium and large firms had average sales (1993 $) of less than $500 million, $500–600 million and more than $600 million, respectively.

5.2. R&D Costs per Approved New Drug

More relevant, however, are overall costs per approved NCE. Differences in the clinical success rates for different sized R&D programs can significantly change the observed relationship for the clinical testing costs per approved NCE. Secondly, as noted earlier, the preclinical cost (including discovery) is the largest component of overall R&D cost, especially on a capitalized basis. The results in Table 1 pertain only to the clinical testing phase of the R&D process.

Our statistical estimation of the success rates for the three groups reveal that the largest firms have higher success rates in clinical testing. The largest firms in the sample have a clinical trial approval success rate of 27.9% compared with a 23.8% success rate for the smallest firms and 17.4% for the medium-sized firms. This is suggestive of a more rational ‘discovery by design’ approach on the part of larger firms, perhaps reflecting superior drug discovery programs. Differing success rates alter somewhat the relationship between the average costs for the clinical period and the firm size. The relatively low success rate for medium-sized firms contributes to an average clinical cost per approved NCE that is above those of small and large firms.

Up to this point, we have considered only the costs of the clinical development stage. Figures 3 and 4 show our estimates of preclinical expenditures by firm size. The most striking finding is the high relative preclinical cost for the very smallest
firms. Figure 3 shows that small firms have out-of-pocket preclinical expenditures of $131 million, which is 55% larger than for the other groups. This is a very significant cost disadvantage at the preclinical or discovery stage for small firms.

The significantly higher preclinical costs for smaller firms does not appear to be
the result of these firms licensing out NCEs on which they carried out preclinical work but little or no clinical work. A search of the CSDD database of investigational NCEs revealed that only four out of 163 NCEs that were licensed-in and that were first tested in humans during 1970–82 originated from firms in our cost survey sample. Only one of the four originated from a small firm. The CSDD database has been estimated to contain at least 90% of the NCEs investigated in humans for commercial purposes in the US (DiMasi et al., 1994).

In addition, as shown in Figure 2, the small firms have an average preclinical phase time that is approximately 2 years longer than that for medium and large firms. A longer than average preclinical period and a longer than average NDA review period combine to give an average synthesis-to-approval time that is 22.2 and 29.4 months longer for small firms than for medium and large firms, respectively. Consequently, the capitalized costs at the preclinical stage are larger than the out-of-pocket costs for small firms relative to those for medium and large firms (67% and 76% higher than for medium and large firms, respectively).

Both out-of-pocket and capitalized costs per approved NCE decrease with firm size. Higher clinical period costs and a longer clinical development period result in higher costs for medium-sized firms relative to large firms. For small firms, the results are driven by much higher than average out-of-pocket preclinical costs and longer preclinical development times. Despite lower clinical period costs, the total out-of-pocket cost per approved NCE is 24% higher and the total capitalized cost is 50% higher for small firms than is the case for large firms.

Fully allocated capitalized costs decrease with firm size, even when costs and phase lengths are not adjusted for distributional differences in the therapeutic classes of the drugs investigated for firms in different size groups, or when firms are grouped by the number of investigational NCEs that they tested. Table 2 shows preclinical, clinical and total costs per approved NCE for size groups without

---

<table>
<thead>
<tr>
<th>Firm Size</th>
<th>Preclinical</th>
<th>Clinical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>332.5</td>
<td>81.4</td>
<td>413.9</td>
</tr>
<tr>
<td>Medium</td>
<td>198.9</td>
<td>135.8</td>
<td>334.7</td>
</tr>
<tr>
<td>Large</td>
<td>188.7</td>
<td>88.1</td>
<td>276.8</td>
</tr>
</tbody>
</table>

**Figure 4.** Capitalized cost per approved NCE by firm size.
Table 2. Out-of-pocket and capitalized cost\(^a\) per approved NCE by firm size\(^b\)

<table>
<thead>
<tr>
<th>Size groups based on US pharmaceutical sales for 1970–74(^c)</th>
<th>Size groups based on number of investigational NCEs first tested during 1970–82(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>Clinical</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Out-of-pocket</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>130</td>
</tr>
<tr>
<td>Medium</td>
<td>86</td>
</tr>
<tr>
<td>Large</td>
<td>88</td>
</tr>
<tr>
<td>Capitalized(^e)</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>340</td>
</tr>
<tr>
<td>Medium</td>
<td>199</td>
</tr>
<tr>
<td>Large</td>
<td>195</td>
</tr>
</tbody>
</table>

\(^a\)Millions of 1993 dollars. Costs were deflated using the GDP Implicit Price Deflator.\(^b\)No adjustments were made to account for differences in the distribution of NCEs investigated by therapeutic class.\(^c\)Firms were grouped according to their average annual US pharmaceutical sales over the period 1970–74. Small, medium and large firms had average sales (1993 $) of less than $500 million, $500–600 million, and more than $600 million, respectively. Clinical approval success rates of 23.8\%, 17.4\% and 27.9\% were estimated for small, medium and large firms.\(^d\)Firms were grouped according to the number of NCEs that they first tested in humans during 1970–82. Small, medium and large firms investigated less than 20 NCEs, 20–30 NCEs and more than 30 NCEs, respectively. Clinical approval success rates of 19.7\%, 20.9\% and 27.9\% were estimated for small, medium and large firms.\(^e\)Costs were capitalized using a 9% real discount rate.

Accounting for different therapeutic class distributions. The portfolios of firms in the various size groups are sufficiently similar with respect to therapeutic categories, so that adjusting for differences in the classes has little effect on the capitalized cost, as can be seen by comparing the results in Figure 4 (which were adjusted for differences in therapeutic class) with those in Table 2 for firms grouped by sales. When firms are grouped by the number of NCEs investigated, the quantitative results are somewhat different but the qualitative results are similar.\(^f\)

5.3. NCE Output from Different Sized Programs

One key issue that needs to be considered, however, before any definitive statements can be made about scale economies, concerns the quality of NCEs emerging from the different sized R&D programs. As we discussed earlier, the market value of NCE outputs follows a highly skewed distribution. Here, we consider whether or not there are systematic differences in the value of NCE outputs across different sized R&D programs.

Table 3 provides summary information on all the self-originated NCEs initially tested on humans during 1970–82 and that have been introduced into the US market by the survey firms. In other words, we have utilized the same inclusion criteria for NCE output and R&D cost data. However, while the R&D cost data are based on a stratified random sample of investigational NCEs for the survey firms, the NCE output data involve all NCEs that satisfy the inclusion...
Table 3. Sales-weighted NCE output\(a\) by firm size\(b\)

<table>
<thead>
<tr>
<th>Firm size</th>
<th>Number of NCEs approved</th>
<th>Approved NCEs per firm</th>
<th>Mean sales per NCE (millions 1993 $)(c)</th>
<th>Per cent of approved NCEs rated A or B by the FDA(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>11</td>
<td>2 2</td>
<td>30</td>
<td>36.4</td>
</tr>
<tr>
<td>Medium</td>
<td>11</td>
<td>2 8</td>
<td>121</td>
<td>45.5</td>
</tr>
<tr>
<td>Large</td>
<td>26</td>
<td>8 7</td>
<td>201</td>
<td>50.0</td>
</tr>
</tbody>
</table>

\(a\)US-approved self-originated NCEs that were first investigated in humans during 1970–82. \(b\)Firms were grouped according to their average annual US pharmaceutical sales over the period 1970–74. Small, medium and large firms had average sales (1993 $) of less than $500 million, $500–600 million and more than $600 million, respectively. \(c\)US sales for the first 3 years of market life were summed for each NCE and averaged for each size group. Sales for two of the NCEs of firms in the medium-sized group were not included in the computations, since they have not yet had at least 3 years of sales. \(d\)Ratings are those assigned by the FDA at the time of US marketing approval. An A rating represents an important gain over existing therapy, a B rating represents a modest gain and a C rating represents little or no gain.

criteria. There are a total of 48 such self-originated NCEs that were marketed by our survey firms. They span a time period from the mid-1970s to the early 1990s.

The largest R&D programs have more than half of the self-originated NCEs that have emerged on the market place from the new drug candidates first tested by the firms over the 1970–82 sample period, i.e. 26 of 48 NCEs. This amounts to an average yield of roughly nine marketed NCEs per firm. In contrast, the small and medium-sized firms have average yields of only two and three marketed NCEs per firm, respectively, from all their drug candidates that entered testing over this period of 13 years.

It is not surprising that the larger programs would have more approved NCEs, given their larger annual R&D outlays. What is surprising, however, is the much higher average sales per NCE for the larger programs. To put these results in perspective, we can calculate new drug sales per firm by size group for the NCEs developed during the study period, by multiplying the columns in Table 3 on the number of approved NCEs per firm and on mean sales per approved NCE.

While the medium-sized firms were on average about twice as large as the small firms, mean new drug sales from the NCEs developed during the study period by medium-sized firms were five times as high as the new drug sales for the small firms. Similarly, even though the average firm size is only 60% higher for large than for medium firms, sales per firm for NCEs developed during the study period were more than fivefold greater for large firms compared with medium-sized firms. This is a startling difference in new drug sales performance between the largest firms and the other firms in the sample.

To obtain further insights into these results, we have plotted the individual NCE sales values (1993 $) in Figure 5. As shown in the figure, the distribution of sales for large firms includes a small number of drugs with very high sales values. Five of the approved drugs of the large firms had sales in excess of $400 million in the first 3 years on the market. In contrast, only one NCE from the combined output of the medium and small firms had cumulative sales during the first 3 years in excess of $400 million.

As noted above, the sales distribution of NCE outputs is highly skewed. A main message of the analyses by Grabowski and Vernon (1990, 1994a) is that compe-
tition in pharmaceutical R&D now centers around the search for blockbuster drugs with above-average returns. In particular, firms must occasionally obtain a drug in the top few sales deciles to earn positive long-run returns on its portfolio of projects (i.e., to earn returns in excess of the cost of capital). Of course, smaller-selling products may contribute positively to the originating firm's short-term profitability by more than covering the variable development and capital investment costs. (In addition, they may be very useful medical therapies.) However, a disproportionate share of the high fixed costs of R&D (i.e., the common discovery costs and the costs of failed compounds) is now covered by the top decile compounds and these NCEs are critical to the long-term viability of research programs.

However, few (if any) of the NCEs from the medium or small firms are likely to be top-decile sales performers, given the results shown in Figure 5. At the same time, these firms have been observed to have R&D costs for self-originated compounds that are significantly greater than those of their larger competitors. While insufficient information is available to carry out a full rate-of-return analysis at this time, our findings on R&D costs and initial NCE sales strongly suggest that, collectively, these firms will realize a rate of return on R&D outlays that is below their cost of capital.

This conjecture is reinforced by the fact that several drug firms with R&D programs smaller than those of our large firms have already merged into larger entities. Furthermore, many of those firms which have not merged are either looking to make an alliance or are currently among the takeover candidates on Wall Street. One industry executive put the critical mass in R&D expenditures necessary to be a major competitor in 1991 at $500 million, with a growth rate of 10%–15% per year (Waldholz, 1991).

At the same time, the basis for the superior performance of the larger firms
remains an important issue for further consideration. In particular, one would like to know how much of this observed performance results from more innovative products as opposed to from an ability to diffuse and gain acceptance of their products rapidly through superior marketing efforts. The results in Figure 5 probably reflect both influences.

To gain some further insights into this question, we tabulated the percentage of NCEs ranked A or B by the FDA for each group of firms. This is a somewhat idiosyncratic yardstick of innovative importance. Nevertheless, using the FDA ranking of innovativeness, the larger firms have a more innovative set of drug outputs. As shown in Table 3, 50.0% of the NCEs that emerge from the large firms are ranked A or B by the FDA, compared with 45.5% and 36.4% for the medium-sized and small firms respectively.

Other measures of innovative output that have been employed in the case of pharmaceuticals include medical citations and diffusion across international markets (Dranove and Meltzer, 1994). Although none of these measures is ideal, they would be worth investigating in future research. In terms of the economic viability of different sized R&D programs, of course, sales and market performance are the relevant yardsticks.

6. Discussion and Future Implications

In summary, our findings indicate that, although the smallest firms in our sample have lower clinical development times and costs, they have much higher preclinical costs and this dominates the overall cost estimates. Therefore, our results provide some tentative support for the hypothesis that economies of scale exist in pharmaceutical R&D and that they are concentrated in the preclinical or discovery phase of the R&D process. As discussed in Section 3, larger research programs have been hypothesized to have advantages of scale and scope that are particularly concentrated in drug discovery, as a result of the highly skilled and specialized nature of this stage.

The recent wave of consolidations in the pharmaceutical industry is consistent with our findings of much higher returns to R&D on the part of the very largest firms. What does this say about the future evolution of the pharmaceutical industry? One of the industry strengths has been the large number of firms developing new drug products. Is this destined to change in the future?

The pharmaceutical industry may indeed have fewer but larger firms in the future, as a result of the factors discussed here. At the same time, however, there are some strong dynamic forces currently at work, which will also have a significant effect on the evolving structure of the industry. One of the most important of these developments is the entry of new biotechnology firms into pharmaceutical R&D since the mid-1980s. By interacting with and building directly on university research in the basic biomedical sciences, these firms have avoided some of the high fixed costs associated with a large infrastructure in the discovery phase of R&D. In addition, biotechnology firms have increasingly formed alliances and joint ventures with traditional pharmaceutical firms to realize economies in terms of product development and marketing. While it is too early to assess the impact of these firms on industry structure, they have been responsible for some of the most innovative new drug introductions in recent years (Bienz-Tadmor et al., 1992; Grabowski and Vernon, 1994b). They are likely to play a very important role in the future evolution of the industry.
Another important recent development is the growth of managed care on the demand side of the market. The market appears to be evolving toward a capitation approach for pharmaceuticals, possibly as part of an integrated market approach to disease management. As a consequence, the future pharmaceutical industry is likely to reward very different skills in terms of the diffusion and market acceptance of new drug introductions. Increased effort will be devoted to providing evidence from cost-effectiveness studies of new pharmaceuticals and less to traditional detailing of physicians. Furthermore, the growth of managed care has given rise to vertical mergers between pharmaceutical firms and pharmacy benefit managers. These developments are also likely to have major implications for the industry structure.

It will be interesting to observe how the myriad forces at work in the pharmaceutical industry will sort themselves out as the industry evolves during the next several years. The future industry structure may be more concentrated than in the past in certain segments, but it is also likely to accommodate a much greater diversity of organizational structures within its boundaries.

Notes
1 The origins of the basic ideas concerning the sources of economies of scale and scope in R&D activities can be found in the work of Schumpeter and have been developed by a number of industrial organization scholars. For a survey and analysis of this voluminous literature, see Cohen and Levin (1989), Baldwin and Scott (1987), Scherer (1984) and Nelson et al. (1967).
2 An alternative to using CROs, small firms can also form alliances and joint ventures with larger established firms to carry out clinical testing and marketing. This is a more feasible option at the development stage, as opposed to the discovery stage, because one is better able to assess scientific promise and intellectual property rights during development.
3 In a perfect capital market, the riskiness of a specific project would be eliminated through investor diversification, so that the method of R&D financing would not matter. However, a number of theoretical studies have pointed to capital market imperfections that would make internal funds a preferred source for undertaking such risky R&D. These studies have been summarized recently by Hall (1992) and include the fact that firms may have to pay a 'lemons' premium in the case of long-term risky R&D financed by new equity or debt. Firms also are reluctant to reveal information to market competitors through equity funding of their R&D programs. Therefore, these studies imply a lower implicit cost of capital on internal funds for financing R&D. There are a number of empirical studies that actually show a significant relationship between expenditures and the availability of internally generated cash flow and retained earnings (Hall, 1992, Grabowski and Vernon, 1981).
4 Product lifetimes are shortening as a result of increased generic usage and other factors (Grabowski and Vernon, 1992, 1994b, Congressional Budget Office, 1994).
5 For a survey of these studies, see Cohen and Levin (1989).
6 For the NCEs selected, firms provided clinical testing phase beginning and ending dates; phase costs by year of clinical testing; and the date that testing was suspended on those NCEs for which research was abandoned. Data on the time from synthesis to first testing on humans and from NDA submission to NDA approval were obtained for the self-originated NCEs of US-owned firms that were first tested in humans during 1970–82 from a CSDD database of US-approved NCEs. Annual total expenditures by firm for self-originated NCE R&D were also provided by the cost survey firms and broken down according to whether they were incurred during the clinical or preclinical periods. All the reported R&D expenditures were converted to constant dollars using the GDP Implicit Price Deflator.
7 Specifically, we noted the number of NCEs that had been approved through 1989 and, for the NCEs that were still active at the end of 1989, what was the shortest time from the start of clinical testing to the end of 1989. We then estimated the number of future approvals among the open NCEs in two ways. First, we estimated, using the non-censored portion of the data, a probit regression that models the probability of approval as a function of the time from the start of clinical testing. The estimated regression can be used to provide an estimate of the probability of approval.
given that the time from the start of clinical testing is at least as large as the minimum for the open NCEs. Secondly, for the non-censored data, we calculated the percentage of NCEs that have been approved for those NCEs that had been active at least as long as the minimum for the open NCEs. We then averaged the final success rates implied by the two approaches.

The annual sales data were gathered by IMS America, Ltd.

The same grouping of firms into size categories results if done on the basis of sales during the entire 1970s.

Therapeutic class weights were applied to the already weighted sample values (i.e., adjusted for the fate of the NCE). The weights were obtained by using the population therapeutic class distribution for the survey firms as a whole and the sample therapeutic class distributions for each set of firms. Thus, the estimated costs in Section 5 are those that would be incurred if each R&D expenditure group possessed the same distribution of NCEs tested on humans by therapeutic class (the distribution for the survey firms taken as a whole). The therapeutic categories used are those examined by DiMasi et al. (1995) anti-infective, cardiovascular, neuropharmacologic and non-steroidal anti-inflammatory NCEs.

We obtained IMS America, Ltd annual sales data. These data are total US sales to hospital and retail pharmacies, estimated on the basis of extensive surveys.

The weights were chosen to adjust for differences across size groups in the distribution of sample NCEs by therapeutic class.

In our earlier analysis, we found significantly higher costs for innovative drug compounds, measured by FDA ranking of therapeutic importance (DiMasi et al., 1991).

DiMasi (1995b) estimated success rates for small-, medium- and large-sized firms that had filed INDs on self-originated NCEs during 1980–84 and found no appreciable differences in the predicted final success rates. US pharmaceutical sales were also used as the basis for grouping firms but the sales period was different (1986 sales were used). Additionally, the number of firms studied was much larger than the number in our cost sample and the NCEs included here span a much longer period.

The cost per approved NCE is obtained by dividing the expected cost per tested NCE (shown in Table 2) by the approval success rate for clinical testing.

Preclinical-to-total-R&D-expenditure ratios of 70 9%, 50 3% and 58 7% for small, medium and large firms, respectively, were estimated using data aggregated to the firm level. Costs were capitalized at a 9% real discount rate.

In his discussion of adrift of the paper at Yale, Paul MacAvoy raised the possibility that the higher preclinical cost per new drug introduction of the smaller firms in our sample resulted from these firms licensing out their successful projects to larger firms for development (analogous to what happens in the case of wildcat oil and gas drilling companies, or in the fledgling biotechnology industry). The evidence discussed here does not support this contention. It should be remembered that, while our sample spans a size spectrum, all our firms are fully integrated pharmaceutical firms (with research, development and marketing activities). Given that this is the case, it would be surprising if the smaller firms in our sample were to license out their successful NCEs to larger firms in the industry for development and marketing, except on rare occasions where they do not plan to market in a very specialized disease category.

The difference between the groupings by sales and by the number of NCEs investigated is that several firms switch between the medium and small groups. However, the three firms in the large group remain the same. Since the large group is the same, the total capitalized cost estimates for the large firms are the same. However, the total capitalized cost estimates for the medium-sized and small firms are both somewhat higher for the grouping based on sales. This seeming paradox can occur, depending on how many NCEs shift from one size group to another and whether they are high- or low-cost NCEs relative to the remaining NCEs in the other size group.

The sales values in Figure 5 are US sales during the first 3 years of marketing for self-originated NCEs first tested in humans during 1970–82.

In this regard, based on their initial sales, only one of the drugs that emanated from these firms would qualify for the top two deciles of 1980–84 approvals analyzed by Grabowski and Vernon (1994a). Most of these NCEs would be in the lower deciles. Of course, these NCEs span a longer time-frame in terms of market launch, so that the 1980–84 distribution is not the relevant yardstick for many of these NCEs. Nevertheless, even adjusting for this fact, the overall economic performance of the smaller firms is quite poor.

Our cost survey provided data on aggregate annual company pharmaceutical R&D expenditures. The total pharmaceutical R&D expenditures of each of our large firms were at least $216 million in 1986. From 1986 to 1993, US pharmaceutical industry R&D expenditures increased at a...
compound annual real rate of 5% (Pharmaceutical Manufacturers Association, 1993). Applying an 5% real growth rate to the 1986 minimum yields an R&D threshold for the large firms of $575 million in 1993.

22. Among other things, the FDA tends to give higher ratings to 'orphan' drug compounds (drugs that target diseases which affect very small patient populations, often with few alternative therapies) relative to significant but incremental advances that affect much larger patient groups.

23. Henderson and Cockburn (1994) found support for the proposition of program-level economies at the discovery stage. In particular, they found that research productivity, as measured by the number of 'important' patents per dollar spent on discovery research, is higher in research programs located in larger total R&D efforts. In contrast to the studies based on aggregate data cited here, they analyzed disaggregated firm data at the research program level from 10 major pharmaceutical firms over a long time-span. Hence, this work utilizes a much fuller database than did earlier studies of scale economies. However, one limitation of their analysis, in our view, is the use of patent data as the measure of output. Important patents are defined as those granted in at least two of three major markets (US, Japan and the European Community). Some of these patents are never commercialized (i.e. have zero market value) and those that are have a highly skewed distribution in terms of market value.

References


Grabowski, Henry G and Vernon, John, “Innovation and Structural Change in Pharmaceuticals and Biotechnology,” Industrial and Corporate Change, 1994b, 3, 2, 435–49
Scherer, F M., Innovation and Growth Schumpeterian Perspectives Cambridge, MA MIT Press, 1984