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Cost of innovation in the pharmaceutical industry*

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The research and development costs of 93 randomly selected new chemical entities (NCEs) were obtained from a survey of 12 U.S.-owned pharmaceutical firms. These data were used to estimate the pre-tax average cost of new drug development. The costs of abandoned NCEs were linked to the costs of NCEs that obtained marketing approval. For base case parameter values, the estimated out-of-pocket cost per approved NCE is $114 million (1987 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a 9% discount rate yielded an average cost estimate of $231 million (1987 dollars).

1. Introduction

Product innovation in the pharmaceutical industry is risky and time-consuming, with research and development (R&D) costs representing a high

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proportion of sales revenues.[1] Although other forms of pharmaceutical innovation exist, new chemical entity (NCE) development is, on the whole, the most therapeutically and economically significant.[2,3] Typically, the R&D process for NCEs is spread over many years, and only a small proportion of these new drugs are eventually approved for marketing.

Empirical analyses of the cost to discover and develop NCEs are interesting on several counts. First, knowledge of R&D costs is important for analyzing issues such as the returns on R&D investment.[4] Second, the cost of a new drug has a direct bearing on the organizational structure of innovation in pharmaceuticals. In this regard, higher real R&D costs have been cited as one of the main factors underlying the recent trend toward more mergers and industry consolidation.[5] Third, R&D costs also influence the pattern of international resource allocation, and hence, international competitiveness.[6] Finally, the cost of R&D has become an important issue in its own right in recent policy deliberations involving regulatory requirements and the economic performance of the pharmaceutical industry.[7] In this paper we confine our analysis specifically to the study of R&D costs.

[1]The Pharmaceutical Manufacturers Association (PMA) Statistical Fact Book (1987) reports that, for member firms, U.S. pharmaceutical expenditures expressed as a percentage of U.S. pharmaceutical sales was 15.0% in 1986, up from 10.2% in 1965.

[2]An NCE is defined here as a new molecular compound not previously tested in humans. Excluded are new salts and esters of existing compounds; surgical and diagnostic materials; certain externally used compounds such as disinfectants, antiperspirants, and sunscreens; nutritional compounds such as natural forms of vitamins and sweetening agents; and certain biologic compounds such as vaccines, antigens, antisera, immunoglobulins, or purified extracts of existing drugs.

[3]Data in the PMA Annual Survey Report, 1987–1989, indicate that 82.9% of member firm company-financed human and veterinary use R&D expenditures in 1987 were spent on research for the advancement of scientific knowledge and development of new products and related services. The remainder was spent on research oriented to significant improvements and/or modification of existing products. This percentage has not varied much over the last few decades. The reason why such a high proportion of R&D is spent on new drugs is that a compound patent can usually be obtained covering the active ingredient. This patent confers protection from competition from any generic version of the drug.

[4]The two most recent rate of return analyses in the economics literature use cost estimates in Hansen (1979, 1980). Joglekar and Paterson (1985) estimates an after-tax rate of return for a hypothetical NCE first investigated in 1976. Grabowski and Vernon (1990) provides rate of return estimates for NCEs first marketed in the U.S. in the 1970s. The cost estimates used are applicable to NCEs first investigated in humans during the period 1963–1975. Future studies can benefit from cost estimates relevant to a later period.

[5]Within the past few years, there have been several major mergers and acquisitions in the pharmaceutical industry including SmithKline–Beecham, Bristol Myers–Squibb, Eastman Kodak–Sterling Drug, Merrell Dow–Marion Laboratories, and American Home Products–Robins.

[6]For studies of competitiveness in pharmaceuticals, see the analyses presented in the National Academy of Engineering (1983), Grabowski (1989), and especially Thomas (1990).

[7]In particular, Congressional concern has been focused on increases in relative drug prices and the role of increased R&D costs in explaining higher prices [U.S. Congress (1985, 1987, 1989)].

The ouput from our work can be applied to these various issues in subsequent research.

The approach to estimating an average pre-tax cost of new drug development used in this paper follows, for the most part, that found in Hansen (1979). Micro-level data on the cost and timing of development were obtained through a confidential survey of U.S. pharmaceutical firms for a random sample of NCEs first investigated in humans from 1970 through 1982. Reported development expenditures run through 1987. For every NCE that is approved, several others are abandoned at some point in the development process. Consequently, we associate the costs of failed projects with those of successful projects. R&D is also treated here as an investment with expenditures capitalized to the point of marketing approval.

In this paper, we examine the sensitivity of R&D costs to various parameters such as the clinical success rate and the economic discount rate. We also consider the sensitivity of R&D costs in reductions in Food and Drug Administration (FDA) regulatory review times and the lengths of various phases of NCE development. In addition, results are presented for the costs of developing approved new drugs categorized by an FDA measure of a new drug's medical significance.

The remainder of this paper is organized as follows: section 2 contains an outline of the new drug development process, which serves as background for the rest of the paper; section 3 provides a review of the literature on the cost of drug development; the cost estimation procedures we employ are described in section 4; a description of our sample data and the population from which they were drawn is given in section 5; baseline results on the average cost of NCE development are presented in section 6, while results for subsamples are given in section 7; section 8 contains an analysis using published aggregate pharmaceutical industry R&D data that serves as an external check on some of our baseline results; and some conclusions and prospects for future research are offered in section 9.

2. The new drug development process

New drug development is typically a sequential process. At several points in the process a pharmaceutical firm will review the status of testing on a drug and make a decision on whether to continue with its development.[8] In general, the decision depends on potential therapeutic benefits, the expected frequency and severity of adverse reactions, projected additional development, marketing, distribution, and production costs and estimates of a future revenue stream.

[8]The number and timing of these critical points in the life of an investigational drug vary by firm. See Wiggins (1981) for a discussion of when these decisions are usually made and what considerations are used in making them.

For drugs that make it all the way through to the point of FDA marketing approval, the sequence usually runs as follows. Prior to synthesis considerable discovery research is undertaken by chemists and biologists to develop concepts for new compounds. Once a new compound has been synthesized it will be screened for pharmacologic activity and toxicity in vitro, and then in animals. If, at this point, the drug is still considered a promising candidate for further development, the firm will file with the FDA an Investigational New Drug Application (IND).[9] Unless the FDA places a hold on this application, the firm may begin clinical (human) testing 30 days after filing. Clinical testing normally occurs over three distinct phases, each of which contributes different amounts and types of information on safety and efficacy.

Phase I testing is performed on a small number of (usually healthy) volunteers. These trials are conducted mainly to obtain information on toxicity and safe dosing ranges in humans. Data are also gathered on the drug's absorption and distribution in the body, its metabolic effects, and the rate and manner in which the drug is eliminated from the body.

In the second phase of human testing, phase II, the drug is administered to a larger number of individuals. The groups selected consist of patients for whom the drug is intended to be of benefit. Under the 1962 Amendments to the Food, Drug, and Cosmetics Act of 1938 (FD&C), substantial evidence of efficacy in the intended use of the drug is required before marketing approval can be granted. When successful, phase II trials usually provide the first significant evidence of efficacy. Additional safety data are also obtained during this phase.

The third, and final, premarketing clinical development phase, phase III, involves large-scale trials on patients. Additional evidence of efficacy is sought during this phase. The larger sample sizes increase the likelihood that actual benefits will be found to be statistically significant. Because many patients are typically enrolled in the trials, phase III testing is also useful in detecting adverse reactions that occur infrequently in patient populations. In addition, this testing may more closely approximate the manner in which the drug would be utilized after marketing approval.

Although extensive toxicology experimentation on animals occurs during the preclinical period, to detect teratologic and carcinogenic effects firms usually perform long-term animal testing concurrent with phases II and III. Long-term stability testing, and sometimes additional dosage formulation work and process development for manufacturing the compound in sufficient quantities for clinical testing, also occurs during the clinical period.

Once the clinical development phases have been completed and the firm believes that it has sufficient evidence for approval, it will submit a New

[9]See Mattison et al. (1988) for analysis of trends in the number of INDs filed by U.S. firms.

Drug Application (NDA) to the FDA for review. Marketing for approved uses may begin upon notification from the FDA.[10]

We designed our procedures for estimating average costs to utilize this categorization of drug development by phase. Not all new drug testing fits neatly into this framework, but the firms were able to allocate clinical costs satisfactorily to phases.

3. Previous estimates of new drug R&D costs

A number of studies, covering various time periods, have attempted to provide estimates of at least a portion of the R&D expenditures required to bring new drugs to market. Although comparing results from studies with different methodologies is risky, taken as a whole these analyses point to rising real R&D costs over time.

Table 1 presents the main results from these studies, the nature of the data analyzed, and the periods covered. Schnee (1974), Sarett (1974), and Clymer (1970) used out-of-pocket development cost data on limited groups of NCEs. Clymer's estimates for the late 1960s, exclusive of the costs of unsuccessful products, range from $2.5 to $4.5 million. This may be compared to Schnee's estimate of $0.5 million. If both estimates are correct, then R&D costs increased dramatically from the 1950s to the late 1960s.[11]

Mund (1970) and Baily (1972) used annual U.S. industry R&D expenditures and NCE introductions to estimate average costs, and also found a substantial increase in costs over time. An advantege to using aggregate data is that estimates will be based on information from a large group of firms. A serious disadvantage, though, is that aggregate expenditures cannot be associated in any precise manner with particular NCEs.[12]

Figure 1 shows the time pattern between 1963 and 1989 of annual U.S. pharmaceutical industry R&D expenditures and U.S. NCE approvals. As this figure shows, NCE approvals have changed only moderately over time, while real dollar pharmaceutical outlays have increased several times over this 25 year period. Aggregative industry data are therefore strongly suggestive of sharp increases in R&D cost over time, and this upward trend seems to have intensified in the 1980s. There are a number of difficulties, however,

[10]This contrasts with subsequent FDA approval of additional indications, dosage strengths, dosage forms, and delivery systems for the new drug. Further testing is required to obtain approval for such changes in the drug's labelling.

[11]Sarett's estimate for 1967 is also consistent with the Clymer range. A plausible hypothesis for explaining at least part of the large observed post-1962 change is that more extensive testing was required for approval following the implementation of the 1962 Amendments to the FD&C.

[12]Mund utilizes a simple 5-year fixed lag approach. Baily relates the average of aggregate R&D expenditures lagged 4 to 6 years to NCE introductions using a regression analysis framework. In computing the Baily cost estimates in table 1, we employ actual values of his independent variables, as opposed to the 'steady state' equilibrium value used in his article. The former is more appropriate for comparative purposes.

Table 1

Prior R&D cost studies.

Author	Sample	R&D cost/period	Notes
		(A) *Partial cost studies*	
Schnee	17 approved NCEs Single drug firm	0.5 mil/1950s–1960s	Discovery costs and unsuccessful NCEs ignored; no capitalization
Sarret	Successful NCEs Single drug firm	1.2 mil/1962 3.0 mil/1967 11.5 mil/1972	Discovery costs and unsuccessful NCEs ignored; no capitalization
Clymer	New drug candidates Single drug firm	10.5 mil/late 1960s	Discovery costs ignored; no capitalization
Mund	Aggregate industry data on R&D and NCEs	1.5 mil/1950s 10–20 mil/1960s	Five-year lag assumed between R&D and new drug introductions; no capitalization
Baily	Aggregate industry data on R&D and NCEs	2.3 mil/late 1950s 21.8 mil/late 1960s	Fixed lag regression analysis approach; no capitalization
		(B) *Full cost studies*	
Hansen	Representative sample of drugs tested in humans, 1963–1975	54 mil (1976 dollars)	Includes discovery and development costs capitalized to date of marketing introduction
Wiggins	Aggregate industry data on R&D and NCEs approved 1970–1985 (by therapeutic class)	125 mil (1986 dollars)	Fixed lag regression analysis approach; also uses selective parameter estimates from Hansen

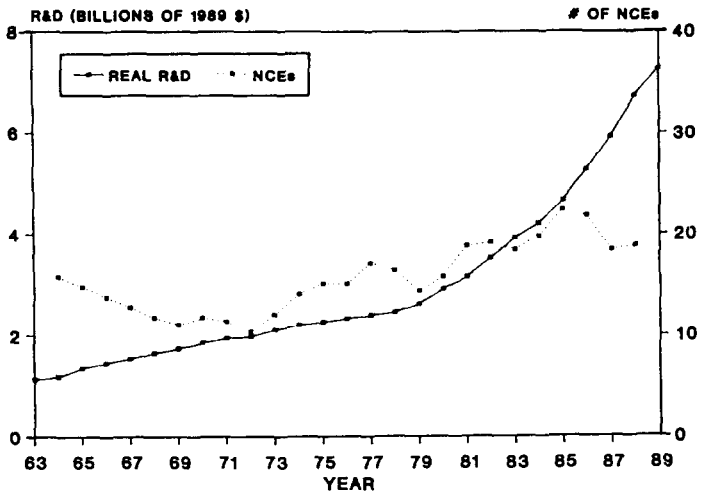

Fig. 1. Annual U.S. pharmaceutical industry real R&D expenditures and U.S. NCE approvals for the period 1963–1989. Expenditures are for PMA member firms and are indexed using the GNP Implicit Price Deflator. The NCE approval line is constructed from 3-year moving averages of annual approvals.

in using aggregate data to obtain precise estimates of R&D cost per approved NCE over particular subperiods. First, one must specify a lag structure between R&D inputs and output. This lag has been lengthening over time. Second, aggregate industry data cover compounds licensed from abroad, in addition to those that are U.S.-discovered. These two categories of drugs are likely to have vastly diferent R&D cost expenditure patterns within the United States.[13] For these reasons, R&D cost studies based on micro data at the individual project level are likely to produce much more accurate cost estimates.

The only prior R&D cost study that utilized multi-firm project level data for new drugs is Hansen (1979). Data were obtained from 14 firms on a large randomly selected group of NCEs first tested in humans during the period 1963 to 1975. Information was requested from surveyed firms on NCEs originated and developed by those firms. Time and cost data by development phase were gathered so that average phase lengths and costs could be computed. Costs of projects that were abandoned at some point in the clinical testing period were included and R&D was treated as an investment

[13]For example, the aggregate industry R&D cost data available from the PMA do not include the R&D expenditures performed abroad for licensed compounds originating in foreign countries. As we show later in the paper, where aggregate data are employed as a check on our results, average U.S. R&D costs for foreign licensed compounds are estimated to be small compared to the self-originated NCEs of U.S. firms. Of course, license fees account for much of the difference in R&D costs, but they are not publicly available.

with returns delayed until marketing approval. Hansen's R&D cost estimate of $54 million (in 1976 dollars) was larger than those of prior studies, but it was also more complete in the sense that it took account of discovery as well as development costs, the costs of failed projects, and the time value of funds invested in R&D.

The most recent drug R&D cost study is Wiggins (1987). It employs industry aggregates calculated at the therapeutic class level to compute an 'R&D production function'. Regression coefficient estimates are then used to infer an R&D cost value. This methodology is similar to that employed in Baily (1972). For NCEs approved during 1970–1985, Wiggins found an uncapitalized cost per NCE of $65 million in 1986 dollars. Wiggins then used the time profile for new drug development estimated in Hansen (1979) to provide capitalized cost estimates. For his base case, Wiggins used Hansen's preferred discount rate of 8% to determine capitalized cost to be $125 million in 1986 dollars. Woltman (1989), however, has pointed out that the Wiggins capitalized value should only be $108 million, given a proper analysis of the time profile utilized in Hansen (1979).[14]

When compared to Hansen's results, the corrected estimates reveal a relatively small real cost increase. General price inflation accounts for 80% of the increase in estimates ($54 million in 1976 dollars translates to $97 million in 1986 dollars). However, the time periods considered in the two studies also do not differ very much. Wiggins used data that were meant to be relevant to 1970–1985 NCE approvals. Given his imposed lag structure, R&D expenditures included run from 1965 through 1982. Hansen's R&D expenditures run from 1963 to the mid-1970s, with expenditures more concentrated in the latter half of this period.[15]

Even for identical periods, however, results from these two types of studies may not be comparable. Wiggins employed data that are a mixture of both licensed and self-originated NCEs, and this is likely to produce a lower R&D cost estimate than from a sample consisting of only U.S. self-originated NCEs.[16] In addition, Wiggins' (and Baily's) estimates, which are obtained from an R&D production function type analysis, are really marginal costs. They are estimates of the additional cost that would have been incurred if one more NCE had been approved during the sample

[14]To obtain capitalized costs, Wiggins multiplied his $65 million uncapitalized cost estimate by the ratio of capitalized to uncapitalized costs in Hansen (1979). Uncapitalized costs per marketed NCE are not presented in Hansen (1979), but can be determined from other data therein. Wiggins claimed that this figure is $28 million. The correct amount, however, is $32.5 million. This changes the Wiggins base amount to $108 million.

[15]Hansen's data are for a sample of NCEs first investigated in humans during 1963–1975. Some of the NCEs first investigated in the early part of this period had long development times with significant expenditures incurred late in the period.

[16]As noted in footnote 13, licensed compounds originating from foreign countries tend to have much lower *U.S.* costs than compounds originating in the U.S. from U.S.-owned firms.

period. Hansen's results, and those of the other studies listed in table 1, are average cost estimates. Unless constant returns to scale with respect to R&D effort exist at the industry level (at or near average expenditure levels for the sample period), marginal and average costs differ.

In summary, results from the studies discussed above suggest that new drug R&D costs have risen over time, at least relative to the pre-1962 Amendments period. However, only Hansen's study employs micro data, and none of the studies includes much data from the 1980s, a period during which real industry R&D expenditures have risen rapidly (fig. 1).[17] This study, like Hansen's, employs project level data, and a significant amount of the data used was taken from this recent time period.

4. Estimating the average cost of new drug development

We use project level data to obtain an estimate of the clinical period average cost per NCE tested in humans. A majority of these NCEs will not be approved for marketing. Our approach uses an estimated clinical approval success rate to link the R&D costs of failed projects to the costs of those NCEs that obtain marketing approval. A representative time profile for an NCE progressing through all testing phases to the point of marketing approval is also estimated and used to capitalize R&D expenditures. Preclinical discovery and development costs are accounted for and treated in a more refined manner than was the case in Hansen (1979).

Since the full R&D costs for licensed or acquired NCEs are not typically reflected in R&D budgets of the firms that acquired them, we restricted our analysis to self-originated NCEs. The various steps we use to determine an estimate of the total cost per approved self-originated NCE (inclusive of unsuccessful efforts, preclinical expenditures, and the opportunity cost of funds invested) are formally described below.

4.1. Expected out-of-pocket costs

Let h be the clinical period development cost of a randomly selected NCE tested in humans. This can be decomposed into a sum of random variables. Specifically, $h = x_{\mathrm{I}} + x_{\mathrm{II}} + x_{\mathrm{III}} + x_{\mathrm{A}}$, where x_{I}, x_{II} and x_{III} represent the NCE's development costs for phases I, II, and III, respectively, and x_{A} is its long-term animal testing cost. If the project was terminated prior to entering a phase, then the random variable for that phase assumes the value zero. The expected value of clinical period costs is then $E(h) = p_{\mathrm{I}}\mu_{\mathrm{I}|\mathrm{e}} + p_{\mathrm{II}}\mu_{\mathrm{II}|\mathrm{e}} + p_{\mathrm{III}}\mu_{\mathrm{III}|\mathrm{e}} +$

[17]Data from the PMA Annual Survey Report, 1987–1989, can be used to compute growth rates for real pharmaceutical R&D expenditures for different time periods. From 1963 to 1979 real R&D expenditures grew at a 5.3% compound annual rate; from 1980 to 1989 expenditures grew at a 10.7% compound annual rate.

$p_A\mu_{A|e}$, where p_I, p_{II}, and p_{III} are the probabilities that a randomly selected NCE tested in humans will enter phases I, II, and III, respectively, p_A is the probability that long-term animal testing will be done, and $\mu_{I|e}$, $\mu_{II|e}$, $\mu_{III|e}$, and $\mu_{A|e}$ are conditional expectations. Specifically, $\mu_{I|e}$, $\mu_{II|e}$, $\mu_{III|e}$, and $\mu_{A|e}$ are the population mean costs for phases I, II, III, and long-term animal testing, respectively, for those NCEs that enter the respective phase.

The proportion of NCEs tested in humans that are taken through the various clinical period testing phases diminishes with each successive phase. As will be shown below, only a small minority undergo all testing phases. Thus, a simple random sample of this population will likely contain a good deal of information about NCEs that do not last very long in testing and little information about NCEs that reach the point of NDA submission or approval. Furthermore, we expect phase costs to be more variable for later testing phases. The later clinical trials are larger, last longer, and should be more subject to variability in size and duration depending on the type of drug tested and the condition it is meant to treat.

Therefore, to reduce overall sampling error, we grouped NCEs into strata according to the time spent in active testing if research was abandoned, whether research was still in progress, and whether an NDA had been submitted or approved. Successful NCEs were deliberately oversampled and unsuccessful NCEs lasting only a short time in active testing were undersampled. The sample percentage distribution for the strata was specified before sample selection. In preparing our estimates, we reweighted the responses to replicate the population.

The population from which our sample was selected consisted of a subset of the investigational NCEs contained in a Center for the Study of Drug Development (CSDD) database. The proportions of population NCEs that fall in our strata can be determined from information in this database. Thus, we were able to define a set of weights to be applied to the sample data that transform the sample from one that is unrepresentative with respect to the strata to one that is perfectly representative. Mean phase cost (in constant dollars), $\bar{x}_i$, and the probability that an NCE tested in humans will enter a phase, s_i, can then be estimated from the weighted sample (see appendices A and B for computational details). The expected clinical period cost per new drug tested in humans can be expressed as $\hat{E} = s_I\bar{x}_I + s_{II}\bar{x}_{II} + s_{III}\bar{x}_{III} + s_A\bar{x}_A$.

To estimate the expected cost per approved drug, C_u, one needs to multiply $\hat{E}$ by the ratio of the number of drugs taken into humans, n_T, to the number approved, n_a (i.e., $C_u = \hat{E}(n_T/n_a)$). Alternatively, C_u can be expressed as $\hat{E}/s$, where s is the successful rate for NCEs tested in humans (the ratio of n_a to n_T). Data from CSDD databases on investigational and approved NCEs for the survey firms can be used to estimate s.

The final step in estimating R&D costs is to incorporate preclinical expenditures. Firms are generally not able to allocate all preclinical costs to

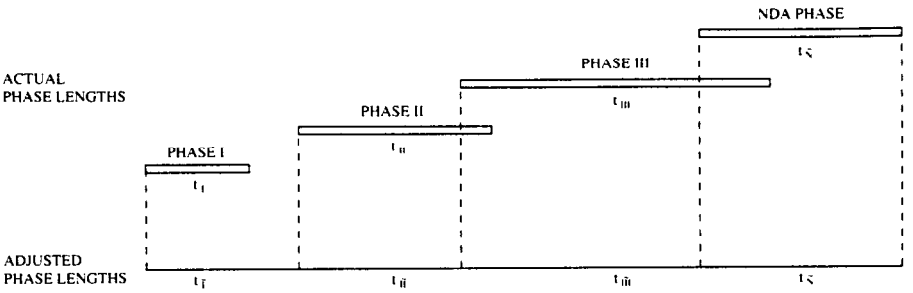

Fig. 2. Representative time profile for an NCE passing through all clinical development phases.

specific NCEs in a precise manner. Consequently, we use reported aggregate annual firm R&D expenditure data for the preclinical and clinical periods, and our previously estimated cost per approved NCE estimate, C_u, to derive P_u, the uncapitalized preclinical cost per approved NCE. Specifically, we use aggregate data to estimate the ratio of preclinical period to total expenditures, λ. We then estimate P_u from the identity $\lambda \equiv P_u/(C_u+P_u)$, or $P_u \equiv [\lambda/(1-\lambda)]C_u$. Estimated total uncapitalized cost per approved NCE is given as C_u+P_u.

4.2. Expected capitalized costs

To include the opportunity cost of funds invested in NCE R&D for a full cost estimate, we capitalize the mean phase costs to the point of marketing approval using a representative time profile for an NCE passing through all clinical period testing phases; use of a representative time profile yields a lower bound on costs. Weighted mean phase lengths, t_i, are calculated for our survey NCEs in the same manner as weighted mean phase costs.

It is generally not the case that a phase will begin exactly when the preceding phase ends. In many instances there is a significant overlap for successive phases. There can also be gaps between phases. To construct a time profile we reduce each calculated mean phase length by the weighted average overlap of that phase with the next (or add to the phase length for a gap).[18] Figure 2 depicts a hypothetical time profile. The adjusted mean phase lengths, $t_{\tilde{i}}$, are used to determine where in the time profile phase costs begin. Hence, the time from the start of phase I to NDA approval, T, is given as $T=t_{\mathrm{I}}+t_{\tilde{\mathrm{II}}}+t_{\tilde{\mathrm{III}}}+t_{\tilde{N}}$, where $t_{\tilde{N}}$ is average NDA review time. We measure the time from the start of a phase to the expected approval date, z_j, as $z_j=\sum_{\tilde{i}=0}^{j-1} t_{\tilde{i}}$, with $t_0=0$.

Mean long-term animal testing time, t_A, is calculated in a manner identical

[18]For phase III the succeeding phase is the period during which the NDA is under review.

to that used for the actual mean durations of the clinical trial phases. The length of this phase, however, is not adjusted for an overlap (or gap) with other phases. We need to determine, though, how this testing fits into our representative time profile. The weighted mean time from the start of phase I to the start of long-term animal testing, t_{IA}, can be calculated. We then consider long-term animal testing costs to begin t_{IA} units of time after the start of phase I.

Phase costs are assumed to be distributed uniformly over actual mean phase lengths and capitalized at the discount rate r. Specifically, capitalized mean phase costs, c_j, are determined as follows, where the index values 1, 2, and 3 refer to phases I, II, and III, respectively.

$$c_j = \int_{z_j - t_j}^{z_j} (\bar{x}_j/t_j)\, e^{rt}\, dt \quad \text{for } j = 1, 2, 3. \tag{1}$$

Capitalized long-term animal testing costs, c_A, can be found in a similar fashion.[19]

An estimate of expected capitalized clinical period cost per NCE tested in humans, $\hat{c}$, can be obtained as $\hat{c} = s_I c_I + s_{II} c_{II} + s_{III} c_{III} + s_A c_A$. Transforming this into a cost per marketed NCE, C_c, requires only the approval success rate. In particular, we have $C_c = \hat{c}/s$.

Eq. (1) implies continuous compounding. The discount rate estimates we use are based on discrete compounding. It is possible, though, to find a continuous rate, r, that is equivalent to any discrete rate (with regard to monetary value after the same amount of time).[20]

Preclinical costs can be capitalized to the point of marketing approval in the same way that phase costs are in eq. (1). The average duration of the preclinical period, t_p, can be estimated using data on preclinical development times from a CSDD database on approved NCEs. Capitalized preclinical cost per approved NCE, P_c, can then be given as

$$P_c = \int_{T}^{T+t_p} (P_u/t_p)\, e^{rt}\, dt. \tag{2}$$

4.3. Cost of capital for pharmaceutical R&D

In selecting a baseline cost of capital for this analysis, we sought a

[19]Specifically, capitalized long-term animal testing costs can be computed as

$$c_A = \int_{t_A^L}^{t_A^U} (\bar{x}_A/t_i)\, e^{rt}\, dt, \quad \text{where } t_A^U = T - t_{IA} \text{ and } t_A^L = t_A^U - t_A.$$

[20]For example, if the relevant discrete rate is 10%, we use $r = 0.095$.

representative value for the pharmaceutical industry over the period spanned by the development of the drugs in our study. Our sample includes NCEs first tested in humans between 1970 and 1982. The marketing approval dates for this sample centers around the mid 1980s, with a few compounds still in active research. Hence, we want a cost of capital measure that essentially covers the period between 1975 and 1985 where the bulk of the expenditures are concentrated.

Our baseline analysis employs a 9% real cost of capital. This value is based on a recent study on R&D returns [Grabowski and Vernon (1990)]. The study applied the capital asset pricing model (CAPM) to a portfolio for a representative sample of pharmaceutical firms for each of the years from the mid 1970s to the mid 1980s. Over this period, the equity cost of capital for this representative group of firms clusters around 9%.[21] The capital structure of the pharmaceutical industry is overwhelmingly equity financed (in excess of 90%). Hence, their estimated 9% cost of equity capital offers a good proxy for the overall cost of capital.[22]

Hansen (1979) utilized an 8% cost of capital. That study focused on an earlier time period (i.e. R&D expenditures in the 1960s and 1970s). Although the 8% value was not based explicitly on a CAPM analysis, it is generally consistent with the values emerging from analyses for the relevant period of that study [see, e.g., Statman (1983)]. The slightly higher cost of capital utilized in the present study essentially reflects the trend toward higher real interest rates during the past decade [Feldstein (1988)]. Although a 9% real cost of capital measure is employed as our preferred estimate in the baseline analysis, we also perform sensitivity analysis using values significantly above and below this value.[23]

5. Data

Twelve U.S.-owned pharmaceutical firms agreed to participate in this study and provide, on a confidential basis, information on their self-

[21]An analysis of investment riskiness for this portfolio of pharmaceutical firms was undertaken and indicated that pharmaceutical firms generally had comparable riskiness to the market over the period (i.e. betas approximately equal to one). Long-term estimates on risk-free rates and market rates were obtained from Ibbotson Associates [Grabowski and Vernon (1990, p. 806)].

[22]One can compute a weighted cost of capital, taking account of how much debt relative to equity is held by pharmaceutical firms, as well as the tax deductibility of debt compared to equity [see Statman (1983)]. Since the percentage of capital held in the form of debt is minimal over this period, this does not change the computed 9% value in an appreciable manner.

[23]An alternative approach for estimating the cost of capital would be to utilize the arbitrage pricing model (APT). Some preliminary analysis applying the APT to the pharmaceutical industry by one of the authors suggests higher values for the cost of capital than that obtained from the CAPM. The hurdle rates employed by pharmaceutical firms also tend to suggest somewhat higher values for the cost of capital [Grabowski and Vernon (1990)].

originated NCE development activities (a copy of the questionnaire is available upon request).[24] These firms include a number of the largest in the U.S. pharmaceutical industry, as well as some that are small in size. From 1980 to 1986, these firms accounted for approximately 40% of U.S. industry R&D expenditures on ethical pharmaceuticals.[25]

We limited our study to self-originated NCEs since the full research and development expenditures for licensed and acquired NCEs would not be reflected in the acquiring firm's R&D accounts. The NCEs included in the study were first tested in humans during the period 1970–1982. Most of the NCEs from this period that eventually emerge as approved drugs will have entered the market in the 1980s or early 1990s. We did not extend the sample past 1982 since many of the later NCEs would still be in early testing at the time of the survey.

To construct a representative sample of NCEs tested during this period we used information from a CSDD database on investigational NCEs. This database, obtained from a triennial survey of the U.S. pharmaceutical industry,[26] provided us with information on the origin, therapeutic area, and development status of NCEs first tested in humans during the period 1970–1982. This information allowed us to identify the survey firm NCEs that met our study inclusion criteria (i.e. self-originated NCEs first tested in humans during the period 1970–1982), and to select a random sample of survey firm NCEs.[27] Detailed information was requested from each firm for the NCEs that we selected.

The firms provided data on 93 NCEs, or 19% of all NCEs in the CSDD database that met inclusion criteria. The NCE therapeutic class distributions for the sample and population are nearly identical. For the NCEs selected, firms provided clinical period phase beginning and ending dates, costs by year of clinical testing, and the date testing was suspended on those NCEs for which research was abandoned.

Aggregate pharmaceutical R&D expenditure data for the years 1970–1986 were also provided by the survey firms. The firms reported total annual pharmaceutical R&D expenditures broken down into expenditures on self-originated NCEs, on licensed or otherwise acquired compounds, and on existing approved products. For firms as a whole during the period 1970–

[24]A number of these firms had several major pharmaceutical divisions. Counting these as separate units, data were obtained from 15 divisions.

[25]One of the survey firms was not able to break out pharmaceutical R&D from total R&D expenditures for the 1970s. The industry level is the aggregate of PMA member firm real pharmaceutical R&D expenditures over the period 1980–1986 (computed from data in PMA Annual Survey Report, 1987–1989).

[26]At the time the sample was selected, 43 firms were included in the database, 34 of them U.S.-owned.

[27]The eligible NCEs were first stratified as described in section 4, and a random sample was selected from each strata.

Table 2

Average out-of-pocket clinical period costs for NCEs tested in humans (in thousands of 1987 dollars).[a]

Testing phase	Mean cost	Standard deviation of phase costs	Median cost	N^b	Probability of entering phase (%)	Expected cost
Phase I	2,134	4,519	960	87	100.0	2,134
Phase II	3,954	5,230	2,175	70	75.0	2,966
Phase III	12,801	13,974	7,888	36	36.2	4,634
Long-term animal	2,155	2,411	1,336	49	56.1	1,209
Other animal	648	1,183	129	15	15.8	102
Total						11,045

[a]All costs were deflated using the GNP Implicit Price Deflator. Weighted values were used in calculating means, standard deviations, medians and the probability of entering a phase.

[b]N = number of NCEs with full cost data for the phase.

1986, 73.7%, 16.3%, and 10.0% of total pharmaceutical R&D expenditures were spent on self-originated NCEs, existing approved products, and licensed and acquired compounds, respectively. Annual total expenditures for self-originated NCE R&D were further broken down according to whether they were incurred during the preclinical or clinical periods (since firms are generally unable to allocate all preclinical costs to individual NCEs, data were not obtained on preclinical expenditures for specific NCEs).

The firms did not provide full phase cost data for every NCE that entered a given phase, either because that phase was ongoing on the survey date or records were incomplete. Costs were not included in computations if the phase was ongoing or cost data were missing. Only nine NCEs were continuing in research on the survey date, and for each of them complete information is available for some phases.

6. Baseline cost estimates

6.1. Clinical cost per investigational NCE

Using the weighting procedure described in section 4, mean phase costs were calculated and are presented in table 2. All costs were deflated using the GNP Implicit Price Deflator and are given in 1987 dollars.[28] Since a

[28]The GNP Implicit Price Deflator measures changes in the prices of the nation's output. Ideally, we would want to use an index based on pharmaceutical R&D input prices. No such index, however, exists. Other indices which we considered were judged to be less appropriate than the GNP Implicit Price Deflator. The Producer Price Index is determined solely by manufacturing output prices. Mansfield (1987) develops an R&D input price index applicable to a number of industries for the years 1969–1983. The closest match to the pharmaceutical industry is the chemicals and oil category. Only a few pharmaceutical firms, however, were

number of firms reported clinical period animal testing other than the long-term animal tests, we reported their costs as other animal costs. On average, however, they constitute a very small portion of total costs.

The phase to phase attrition rates in column 6 of table 2 are roughly consistent with alternative estimates in an FDA study [Tucker et al. (1988)]. That study used FDA records to follow the progress of the new molecular entities (NMEs)[29] for which INDs were filed during the years 1976–1978. Based on their records and a mathematical model to project future outcomes, they found 70% of the NMEs entering phase II and 33% entering phase III.

Average costs vary substantially by clinical development phase. Phase II costs are nearly twice as large as phase I costs. The large-scale clinical trial costs of phase III are about six times as large as phase I costs. These are averages, however, and the third column of table 2 reveals substantial variation in individual NCE testing costs for each phase. The phase cost distributions are also positively skewed, as indicated by the differences between mean and median costs.

Since there is substantial attrition of NCEs prior to the more expensive phases II and III, expected phase costs rise less steeply than mean costs. For example, expected phase III costs are only slightly more than twice as large as expected phase I costs. Our estimate of the expected clinical period cost for NCEs tested in humans is $11.0 million in 1987 dollars.

6.2. *Capitalized clinical cost per investigational NCE*

To calculate the capitalized value of clinical period expenditures, we computed adjusted phase lengths and constructed a representative develop-

(footnote 28 continued)

included in the sample. We deemed the chemicals and oil index too broad-based to use. Extrapolation of the index through 1987 would also have been necessary. We also considered an index developed for biomedical R&D [U.S. Bureau of Economic Analysis (1986)], but judged it to be too dependent on the university research sector. However, we did apply alternative price indices to our cost data and found the following to be the case in general. The Producer Price Index resulted in overall cost estimates that were roughly 10% lower than those obtained with the GNP Deflator. We regressed Mansfield's chemicals and oil index on the GNP Deflator to obtain predicted Mansfield index values for 1983–1987. Applying the expanded Mansfield index resulted in overall costs that were approximately 10% higher than the GNP Deflator estimates. Use of the biomedical R&D index resulted in about a 10% increase in costs relative to those for the Mansfield index.

[29]The FDA definition of an NME differs somewhat from our definition of an NCE. One difference is that the FDA includes diagnostic agents and we do not. Another difference is that we include a few therapeutically significant biologics, whereas the FDA does not include any. Aside from the fact that we study a longer time period, an additional reason why the FDA study results are not precisely comparable to ours is that their drugs include some that were licensed or acquired. Presumably these drugs were prescreened to some extent, and so we might expect them to have success rates higher than those for self-originated new drugs. The impact of the other differences, however, is unclear.

Table 3

Average phase lengths and clinical period capitalized costs for NCEs tested in humans (in thousands of 1987 dollars).[a]

Testing phase	Mean phase length (actual)[b]	Mean phase length (adjusted)[b]	Time from phase start to approval[c]	Capitalized mean phase cost[d]	Capitalized expected phase cost
Phase I	15.5	16.2	98.9	4,103	4,103
Phase II	24.3	22.5	82.7	6,564	4,924
Phase III	36.0	29.9	60.2	17,370	6,288
Long-term animal	33.6	33.6	78.7	3,366	1,889
Other animal	33.6	33.6	78.7	1,012	159
Total					17,363

[a]All costs were deflated using GNP Implicit Price Deflator.
[b]Mean phase lengths and the time from the beginning of a phase to NDA approval are given in months. Weighted values were used in calculating mean phase lengths.
[c]The NDA review period was estimated to last 30.3 months. Animal testing was estimated to start 4.0 months into phase II.
[d]Costs were capitalized at a 9% discount rate.

ment time profile as described in section 4.2. The actual and adjusted phase lengths presented in table 3 indicate, on average, a very small gap (0.7 months) between the end of phase I and the beginning of phase II, and an overlap of phase III with both phase II (1.8 months) and the NDA review phase (6.1 months). The mean NDA review time for self-originated NCEs first tested in humans during 1970–1982 by U.S.-owned firms (30.3 months) was determined from a CSDD database. Long-term animal testing began, on average, 20.2 months after phase I testing commenced.[30] Our estimated time profile has a length of 98.9 months from the initiation of clinical testing to NDA approval. The time from the start of phase I testing to NDA submission is 68.6 months.

The expected capitalized cost per NCE tested in humans for the entire clinical period is $17.3 million in 1987 dollars. Of that amount, 36% is accounted for by interest costs.

6.3. Clinical costs per approved NCE

To relate costs to the number of approved NCEs, we need a clinical period approval success rate estimate. While phase success rates could only be obtained from information in our cost survey, approval success rate estimates can be obtained using a broader sample contained in CSDD databases on investigational and approved NCEs. Our methodology for estimating the

[30]Other animal testing sometimes occurred before long-term animal testing, sometimes after it, and at still other times both before and after it. No tendency in relation to the timing of long-term animal testing was apparent. As an approximation, then, we distributed other animal costs over the long-term animal testing period.

approval success rate is similar to that used in Sheck et al. (1984) and is described in appendix B. Evidence that the predictive power of our model is quite high is presented in the appendix.

The base clinical success rate for the cost survey firms (23%) is utilized to determine clinical cost *per approved NCE* from our prior estimates of clinical cost *per investigational NCE* presented in tables 2 and 3. In particular, dividing our prior cost estimates by the success rate of 23% yields estimates of clinical costs per approved NCE. Utilizing a 9% discount rate, the capitalized clinical cost per approved NCE is estimated to be $75 million, while the uncapitalized cost per approved NCE is $48 million. This contrasts with estimates of $17.3 and $11 million for capitalized and uncapitalized cost per investigational NCE, respectively.

6.4. Preclinical costs

In the preceeding sections we reported expected clinical period development costs calculated from project specific data. Many costs incurred during the preclinical period cannot be directly assigned to specific NCEs. Moreover, some specific development projects are abandoned prior to reaching the clinical stage. The activities in the preclinical period are essential to the eventual development of NCEs and the expenditures during this period should be allocated to approved NCEs to determine the total cost of developing a new pharmaceutical.

The activities during the preclinical period lead to a flow of NCEs into clinical testing. As described in section 4.1, we use the ratio of uncapitalized preclinical to clinical expenditures and our estimate of the uncapitalized clinical period cost per approved NCE to allocate preclinical costs to approved NCEs. In order to estimate λ, the preclinical period portion of total R&D costs, we need to confine our analysis to those expenditures that involve self-originated NCEs. Therefore, in our survey we requested annual expenditures on self-originated NCE R&D by preclinical and clinical periods for each of the survey firms for the years 1970–1986.

In the aggregate, 66.1% of total self-originated NCE R&D was spent during the preclinical period. Both the preclinical and clinical expenditure series, however, tend to increase in real terms over the survey period. Since clinical period expenditures lag behind preclinical costs, the ratio of preclinical period real R&D expenditures to total real R&D expenditures overestimates the true preclinical period contribution to the total. A lag structure for the aggregate data, based on average lengths of the preclinical and clinical periods, can be imposed to better estimate λ.

The mean length of the preclinical period for self-originated NCEs of U.S.-owned firms first tested in humans during 1970–1982 was estimated from data in a CSDD database on approved NCEs to be 42.6 months. Our

Table 4

Expected phase costs per marketed NCE (in millions of 1987 dollars).[a]

Testing phase[b]	Uncapitalized expected cost	Mean phase length (actual)	Capitalized expected cost[c]
Preclinical	65.5	42.6	155.6
Phase I	9.3	15.5	17.8
Phase II	12.9	24.3	21.4
Phase III	20.2	36.0	27.1
Long-term animal	5.3	33.6	8.2
Other animal	0.4	33.6	0.7
Total	113.6		230.8

[a]All costs were deflated using the GNP Implicit Price Deflator. A 23% clinical approval success rate was utilized.

[b]The NDA review period was estimated to last 30.3 months. Animal testing was estimated to start 4.0 months into phase II.

[c]Costs were capitalized at a 9% discount rate.

representative time profile suggests a clinical period duration (inclusive of phase III testing after NDA submission) of 74.7 months. We approximate the lag between preclinical and clinical period aggregate expenditures by computing the time between the midpoint of the preclinical period to the midpoint of the clinical period.[31] Thus, our base case lag is 5 years and the corresponding value of λ is 0.577. Hence, our previously estimated uncapitalized clinical cost is multiplied by a factor of 1.36 to obtain an estimate of uncapitalized preclinical cost ($P_u \equiv [\lambda/(1-\lambda)]C_u$).

Using the 5 year lag, uncapitalized and capitalized preclinical costs are \$66 and \$156 million, respectively. For lags of 4 and 6 years (adjusting at the same time the assumed duration of the preclinical period), the uncapitalized costs are \$69 and \$63 million and the capitalized costs are \$152 and \$166 million, respectively. Thus, our preclinical cost estimates are not very sensitive to reasonable variation in the lag.

6.5. Total expected cost per approved NCE

Given the preferred 5 year lag, discount rate of 9%, and clinical success rate of 23%, total capitalized cost per approved NCE is shown in table 4 as \$230.8 million. Preclinical research activities, because they occur much earlier in time, entail significantly greater interst costs than do clinical activities. In particular, interest costs represent 58% of preclinical costs (\$90 million of

[31]Survey data on phase costs were provided by year of clinical testing. Computing costs by year from the start of phase I testing revealed that the midway point of the clinical period (37.35 months) corresponds roughly to the time of maximum expected cost per NCE tested in humans.

Table 5

Preclinical, clinical, and total capitalized expected costs per marketed NCE at alternative approval success rates and discount rates (in millions of 1987 dollars).[a]

	Capitalized costs					
	0%	5%	8%	9%	10%	15%
(A) *Success rate*: 25%						
Preclinical	61	98	131	144	156	247
Clinical	44	57	66	69	73	93
Total	105	155	197	213	229	340
(B) *Success rate*: 23%						
Preclinical	66	107	142	156	170	269
Clinical	48	62	72	75	79	101
Total	114	169	214	231	249	370
(C) *Success rate*: 20%						
Preclinical	76	123	163	179	196	309
Clinical	55	71	83	86	91	116
Total	132	194	246	265	287	425

[a]All costs were deflated using the GNP Implicit Price Deflator. Clinical period expenditures were assumed to represent 42.3% of total R&D expenditures. The corresponding assumed preclinical phase length is 42.6 months.

$156 million), whereas they represent only 36% of clinical costs ($27 million of $75 million).

Table 5 allows us to examine how sensitive our estimate of total R&D cost per approved NCE is to variations in two key parameters – the clinical success rate and the discount rate. If we take as plausible ranges on these parameters a discount rate of 8 to 10% and a clinical success rate of 20 to 25%, the corresponding range in R&D cost per approved NCE is between $197 and $287 million. This provides some bounds around our estimate of $231 million per approved NCE by allowing for uncertainty in the values of these important parameters.

6.6. Comparison with Hansen's analysis

It is interesting to compare our base case average cost estimates with the preferred estimates in Hansen (1979), and measure the contribution to the apparent increase in costs of changes in several factors. In 1987 dollars Hansen's total capitalized cost estimate is $100.5 million, while his clinical period capitalized cost estimate is $39.2 million, Thus, in real terms, total capitalized costs are about 2.3 times larger here than in Hansen; clinical

period capitalized costs are about 1.9 times larger. Assuming both sets of estimates are correct for their respective covered time periods, we can examine how much of the cost increases are due to differences in a given determinant of cost, holding all other determinants fixed.

Ignoring second-order interaction effects we may state the following. Table 5 reveals that the higher opportunity cost of capital used here (9% as opposed to 8%) results in an increase in cost amounting to 13.0% of the measured increase in total cost between the two studies.

R&D and regulatory review times are somewhat longer here. Our results show essentially no difference in phase II duration, but there is a 7.1 month increase in phase I duration and a 7.3 month increase for phase III. Regulatory review time and the preclinical period are 6.3 and 6.6 months longer here, respectively. Our longer development and regulatory review times result in total cost increases amounting to 23.9% of the measured increase in total costs.

The effects on total costs of changes in the discount rate and phase development times, taken together, constitute the change in time costs between the two studies. The residual proportion of the measured increase in total costs (63.1%) can be viewed as that part of the change in measured total costs that is due to changes in out-of-pocket costs. Out-of-pocket costs are dependent on the clinical approval success rate, the probabilities of entering the various phases, and the mean uncapitalized phase costs.

Mean uncapitalized preclinical period and clinical phase costs are substantially higher here and account for the bulk of the increase in out-of-pocket costs. In constant dollars, phases I, II, and III mean uncapitalized costs are 3.9, 1.4, and 2.5 times larger here than in the Hansen study. Similarly, long-term animal and preclinical costs are 1.6 and 3.7 times larger here, respectively. The phase-to-phase success rates estimated here are higher than those reported by Hansen,[32] but their cost increase effect is more than offset by the cost reducing effect of a higher clinical approval success rate.

6.7. *Reductions in development and review times*

Since our estimates of the full cost of developing a new pharmaceutical include an implicit interest charge, changes in the timing of expenditures will affect the full cost. Firms may be able to shorten development times by doing parallel, rather than sequential, studies. Clinical trial phase lengths may also

[32]Fewer drugs are screened out in phases I and II here relative to the earlier study. The probability of reaching phases II and III are 75% and 36% in this study and 50% and 19% in the Hansen study, respectively. The probability of approval conditional on reaching phase II has increased from 25% to 31%, but the approval probability conditional on entering phase III has remained virtually unchanged (65.8% previously vs. 63.5% currently).

Table 6

Impact on capitalized expected costs per marketed NCE of one-year reductions in average phase lengths (in millions of 1987 dollars).[a]

One-year reduction	Total capitalized expected cost[b]	Reduction in total cost
Preclinical	224	8
Phase I	218	13
Phase II	215	16
Phase III	213	18
NDA review	212	19

[a]All costs were deflated using the GNP Implicit Price Deflator. A 23% clinical approval success rate was utilized.
[b]Costs were capitalized at a 9% discount rate.

be shortened if the conferences now held between the FDA and sponsor firms during the development period provide firms with a better understanding of what will be necessary for approval. Reductions in the average length of the NDA review phase would shorten the time between R&D expenditures and marketing approval and so lower total costs.

In table 6 we present estimates of the effects of a 1-year reduction in phase duration (holding mean phase costs constant). The largest cost reduction ($19 million or 8.2% of total cost) is for a 1-year reduction in the NDA review phase. The reason the NDA phase carries the greatest impact is that a reduction in any phase length decreases the capitalized cost for that phase and for all prior phases.

Since preclinical costs are a large portion of the total cost, even a 1-year reduction in phase I produces savings of $13.5 million per approved NCE. Approval rates during the 1980s have averaged 19 per year. Thus, our results suggest that 1-year reductions in the clinical development or regulatory review phases would, holding all else constant, produce annual savings of $257 to $361 million in 1987 dollars.[33]

The activities required to shorten development times may require additional out-of-pocket costs. For example, doing studies in parallel may result in performing tests that would not have been performed had the results of the other tests been known. Shortening the NDA review period may require additional resources for the FDA. The cost of achieving a reduction in development times must be compared to the estimated savings in implicit interest costs. Within a broader context, one should also consider the effects on product lifetimes and associated sales revenues from having earlier marketing dates, and the benefits to society from having effective medications available for patient use sooner.

[33]It is worth noting that the entire FDA budget for fiscal year 1988 was $478 million, with $169 million spent on salaries and expenses for the human drugs and biologics divisions [U.S. Department of Health and Human Services (1990)].

7. Cost estimates for subsamples

7.1. Within-sample period effects

We examined whether it is possible to discern time trends in our data. The sample did not contain enough information to investigate costs on a year-to-year basis, so we divided the sample into two time periods (NCEs first tested in humans during the periods 1970–1976 and 1977–1982). The distribution of population NCEs over the strata used in the weighting scheme for the full sample differed by period. Consequently, we reweighted NCEs for each period according to the sample and population strata proportions for that period.

Mean phase III development time and cost are significantly lower for the more recent period, but these data are not complete. In particular, NCEs with long development times will be underrepresented in the late period. At this point, meaningful comparisons across periods of phase III costs cannot be undertaken. However, counting only phase I and phase II costs, the 1977–1982 period uncapitalized costs are 100.5% higher than those for the 1970–1976 period. This suggests a strong upward time trend in out-of-pocket clinical costs.

7.2. Clinical period costs for approved NCEs

The cost of development may differ between successful and unsuccessful projects. To investigate this, we examined costs for the approved NCEs in our sample. We had complete cost data on 22 of the 27 NCEs that had obtained marketing approval as of October 31, 1990. One of the 22 NCEs is an extreme outlier with respect to cost and was removed from the approved NCE subsample.[34] It was retained for the full sample results. Given the much larger sample size and the small weight this NCE received in the weighting scheme used for the full sample, its impact on the full sample results is minor.

Table 7 offers a comparison between mean phase costs and lengths for the approved NCEs and those for all sample NCEs. Development times are very similar. However, except for early clinical testing (phase I), phase costs are significantly higher for the approved NCEs. This may reflect a tendency to direct more resources, perhaps through conducting more studies concurrently, to the NCEs that early clinical testing suggests have the greatest promise of approval. Table 7 also shows that, as is the case for the full

[34]Both the uncapitalized and capitalized clinical costs of the outlier are roughly double those of the approved NCE with the next highest clinical costs.

Table 7

Clinical period average phase costs and phase lengths for approved NCEs and for all sample NCEs (in thousands of 1987 dollars).[a]

	Approved NCEs[b]			Full sample[c]		
Testing phase	Mean phase cost	Standard deviation of phase costs	Mean phase length (actual)	Mean phase cost	Standard deviation of phase costs	Mean phase length (actual)
Phase I	2,475	2,957	14.0	2,134	4,519	15.5
Phase II	5,629	4,138	25.9	3,954	5,230	24.3
Phase III	20,024	14,016	36.8	12,801	13,974	36.0
Long-term animal	3,646	3,065	37.4	2,155	2,411	33.6
Other animal	1,777	2,300	37.4	648	1,183	33.6

[a]All costs were deflated using the GNP Implicit Price Deflator.
[b]Estimates for approved NCEs are based on data for 21 of the 93 sample NCEs.
[c]Weighted values were used in calculating means and standard deviations for the full sample estimates.

sample, substantial variation exists in the costs of individual approved drugs for each phase.

The uncapitalized mean clinical period cost for the approved NCEs is \$31.9 million; the median cost is \$31.0 million. The 95% confidence interval for mean out-of-pocket clinical period cost is \$31.9 ± 7.7 million.[35] Since we have approval dates for these drugs, it was not necessary to use a representative time profile; costs were capitalized to the point of actual marketing approval. Mean capitalized clinical period cost for approved NCEs is \$43.0 million; median capitalized cost is \$40.9 million. The 95% confidence interval is \$43.0 ± 11.3 million.[36,37]

The FDA rates new drugs according to whether the drug represents an important therapeutic gain (A), a moderate therapeutic gain (B), or little or no therapeutic gain (C) over existing therapy. To get a sense for whether the cost of developing NCEs is related to their therapeutic importance, we

[35]A chi-squared goodness-of-fit test was used to compare the sample frequency distribution of uncapitalized clinical period costs to a normal probability distribution. The hypothesis of no difference in distributions could not be rejected. Hence, we used a t-distribution in constructing the confidence interval.

[36]As is the case with uncapitalized costs, the hypothesis that the capitalized costs were taken from a normal population cannot be rejected.

[37]Given the right-censored nature of the data, approved NCEs with very long development times may be somewhat under-represented in the sample. We found a moderate positive correlation between capitalized clinical period cost and the time from the start of clinical testing to NDA approval (Spearman rank correlation coefficient = 0.661). Thus, reported costs for the approved NCEs may be somewhat biased downward.

computed costs for approved NCEs according to their therapeutic ratings.[38] Mean and median capitalized clinical period costs for the A and B rated approved NCEs are $51.7 and $41.5 million, respectively.[39] Costs for the C rated approved NCEs are somewhat lower – mean and median capitalized clinical period costs are $36.5 and $36.2 million, respectively.

8. An external check on the results

As an external check on our results, we analyzed the R&D performance of the U.S. pharmaceutical industry to see if it was consistent with our analysis. In particular, our approach is to relate industry R&D expenditures to the NCE introductions of U.S. firms (see fig. 1) using the same lag structure and time period in our study. However, since our study focuses on the self-originated NCEs of U.S.-owned firms, it is necessary to make various transformations of the publicly available industry data before meaningful comparisons can be undertaken.

For the cost survey firms, we determined the proportions of their aggregate pharmaceutical R&D expenditures that were spent on self-originated NCEs (73.7%) and on licensed or acquired NCEs (10.0%). Published PMA industry R&D expenditure data, however, do not distinguish between what firms spend on self-originated NCEs and what they spend on licensed or acquired NCEs. The procedures we employ to estimate annual industry self-originated NCE R&D expenditures and how they can be related to annual NCE approvals are described in appendix C.

We averaged both lagged R&D expenditures and the number of approvals over the period 1979–1989.[40] Using an average of 7.3 industry self-originated approvals per year for this time frame, we found uncapitalized and capitalized cost estimates of $138 and $270 million, respectively. In 1983 there was only one approval of a self-originated NCE from a U.S.-owned firm. Excluding this outlier year yields 7.9 as an average annual number of

[38]Although the FDA gives an initial rating to investigational NCEs shortly after IND filing, we have information only on the final ratings for the approved NCEs in our sample. The FDA rating system must be viewed with caution when considered as a measure of therapeutic benefit since the FDA has rather limited information when it assigns the ratings. The ultimate clinical significance of some drugs may not become apparent until the drugs have been in widespread use for a number of years for the original approved indications, or until their effectiveness for additional indications has been noted in clinical practice.

[39]The A and B rated drugs were combined since there is only one A rated drug in the subsample. Of the remaining 20 approved NCEs, eight are B rated and 12 are C rated.

[40]Year-to-year cost estimates using aggregate data are highly variable because they are extremely sensitive to the denominator (number of self-originated NCE approvals) used for the calculations. Thus, to reduce variability in the estimate, we used average values for the numerator and denominator, as opposed to an average of the annual ratios of lagged expenditures to current approvals.

approvals, and reduces the uncapitalized and capitalized cost estimates to $127 and $250 million, respectively. Hence, our estimate of $231 million is comparable to what one obtains from a comprehensive aggregate analysis.

9. Conclusions and prospects for future research

We have estimated the average cost of new drug development from a large sample of self-originated NCEs that were first tested in humans during 1970–1982. Data were obtained from a confidential survey of 12 U.S.-owned firms. The average cost of NCE development was estimated to be $231 million in 1987 dollars (with $114 million of that paid out-of-pocket). A representative time profile for an NCE passing through all phases of development from synthesis to marketing approval extended nearly 12 years.

Cost estimates are substantially higher here than in previous studies; some of which, however, did not measure R&D cost fully or adequately. Our period of analysis is also more recent than the periods used for these other analyses. In particular, this study is the only one to date that has reflected in its estimates much of the sharp increase in pharmaceutical R&D expenditures that occurred during the 1980s.

The most recent study on the cost of new drug development [Wiggins (1987)] used R&D expenditure data that covered the period 1965–1982, but with full weight placed only on expenditures from 1967 to 1980. This can partially explain why costs in that study are much lower than those found here. Another, perhaps more important, reason is that Wiggins used expenditure and approval data for all NCE approvals. In particular, he did not differentiate between self-originated and licensed or acquired NCEs. The R&D expenditures incurred on new drugs up to the point of licensing or sale will not be included in U.S. industry (PMA) data if the drug originated from an overseas operation of a foreign firm. Our analysis of industry data revealed substantially lower company expenditures per new drug on licensed or acquired NCEs than is the case for self-originated NCEs.

When results here are compared to those of a previous study [Hansen (1979)] with a similar methodology, total cost is seen to have increased 2.3 times in real terms. Development times are longer and a higher discount rate is used. The bulk of the increase in cost per approved NCE, however, can be attributed to large increases in out-of-pocket costs.

That clinical trial costs have risen sharply in recent years is attested to in F–D–C Reports: The Pink Sheet (1989), where an executive of a major pharmaceutical firm reports that the information required to support NDAs has increased dramatically. Clinical trials for one of the firm's anti-infective NCEs approved in 1979 used 1,493 patients; the trials for a related anti-infective that the firm is currently developing will require testing on 10,000

patients. Also mentioned as factors leading to rising costs are the complexity and scope of the research required and the adoption of expensive new technologies. Another factor often suggested to explain increased costs is that firms are now focusing development more on treatments for chronic and degenerative diseases, which typically require longer and more expensive testing.

In many applications that utilize pharmaceutical R&D cost estimates, the relevant concept is the after-tax cost (e.g., rate of return analyses). R&D is typically expensed immediately, rather than depreciated during the life of the marketed product. If the firm has sufficient profits against which to expense the R&D, the net cash flow required to finance the R&D will be reduced by the amount of the tax savings. However, in contrast to an investment in an asset such as a building, which can be depreciated over its useful life for tax purposes, the investment in R&D necessary to bring a product to market cannot be depreciated during the years in which sales occur. Thus, the effect of expensing rather than depreciating R&D is one of changing the time at which the deduction occurs.

The R&D tax credit, enacted in 1981, was in effect for only part of our study period. Depending on changes in firm spending levels, the credit had differential impacts across firms. In aggregate, though, the impact of the credit on our cost estimates is likely to be minor.[41] Since we were only interested here in estimating social cost, rather than rates of return, we did not adjust for the timing of taxes or the extra credits.[42]

Further research on the cost of new drug development could profitably be directed at a detailed analysis of differences in costs across therapeutic classes. We will address this issue in future research. Another interesting topic for future research is whether trade-offs exist on the margin between clinical trial expenditures and NCE failure rates.

Our analysis has been directed to the R&D cost of self-originated NCEs from U.S.-owned firms. In future research it would be interesting to analyze the R&D costs of NCEs originating in other countries. This would be especially the case for Japan. Aggregate data suggests that R&D costs per

[41]If we use U.S. pharmaceutical industry R&D expenditure data, we can obtain a rough upper bound estimate of the effect of the R&D tax credit. Until the Tax Reform Act of 1986 was enacted, the annual credit was 25% of the increase in covered R&D expenditures over the average of R&D expenditures for the previous three years. The Tax Reform Act of 1986 reduced the credit to 20%. Nominal U.S. pharmaceutical industry R&D expenditures grew at an 11.7% compound annual rate of growth from 1978 to 1986. This implies a 6.8% subsidy if all expenditures are covered and the credit is 25%. Much of our clinical cost data and the bulk of the related preclinical expenditures, though, predate the credit. Thus, the tax savings relevant to our study are likely much less than 6.8% of total expenditures.

[42]The impact of the tax rate in rate of return studies may not be substantial. Grabowski and Vernon (1989) found their results little affected when sensitivity analysis was conducted on the tax rate parameter.

NCE originating in Japan are significantly lower than those in the United States [Grabowski (1990)]. At the same time, pharmaceutical R&D in Japan has different characteristics from that undertaken in the United States, and has produced significantly fewer NCE introductions in major markets outside of Japan. Given the increased policy interest in international competitiveness, the cost and determinants of R&D performed in different countries is likely to be an important question for future research.

It would also be instructive to compare the total costs for U.S. firms of originating a new drug in-house versus licensing or acquiring one externally. Our survey data indicate that the R&D costs incurred by U.S. firms for a self-originated compound is several times what they spend for a licensed or acquired NCE. This raises the issue of whether the licensing fees and other costs for externally acquired compounds exactly offset the higher R&D costs of self-originated NCEs. This is what would be expected in equilibrium, if the market for licensed and acquired NCEs is perfectly competitive. Whether this in fact has been true of recent experience in the pharmaceutical industry is an interesting topic for future research.

Another important topic for future work is the effect of firm size and the scale of R&D activities on the costs of new drug introductions. This topic is also likely to have significant policy interest, given the recent tendency toward increased consolidation of the pharmaceutical industry. In this regard, it would be useful to know whether this consolidation is motivated in part by higher real R&D costs or potential R&D scale economies.

Our R&D cost estimates should be a useful input to studies of the returns to current new drug introductions. It should be emphasized that rising real R&D costs do not necessarily represent a problem for pharmaceutical innovative activity. In particular, if the higher costs are reflective of higher probabilities of commercial success and/or higher average sales per new drug introduction, then strong incentives to undertake pharmaceutical R&D can be maintained even in the face of rising R&D costs. Hence, it will be important in future research to examine trends in innovative output and sales revenues, as well as R&D costs.

Finally, it should be emphasized that while our estimates are presented in 1987 dollars, they are not estimates of the cost of developing a new drug in 1987. The drugs included in the sample were first tested in humans between 1970 and 1982, and many of the successful candidates from this sample are entering the market in the 1980s and 1990s (the mean approval date for approved drugs in the sample was in early 1983, with future approvals expected to raise the mean to early 1984). However, the expected cost of developing a new drug for which testing begins in the late 1980s or the 1990s will be affected by changes in the process which have occurred since our sample period. The trends suggest that the cost will be higher than our estimate.

Appendix A

Estimated weighted mean phase cost, $\bar{x}_i$, is determined as follows (where the index values 1, 2, 3 and A refer to phases I, II, III and long-term animal testing, respectively):

$$\bar{x}_i = \sum_{j=1}^{n} w_j x_{ij} \Big/ \sum_{j=1}^{n} w_j n_{ij} \quad \text{for } i = 1, 2, 3 \text{ and A}, \tag{A.1}$$

where

n = number of NCEs in the sample,

w_j = ratio of the % of population NCEs to the % of sample NCEs for the stratum in which NCE j falls,

$$x_{ij} = \begin{cases} j\text{th NCE phase } i \text{ cost} & \text{if the } j\text{th NCE has phase } i \text{ costs}, \\ 0 & \text{otherwise}, \end{cases}$$

$$n_{ij} = \begin{cases} 1 & \text{if the } j\text{th NCE has phase } i \text{ costs}, \\ 0 & \text{otherwise}. \end{cases}$$

For phases I, II, and III the estimated probability of entering a phase, s_i, is the product of the estimated conditional probability that the NCE will undergo testing in the phase given that the previous phase was entered, and the estimated probability of entering the preceding phase. For long-term animal testing, the estimate, s_A, is a weighted proportion of the sample NCEs that underwent that type of testing. Specifically, we have

$$s_i = \left(\sum_{g=1}^{G} \Theta_g \delta_{ig} \Big/ \sum_{g=1}^{G} \Theta_g \delta_{(i-1)g} \right) s_{i-1} \quad \text{for } i = 1, 2, 3, \tag{A.2}$$

$$s_A = \sum_{g=1}^{G} \Theta_g \delta_{Ag} \Big/ \sum_{g=1}^{G} \Theta_g \delta_g, \tag{A.3}$$

where

Θ_g = ratio of the % of population NCEs to the % of sample NCEs for stratum g,

δ_{ig} = number of sample NCEs in stratum g that entered phase i,

δ_g = number of sample NCEs in stratum g,

$s_0 = 1$,

$\delta_{0g} = \delta_g$.

With (A.1) and (A.2) an estimate of expected clinical period costs for a randomly selected NCE tested in humans, $\hat{E}$, can be expressed as $\hat{E} = s_I \bar{x}_I + s_{II} \bar{x}_{II} + s_{III} \bar{x}_{III} + s_A \bar{x}_A$. Given that the sample strata are prespecified, the

weights, w_j and Θ_g are not random variables. We can see, then, that $\bar{x}_i$ and s_i are unbiased estimates of the population mean phase i cost and the population proportion of NCEs entering phase i, respectively. There is no reason to expect that the weighted mean cost for a phase and the weighted proportion of NCEs entering that phase are correlated across independent samples. Under the assumption that $\bar{x}_i$ and s_i are stochastically independent, it can easily be shown that $\hat{E}$ is an unbiased estimate of $E(h)$.

Appendix B

The problem of estimating an approval success rate for the population of cost survey firm NCEs that meet survey inclusion criteria is modelled in two stages. Since the ultimate fate of some NCEs first tested in humans from 1970 to 1982 is, to our knowledge, not yet determined, survival analysis should prove useful [see Cox and Oakes (1984)].

In the first stage we estimate the distribution of times that the NCEs are in residence. For NCEs that have either been abandoned or approved by the end of 1986, we define residence time to be the time from first testing in humans to either research abandonment or NDA approval. Some NCEs were continuing in research as of the end of 1986. Data for such NCEs are right-censored. Survival analysis techniques utilize the information provided by censored observations.

In the second stage of the model, we estimate the probability that an NCE will meet a given fate (research abandonment or NDA approval) as a function of residence time. Thus, the cumulative probability of success (NDA approval) as a function of residence time, t, can be given as

$$S(t) = \int_0^t f(u)P(u)\,\mathrm{d}u, \tag{B.1}$$

where $f(u)$ is the probability density function for residence time, and $P(u)$ is the probability that an NCE with a residence of u receives NDA approval at that time. The density function can be estimated by a nonparametric product-limit technique.

The data on approvals at various residence times indicate that the process may be adequately approximated by a sigmoidally shaped distribution. Thus, we applied the logit and probit models to estimate $P(u)$. Both the logit and probit models provided good fits and, in fact, were virtually indistinguishable from one another.[43] Computed values of the likelihood ratio index deve-

[43]The transformation suggested in Amemiya (1981) for comparing coefficients in logit and probit models showed very small differences in the coefficients. The results on cumulative success rates are also virtually the same when logit and probit specifications for $P(u)$ are used.

loped in McFadden (1974) shows the probit model to have a slightly superior fit, and so the success rate estimates utilize the probit specification for $P(u)$.[44]

The cost survey firms investigated in humans 279 NCEs that met cost survey inclusion criteria.[45] As of December 31, 1989, 17.2% of these NCEs had been approved. Our model predicts that approximately 23% of the population NCEs will have been approved 14 years after first testing in humans. By the end of 1986 only four NCEs had been in residence longer than 14 years, and information obtained in the cost survey indicated that two of these NCEs had been abandoned. We use 23% as our base case clinical approval success rate.

Evidence of the predictive power of eq. (B.1) can be obtained by focusing on one subclass of NCEs. Taking note of dates of research abandonment obtained from the cost survey and approvals after 1986, we were able to completely characterize the fate of all anti-infective NCEs. The model (using data through 1986) predicted an approval success rate of 31.7% for this class, which compares very well with the actual final cumulative success rate of 31.0%.

Appendix C

The PMA publishes R&D expenditure data for its member firms (PMA Annual Survey Report, various years). From these data it is possible to extract annual expenditures for human use ethical pharmaceuticals. These expenditures, in real terms for the years 1967–1987, are given in the first column of table C.1.

At our request, we also obtained information from the PMA on the percentage of total R&D expenditures accounted for by U.S.-owned member firms. The PMA had such data only for recent years. We utilized the 1987–1988 percentage (84.3%) to estimate annual R&D expenditures by U.S.-owned firms (column 2 of table C.1). There is some evidence of a slight decrease in this percentage over time. Given the downward trend in this percentage, the values in column 2 are likely to be conservative estimates.

We next subtract foreign expenditures from the values of U.S.-owned R&D expenditures to obtain their domestic R&D expenditures (column 3 of table C.1). We include only domestic expenditures in our analysis under the assumption that the foreign expenditures of U.S.-owned firms will be directed

[44]Specifically, we used an iteratively reweighted non-linear least squares routine to estimate $P(u)=F(\alpha+\beta u)$, where u represents residence time in months and $F(\cdot)$ is the cumulative distribution function of the standard normal random variable. The maximum likelihood estimates of α and β are -2.3720 and 0.0244, respectively.

[45]The information needed to conduct the survival analysis was available for 276 of these NCEs.

Table C.1

U.S. pharmaceutical industry real human use R&D expenditures 1967–1987 (millions of 1987 dollars).[a]

Year	(1) All PMA firms	(2) U.S.-owned PMA firms[b]	(3) U.S. R&D of (2)[c]	(4) Self-originated R&D of (3)
1967	1,363	1,149	972	670
1968	1,400	1,180	1,058	729
1969	1,492	1,258	1,135	782
1970	1,583	1,334	1,203	829
1971	1,663	1,402	1,264	871
1972	1,684	1,420	1,253	863
1973	1,785	1,505	1,247	859
1974	1,870	1,576	1,282	883
1975	1,928	1,625	1,338	922
1976	1,989	1,677	1,367	942
1977	2,061	1,737	1,393	960
1978	2,123	1,790	1,468	1,011
1979	2,275	1,918	1,501	1,034
1980	2,549	2,149	1,593	1,098
1981	2,762	2,328	1,771	1,220
1982	3,100	2,613	2,047	1,410
1983	3,462	2,918	2,324	1,601
1984	3,726	3,141	2,513	1,731
1985	4,142	3,492	2,774	1,911
1986	4,703	3,965	3,101	2,137
1987	5,310	4,476	3,508	2,417

[a]Expenditures on R&D for ethical pharmaceuticals intended for human use were obtained from the PMA Annual Survey Report (various years) and deflated using the GNP Implicit Price Deflator.

[b]The expenditures for all firms in a year were reduced by the average percentage of member firm R&D expenditures accounted for by U.S.-owned firms for 1987 and 1988 (source: Gary Persinger, PMA).

[c]Computed based on U.S.-owned firm aggregate expenditure levels and data contained in the PMA Annual Survey Report (various years).

primarily to non-U.S. introductions. This assumption will also tend to produce conservative estimates, since at least some of the foreign expenditures of U.S.-owned firms are obviously directed towards approval of new drugs in the United States and other major world markets.[46]

The last step in the analysis is to determine the percentage of R&D that is devoted to self-originated NCEs by U.S.-owned firms. In particular, we need to separate such R&D expenditures from those on licensed or acquired NCEs and on R&D for improvements in existing products. It would be

[46]Although some of the domestic R&D expenditures of U.S. firms may be targeted specifically to products only introduced abroad, our approach will produce a conservative estimate so long as these outlays are smaller in value than the foreign R&D expenditures of U.S. firms that are related to domestic introductions. This appears to be a reasonable presumption given the tendency of U.S. firms to prescreen compounds abroad for the U.S. market.

Table C.2

New chemical entity approvals in the United States, 1979–1989.

Year	Total NCEs	U.S.-owned PMA member firm NCEs	Self-originated NCEs of U.S.-owned PMA firms[a]
1979	13	13	9
1980	11	9	6
1981	23	15	6
1982	22	18	11
1983	12	6	1
1984	21	15	8
1985	26	16	12
1986	20	13	8
1987	18	13	10
1988	16	8	5
1989	21	10	4

[a]Information on the origin of compounds was obtained from a Center for the Study of Drug Development annual survey of firms with U.S. NCE approvals and supplemented, when necessary, with published sources.

inappropriate to assume that the firms who did not participate in our survey have the same pattern of R&D allocations as our survey firms. NCE output data show that non-survey U.S.-owned firms are somewhat more reliant on licensed or acquired NCEs.[47] We assume that the R&D effort necessary to produce a self-originated NCE relative to a licensed or acquired NCE is the same for the survey and non-survey firms.[48] Using this approach, we estimate that the non-survey U.S.-owned firms devoted 60.6% of their pharmaceutical R&D to self-originated NCEs. Given this estimate, and the fact that our cost survey firms account for 48.3% of the total pharmaceutical R&D expenditures of all U.S.-owned firms, we can compute a weighted

[47]For the cost survey firms, 66.7% of their NCE approvals during the period 1979–1989 are self-originated. For the same period, only 48.1% of the approvals of other U.S.-owned firms are self-originated.

[48]In particular, the ratio of expenditures on self-originated NCEs per approval of NCEs of this type to the expenditures on licensed or acquired NCEs per approval of such NCEs was estimated to be 3.7 for firms in our survey. In other words, it takes nearly four times the R&D outlays to produce a self-originated NCE compared to the R&D necessary for a licensed or acquired NCE for our survey firms (ignoring licensing and acquisition fees). We assume that this ratio is the same for the U.S.-owned firms that are not in our survey sample. We also assume that the group of foreign-owned PMA member firms spent the same proportion of their U.S. pharmaceutical R&D on new products as did the survey firms. We then used information available in the PMA Annual Survey Report (various years) to estimate that non-survey U.S.-owned firms spent 78.3% of their pharmaceutical R&D on new products. Using these two estimates, together with information on the breakdown of NCE approvals between self-originated and licensed or acquired NCEs for non-survey U.S.-owned firms, we estimated that these firms spent 60.6% of their pharmaceutical R&D for self-originated NCEs.

average estimate of the percentage of pharmaceutical R&D performed by U.S.-owned firms for self-originated NCEs (66.8%) and apply it to the previously calculated values in column 3 of table C.1.

We also performed a parallel analysis for the U.S. NCE approvals between 1979 and 1989. These results are presented in table C.2. We first separated total NCE approvals into those emanating from U.S.-owned PMA member firms and all other firms. The NCEs from U.S.-owned PMA firms (shown in column 2) were then further subdivided into self-originated versus licensed or acquired NCEs. To classify NCEs into these sub-categories, we used the CSDD annual survey of NCE approvals together with information from related sources. For the 1979–1989 period, the last column of table C.2 shows the annual number of self-originated NCEs accounted for by U.S.-owned PMA member firms. We found that approximately 39% of all U.S. NCE approvals for this period were for self-originated NCEs of U.S.-owned PMA firms.

For a lag structure, we use the phase time profile and cost levels found in this study. This implies that approvals in one year should be associated with R&D expenditures lagged 2 to 12 years. Monthly expenditures were calculated and spread over this period according to the phase time profile.[49] Weights to be attached to each of the lag years can then be determined,[50] and used to estimate uncapitalized cost per approval. Given the time profile, weights for capitalized cost estimates can also be calculated.

[49]Data from a CSDD database were used to determine that NCEs approved over the last 15 years received their approvals, on average, eight months into the year of approval. This was used to establish the endpoints of the time profile.

[50]If approval occurs in year t_0, then the weights for years t_{-2} to t_{-12} are 0.038, 0.059, 0.075, 0.083, 0.072, 0.058, 0.105, 0.163, 0.163, 0.163, and 0.020, respectively. These weights represent the proportions of out-of-pocket expenditures incurred in the years prior to approval.

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