

# UPDATING THE COST OF A NEW CHEMICAL ENTITY

Dr Hannah E Kettler





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Office of Health Economics  
12 Whitehall, London SW1A 2DY

© February 1999. Office of Health Economics. Price £7.50

ISBN 1 899040 80 3

Printed by BSC Print Ltd, London.

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# 1 INTRODUCTION

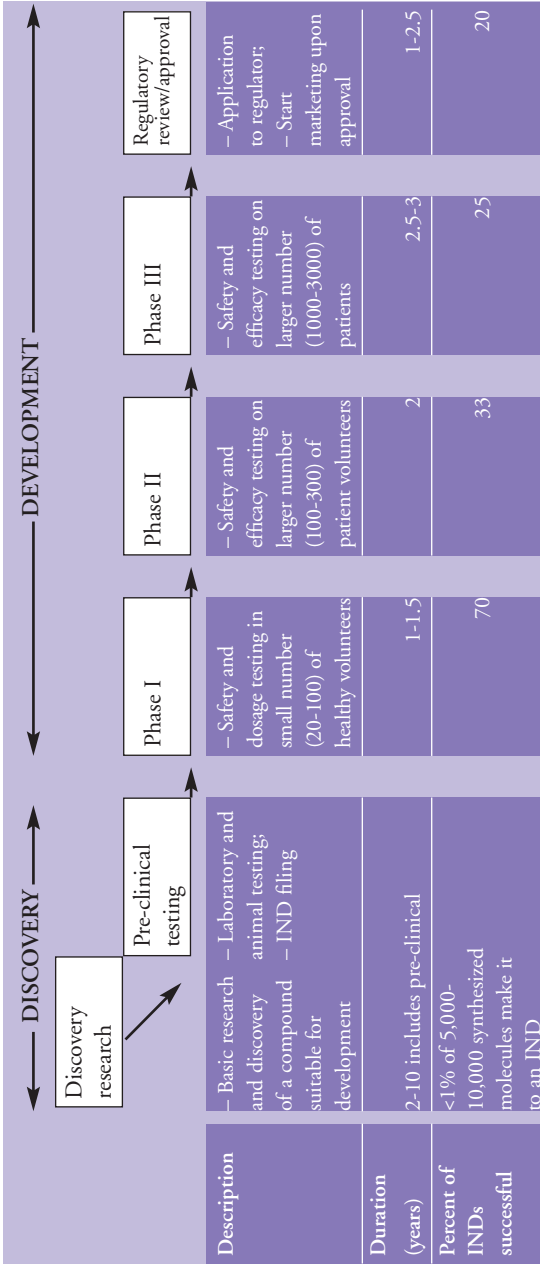
Pharmaceutical companies argue that they need to be able to charge prices sufficient to cover the high and increasing costs of discovering and developing new drugs. The funders of health care are understandably keen to pay no more than is necessary for new medicines. To determine what companies need to earn to achieve a reasonable return on their research and development (R&D) and so sustain future investment, economists need up-to-date estimates of R&D costs. Unfortunately even the best cost estimates in the existing literature are outdated, based on a sample of products that first entered clinical trials in humans in the US between 1970 and 1982. I argue in this paper that these old estimates no longer reflect the companies' actual costs structures because of changes in the pharmaceutical industry's scientific potential, technology and organization in the 1980s and early 1990s. The net positive result of these changes means it costs more to bring a new chemical entity (NCE) to market now than inflation-adjusted estimates based on old figures suggest.

To a greater degree than other industries, the costs of new pharmaceutical products' R&D are difficult to predict in advance because of the lengthy and uncertain processes of discovery, screening, clinical testing, and regulatory approval each product goes through. These processes take an average of 12-15 years in the United States (DiMasi et al., 1994) although some NCEs take considerably less time to get to market (Centre for Medicine's Research (CMR) International, 1998). Furthermore, it is commonly asserted that only 1 in 10 compounds which enter the clinical evaluation stage eventually enter the market (Jones, 1995). Figure 1 shows the R&D life cycle for a NCE, the average time a company takes to complete each stage, and estimates of the percent of investigational new drugs (INDs) – drugs the US Food and Drug Administration (FDA) approves for human testing<sup>1</sup> – that successfully complete each phase<sup>2</sup>.

1 The Clinical Exemption Certificate is the British equivalent to the US's IND. The process to initiate clinical testing is much more involved in the US however.

2 In Figure 1, the discovery phase includes basic research and the pre-clinical testing stages and the development phase includes the three clinical trial stages and regulatory approval. Some authors refer to the discovery phase as the 'pre-clinical phase', and separate the development phase into 'the clinical phase' and the 'approval phase'. In other cases terms are not clearly defined. Through-out the text, I alert the reader to cases where the author seems to be employing the terms differently from how they are presented in Figure 1.

Figure 1 Life cycle of a NCE from synthesis to market



Sources: Row 1 – Myers and Howe, 1997, Figure 2; Row 2 – DiMasi et al., 1991; Lehman Brothers, 1997b; PhRMA, 1997; Row 3 – Lehman Brothers, 1997b, 4.

Notes: IND= Investigational new drug. In the UK companies must fill out a Clinical Exemption Certificate (CTX), but there are currently fewer hurdles to initiating clinical trials in the UK than in the US (CMR International).

The duration and success rate figures represent typical performance in US companies rather than averages of a specific sample of NCEs.

The diagram uses US data. Because companies in the US face the additional hurdle of filing an IND before they can start clinical trials, the total development time in the US may be longer than in other major markets. According to CMR International, the mean development time for a product to reach any global market was 10 years in 1996.

A good measure of the R&D costs for a NCE must take into account the fixed and variable costs of product discovery and development, the cost of failed as well as successful projects, and the time value of funds invested. Economists have generally employed two different methods to estimate these costs: the first draws on industry level data; the second draws on company project level data. While industry level data are easier to obtain, “a serious disadvantage is that aggregate expenditures cannot be associated in any precise manner with particular NCEs” (DiMasi et al., 1991, 111). With aggregate data, for example, one cannot distinguish between the costs of licensed-in (and licensed-out) products and self-originated products though the cost patterns of these types of products are quite different (DiMasi et al., 1991, 1994). More importantly, discovery costs for products licensed-in from companies not included in the industry level data will be excluded. There is also some debate as to how to estimate the lag between R&D inputs and outputs for aggregate figures.

Estimates based on micro-level data, on the other hand, are considered more complete, but it is difficult and time consuming to gain access to and to analyse company-level information. DiMasi et al., (1991) completed the most extensive project level study to date. They calculated average costs per NCE for a sample of 93 NCEs that first entered human clinical tests between 1970 and 1982 from 12 US owned pharmaceutical firms. Their estimate of \$231 million cost per NCE in 1987 dollars was more than double earlier estimates based on projects started in the 1960s.

The DiMasi estimate is widely used by economists and policy makers. For example, Grabowski and Vernon (1994) used this figure as a base to determine the profitability of R&D, given the revenues companies earned from NCEs. Some policy makers use the estimate and DiMasi et al.’s argument that costs are growing rapidly over time, to support arguments that price controls would severely limit companies’ ability to make future R&D investments (PhRMA, 1997). To update the cost figure, most have simply adjusted it for changes in the overall price level using the US GDP price deflator. This approach implies that a NCE costs **\$312 million in 1997 dollars**.

If we accept the DiMasi estimate as accurate for products initiating clinical trials between 1970-82, empirical evidence suggest that the cost per NCE for the 1990s exceeds this figure, even after adjusting for inflation<sup>3</sup>. The cost per NCE is a function of the success rate (the percentage of NCEs entering clinical testing that gain market approval), the amount of time it takes for a

3 Love (1997) suggests that DiMasi et al. overstated the costs, an argument based on his observation of large disparities between the DiMasi et al. estimate and information about tax credits for research expenditures into orphan drugs in the US in the 1980s.

company to discover, test, and gain marketing approval for a product, the discount rate used to capitalise out-of-pocket costs to the date of market approval, and the quantity and cost of labour and capital inputs. While there is little evidence of substantive changes in success rates, the time profile<sup>4</sup>, discount rate, amount and cost of inputs for the average product have all increased, in the 1980s and early 1990s, pushing up average costs.

Companies have also started to integrate new technologies and organizational strategies that impact on the structure of pharmaceutical costs (Gambardella, 1995). Using new technologies, scientists can identify thousands more potential leads, thereby improving the productivity of drug discovery (Lehman Brothers, 1997b). However, the clinical testing process for new drugs has also become longer and more complex. At the same time, companies are extending their inter-firm network, out-sourcing development work to companies specialising in clinical trials and licensing-in discovery work, either from companies specialising in research or from other pharmaceutical companies. These changes must be considered in any new estimate of R&D unit costs.

The objective of this paper is to analyse the existing estimates of NCE costs and look at the subsequent changes in cost components and at the impact of structural change in the R&D process. These discussions cannot substitute for new estimates that are based on more recent company data but, in the absence of such new estimates, they do provide some indication of the direction and magnitude of likely cost changes that have occurred in the 1980s and 1990s<sup>5</sup>.

In the second section, I summarise the methods and cost estimates of existing studies. Using the US GDP implicit price deflator, the figures are updated to 1997 dollar amounts. In section three, I describe the structure of R&D costs and explore how current changes in technology and corporate strategy in the industry would affect these costs. I argue: 1) that total R&D costs have increased faster than the rate of general price inflation; and 2) that the structure of these costs has changed over time.

4 How much time profiles have increased over this period depends on what market the product enters. CMR International, which looks at the time it takes a product to enter its first global market, reports shorter time profiles than does the Center for the Study of Drug Development (CSDD), which looks at the time it takes a product to enter the US market suggesting time to market is quicker in some countries than in the US. CMR International also finds that the trend of increasing time for products to enter their first global market levels off in the mid 1990s.

5 At this time, DiMasi and colleagues at the CSDD are conducting a new study to update their estimates with cost figures for products introduced into clinical studies in the 1980s. Their report is expected some time in 1999.

## 2 MEASURING R&D COSTS FOR NCEs<sup>6</sup>

To estimate the R&D costs of a NCE two types of costs must be examined: i) out-of-pocket costs for the discovery and development phases; ii) the opportunity costs of money invested in these phases, i.e., the amount of interest investors forgo when they commit their resources to the R&D process. The amount of opportunity costs depends on how long it takes a company to bring a product to market and the industry's real discount rate. The discount rate is the rate of interest that money invested at a given level of risk must earn in exchange for being tied up in the investment. 'The opportunity cost of capital for pharmaceutical R&D is higher than the interest rate on safe investments, such as insured bank deposits or government bonds, but just how high it is depends on how investors evaluate the risks of these investments' (OTA, 1993, 48) (See Section 2.4).

Economists have used two different types of data to estimate total costs per NCE: project level data and industry level data. In general, industry level data are more readily available and verifiable. It is, however, difficult to correlate industry R&D expenditures to particular groups of NCEs because of the lag in time between inputs and outputs. Pharmaceuticals that come onto the market today are the product of expenditures over the preceding decade or more. Project-level studies, on the other hand, can provide detailed estimates of the costs of particular projects, and of the time lags involved. But to construct a complete project level cost data set requires a lot of time and the cooperation of a large number of companies.

In this section, I:

- describe the DiMasi et al. (1991) project-level study;
- compare their findings with those of Hansen (1979) who conducted a similar study about 10 years earlier;
- compare the project level study method with the industry level method employed by Wiggins (1987);

<sup>6</sup> This summary draws on the literature reviews of measuring NCE costs presented in the Office of Technology Assessment (OTA), 1993, chapter 3 and DiMasi et al., 1991.

- examine OTA (1993) and Myers and Howe (1997) studies where DiMasi et al.'s out-of-pocket cost data (adjusted for inflation) are combined with new assumptions about how to measure the cost of capital.

All the studies quote pre-tax costs. In the summary, post-tax cost estimates are discussed to demonstrate the impact of tax savings on R&D costs per NCE.

### 2.1 DiMasi et al.'s estimate

DiMasi et al. constructed a cost estimate for NCEs from a sample of 93 self-originated NCEs<sup>7</sup>, from 12 US-based enterprises<sup>8</sup>, that started clinical testing between 1970 and 1982. Their findings are expressed in 1987 dollars<sup>9</sup> but the numbers reflect discovery activities that took place in the late 1960s and 1970s, and development activities from the 1970s to the mid 1980s.

The companies provided data on total R&D expenditures, cost per project for each stage of clinical trials and animal testing and the time it took for a product to move through each phase. The per cent of products that moved through each phase, and the per cent that received US FDA approval for marketing were estimated from the sample and other CSDD database information. Firms could rarely provide discovery expenditures for specific NCEs. DiMasi et al. estimated the discovery costs per approved NCE using a ratio of uncapitalised discovery to clinical expenditures, provided by the companies, and their estimate of the uncapitalised clinical period cost per approved NCE. As they focused on self-originated products, they requested

7 For a self-originated product, each step of bringing a NCE to market, from discovery to regulatory approval is completed inside one company. DiMasi et al. 'limited the 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' (DiMasi et al., 1991, 120).

8 DiMasi et al., Hansen, Wiggins, the OTA, and Myers and Howe based their calculations on products in US-based companies and thus this survey of estimates is biased towards the US experience. According to DiMasi, however, the US firms in his sample provided international data. This means that the products included in the sample could have been taken through human testing anywhere in the world (personal interview, 1998). The Lehman Brothers estimate, discussed later, is based on data from a UK-owned company.

9 To facilitate inter-study comparisons I have adjusted all the studies' results for general price inflation to 1997 dollars using the US GDP implicit price deflator. The adjustments for the studies are as follows:

\$1 1987 = \$1.35 1997 (relevant for the DiMasi Study); \$1 1990 = \$1.20 1997 (relevant for the OTA Study); \$1 1994 = \$1.07 1997 (relevant for the Myers Study); \$1 1995 = \$1.04 1997 (relevant for the Lehman Brothers Study).

that companies break down their total R&D expenditure data into expenditures on self-originated NCEs, on licensed or otherwise acquired compounds and on existing approved products.

DiMasi et al. used these pieces of information to calculate total average cost per approved NCE in three steps. By discussing each step in detail, the important factors influencing total cost can be identified. Table 1 summarises the results.

DiMasi et al. distinguished between investigational NCEs – products that undergo at least one of the three phases of clinical trials – and approved NCEs – products that complete clinical testing and are approved for marketing. In step one, the authors determined average<sup>10</sup> expected out-of-pocket costs per investigational NCE for drug development by multiplying the mean input cost data and the phase-to-phase attrition rates. Oversampling of successful products to get sufficient information about products that reach the point of NDA submission and approval meant it was necessary to multiply the ratio of total costs for each Phase to the total number of drugs that enter the pipeline to get expected mean costs per investigational NCE. High attrition rates meant that Phase III's share of total expected costs was only 42 percent despite higher mean out of pocket costs. Only 36 percent of the sampled NCEs that entered Phase I of clinical testing made it to Phase III (see column B of Table 1)<sup>11</sup>.

In the second step, DiMasi et al. estimated the capitalised cost per investigational NCE for each development phase by calculating opportunity costs. Opportunity costs are positively related both to the discount rate and to the time it takes to get to the point of marketing approval at which time it is possible earn a return on R&D investments. In pharmaceuticals, opportunity costs make up a significant share of total capitalised costs because of the many years it takes to get a product to market.

10 Mean phase costs varied substantially in individual NCE testing costs for each phase. The standard deviations for Phases I, II, and III in thousands of 1997 dollars were \$6,100, \$7,061, and \$18,865 respectively (DiMasi et al., 1991, 121-122).

11 The attrition rates in Table 1 column B look different from those in Figure 1 because DiMasi et al. looked at the probability of entering a phase while Lehman Brothers looked at the probability of completing a phase. According to DiMasi et al., 75 percent of products starting clinical trials start Phase II. That is, according to DiMasi et. al., 75 percent of products starting clinical trials successfully complete Phase I. Lehman Brothers estimate this proportion to be slightly lower at 70 percent.

*Table 1* The DiMasi estimate of average R&D costs per NCE (US data) (1997 \$)

Step 1		Step 2		Step 3		
A	B	C	D	E	F	G
		(A*B/100)		(C*(1.09) <sup>D/12</sup> )	(C/SR)	(E/SR)
Mean out of pocket cost per investigational NCE (\$'000)	Probability of entering phase (%)	Expected cost (\$'000)	Time from phase start to approval (months)	Capitalised expected cost per investigational NCE (\$'000)	Uncapitalised cost per approved NCE (\$m)	Capitalised cost per approved NCE (\$m)
Discovery			141.5	88.4	88.4	210.1
Development:						
Phase I	100	2,881	98.9	5,539	12.6	24.1
Phase II	75	4,004	82.7	6,647	17.4	28.9
Phase III	36.2	6,256	60.2	8,489	27.3	36.9
Long term animal testing	56.1	1,632	78.7	2,550	7.2	11.1
Other animal testing	15.8	138	78.7	215	0.5	0.9
Total development		14,911		23,440	64.9	101.9
Total NCE cost					153.4	<b>312.0</b>

Source: DiMasi et al., 1991, Table 2 (121), Table 3 (123), Table 4 (125). All values are adjusted to 1997 US dollars with the GDP Implicit Price Deflator.

Note: SR = Success rate = 0.23

See Figure 1 for phase definitions. DiMasi et al. (1991) group the costs of getting FDA approval together with the cost of Phase III.



DiMasi et al. constructed a time profile from company data on the number of months a compound spent in each phase and from information about the average overlaps and gaps between phases. Long term animal testing, for example, tended to run parallel with Phase II and Phase III testing in humans. The total NCE R&D cycle averaged almost 12 years. (DiMasi et al. did not provide any information about the variance of overall times around the mean. Figure 8, discussed in Section 3.2 below and based on global data collected by CMR International, shows variation in development times). NCEs spent an average of three and a half years in the discovery phase and at least eight more years to get market approval once human testing was started. DiMasi et al.'s duration data, based on a sample of 93 products, are almost the same as the average times for the US industry as a whole estimated from a CSDD annual survey based on a larger sample of companies (see Figure 1).

For the discount or cost of capital rate, the authors sought a value representative for the pharmaceutical industry over the period spanned by the development of the drugs in the study. They ended up using a 9 percent real annual discount rate, adopted from Grabowski and Vernon's (1990) study on the rate of return on pharmaceutical R&D from the mid-1970s to the mid-1980s<sup>12</sup>. Column E of Table 1 gives the total capitalised costs for each phase of the clinical tests. Opportunity costs comprised 36 percent of development costs per investigational NCE. The earlier the phase in the life cycle, the higher the opportunity costs as a share of total capitalised costs.

Finally, in step three of their calculations, the authors estimated the total costs per approved NCE by dividing the expected direct costs per investigational NCE by an approval success rate of 23 percent (Table 1, column G) to take into account the cost of failures, i.e., investigational NCEs that incur costs but do not get to the approval stage. In essence, it is as if all the costs for each Phase were added and then divided by the number of drugs that make it out of the pipeline to marketing approval. The final estimate of average total capitalised costs per NCE was \$312 million in 1997 dollars. Out-of-pocket costs comprised \$153 million or 49 percent of the total figure. Opportunity costs made up the rest. Two thirds of the total (\$210 million) was spent on drug discovery; one third was spent on development.

<sup>12</sup> Myers has argued in favour of a variable discount rate on the grounds that the risk of investments changes over the R&D time period. Specifically, earlier investments are more risky than later ones. The OTA's and Myers' estimates, based on variable discount rates, are presented below (OTA, 1993; Myers, forthcoming; Myers and Howe, 1997).

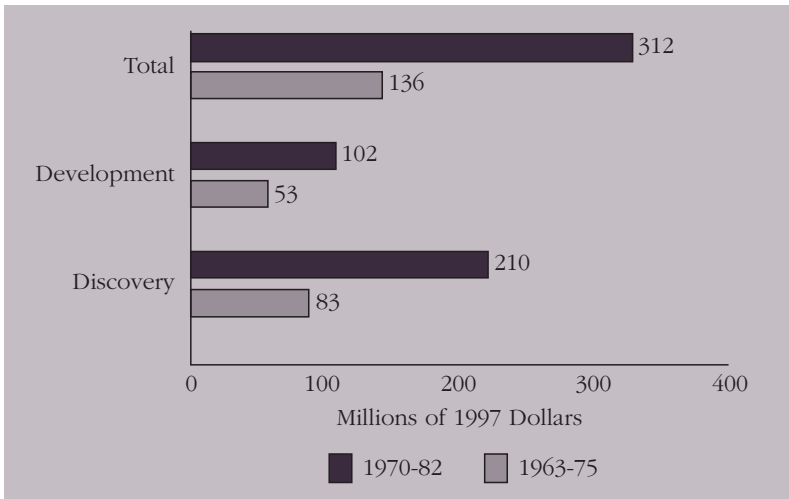
## 2.2 Changes in costs between the 1970s and the 1980s

To see how costs changed between the 1970s and 1980s, Hansen's 1979 study provides the best comparison. Hansen's estimation methods were similar to DiMasi et al.'s and he looked at products that were developed in US based companies approximately ten years earlier than DiMasi et al.'s<sup>13</sup>.

Hansen collected data on 67 products that entered clinical testing between 1963 and 1975. Hansen's products came onto the market starting around 1970, while DiMasi et al.'s products came onto the market after 1978. Between these time periods, uncatalysed costs increased 99 percent while total capitalised costs increased 129 percent (see Figure 2). The bulk of the increase in both the uncatalysed and capitalised costs seems to have occurred in the discovery phase, where costs rose by 106 per cent and 154 per cent respectively between the two studies.

Focusing on total capitalised costs, DiMasi et al. attribute the total \$176 million cost increase between the two studies to three factors: 13 percent (\$23 million) reflects DiMasi's use of a higher cost of capital (nine percent as

Figure 2 Total capitalised costs per approved NCE (US data)



Source: DiMasi, 1995, 377. Adjusted to 1997 dollars with GDP Implicit Price Deflator.

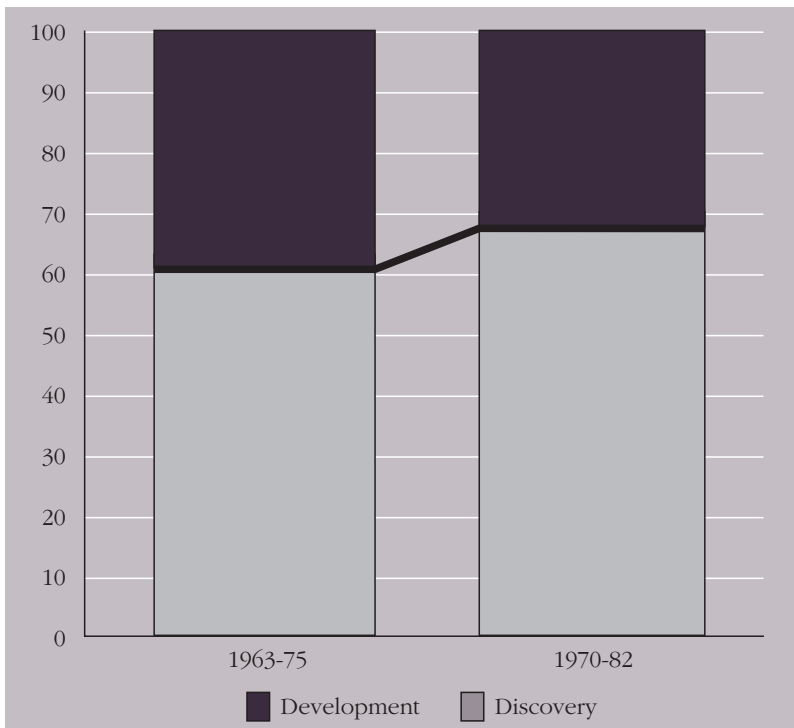
13 Hansen was a co-author of the DiMasi et al. (1991) piece.

opposed to eight percent); 24 percent (\$42 million) reflects the longer time periods for both the discovery and development phases in the later study; and 63 percent (\$111 million) reflects the increase in out-of-pocket costs (DiMasi et al., 1991, 127).

Though coverage in the industrial press of increases in R&D costs commonly emphasises changes in the costs of clinical trials and regulatory requirements, between the 1970s and 1980s, the discovery costs' share of total capitalised costs increased from 61 percent to 68 percent while the development costs' share fell to 32 percent. See Figure 3.

The fact that discovery costs constitute up to two thirds of total R&D costs per NCE in both the Hansen and DiMasi et al. studies contrast with the commonly held perception in the industry that development and approval

*Figure 3* Percentage breakdown of total R&D costs per NCE



Source: DiMasi, 1995, 377.

regulations constitute the greatest share of costs. Their studies do not correspond with UK R&D expenditure data for the early 1980s, provided by CMR International, which show less than one third going to discovery and the rest going to development.

The large percentage of costs going to discovery is in part a function of capitalising the figures to the time of market launch. Because discovery takes place first, the opportunity costs for this phase are higher than for the development phase. However, in both studies, looking only at uncapped costs, the discovery portion makes up 54 per cent in the Hansen study and 58 per cent in the DiMasi et al. study.

DiMasi et al.'s high discovery costs as a share of total costs may reflect their methodology of calculating discovery costs. Unable to get discovery costs per project, their number is essentially the residual of total R&D costs for self-originated projects and their estimate of clinical costs per investigational NCE (DiMasi et al., 1991).

### 2.3 Industry studies

Wiggins (1987) has computed one of the most recent industry level cost estimates for NCEs. He regressed the total number of NCEs that the FDA approved between 1970 and 1985 on the estimated total NCE-oriented research spending in previous years. The regression equation was then transformed into an estimate of the extra cash research outlay required to bring forth one additional NCE (OTA, 1993, 53). His uncapped cost per NCE from US-based companies for this period was \$90.7 million. Using Hansen's time profile and the discount rate of eight percent, he found a \$155.5 million capitalised value (DiMasi et al., 1991, 114).

Using Hansen's proposed average time of 6.5 years between the beginning of clinical testing and product approval, the OTA (1993) argues that 'Wiggins' sample corresponds to NCEs first entering clinical testing between roughly 1963 and 1979, a period that overlaps substantially with the Hansen study' (53)<sup>14</sup>.

Wiggins' uncapped cost estimate of \$90.7 million is close to Hansen's \$79 million. However, the drug projects covered in the two studies are different and caution must therefore be taken when comparing the results. Wiggins' study included licensed-in products, US and non-US as well as self-

<sup>14</sup> Hansen used a shorter time period of 6.5 years (OTA, 1993, 53) than DiMasi et al. (1991).

originated products, whereas Hansen's sample only included the latter. As a result, the discovery expenditures for the NCEs discovered in non-US based companies and companies that were not members of the US pharmaceutical association were probably not included in Wiggins' estimate (DiMasi et al., 1991). This would suggest, however, a smaller rather than a larger figure compared with Hansen's.

DiMasi (1995a) and Lehman Brothers (1995) also suggest that the R&D expenditure patterns differ between non-US and US-based facilities and between licensed-in and self-originated products. No inter-country comparisons of NCE costs have been done but there is some evidence that licensed-in products may have cheaper development stages than self-originated products, probably because they are carefully selected and undergo extensive pre-clinical testing before they are licensed out (DiMasi, 1995a).

Yet, despite these omissions, the Wiggins' estimate is higher than Hansen's. The OTA suggests that the two authors may have focused on different years within the 1963-1975 time period. Specifically, Wiggins' products may have started development later in the period than Hansen's (OTA, 1993, 61). If we assume that out-of-pocket costs increased between the beginning and the end of this period, then that might explain Wiggins' larger number.

#### **2.4 The cost of capital**

This section examines the sensitivity of the total capitalised cost estimates to the analyst's measure of the discount rate for capital invested in pharmaceutical R&D. Hansen and DiMasi et al. both used a constant discount rate based on analyses of the cost of equity capital for the pharmaceutical industry. Myers and Howe (1997) and the OTA (1993) both used variable rates that average out to a rate higher than the eight or nine percent used in the Hansen and DiMasi et al. studies respectively. As a result, their estimated opportunity costs and total capitalised costs are significantly larger, though they both use DiMasi et al.'s raw data.

Capitalising costs to their present value in the year of market approval at a constant interest rate of nine percent more than doubled DiMasi et al.'s cost of R&D cash outlays estimate from \$153 million per approved drug to \$312 million. There is some debate, however, about whether it is appropriate to use a constant cost of capital for all R&D investments across time and across projects. There may also be problems with using the average cost of capital for pharmaceutical companies to estimate capitalised values for R&D

investments which are considered more risky than investments at manufacturing stages in the process (OTA, 1993).

To estimate how much more risky R&D investments are compared with manufacturing investments, Myers and Shyam-Sunder (OTA, Appendix C, 1993) examined the cost of capital for firms investing largely in R&D (small pharmaceutical firms and biotechnology firms). The 14 per cent real cost of capital rate for these companies was four percentage points higher than that of large pharmaceutical companies that also made investments in on-going operations.

The OTA recalculated DiMasi et al.'s estimate with a cost of capital that decreases linearly over the life of the R&D projects from 14 percent to 10 percent, to reflect the higher risk at the beginning of the project. As a result, opportunity costs increased from \$158 million to \$278 million and total capitalised costs increased from \$312 million to \$431 million.

Myers and Howe (1997) employed a life cycle financial model to estimate the costs of pharmaceutical R&D. In this model they allowed the real cost of capital to decline in three successive steps as the drug moves through its life cycle from basic research to market launch. Using DiMasi et al.'s out-of-pocket cost data, time profiles and success rates, they came up with a cost estimate that is slightly higher than that of the OTA: \$459 million<sup>15</sup>.

*Table 2* Estimates of the full cost of bringing a NCE to market (million \$ 1997)

<i>Study</i>	<i>Years<sup>1</sup></i>	<i>Out of pocket costs</i>	<i>Opportunity costs</i>	<i>Total capitalised costs</i>
Hansen, 1979	1963-75	72	66	138
Wiggins, 1987	1963-75	80	76	156
DiMasi et. al., 1991	1970-82	153	158	312
OTA, 1993	1970-82	153	278	431
Myers and Howe, 1997	1970-82	153	306	459

Sources: OTA, 1993; Myers and Howe, 1997.

Note: 'Years' refers to the years the products in the study entered the clinical trials phase.

<sup>15</sup> Myers and Howe's estimate is higher than the OTA's because they use a different discount rate and include the cost of manufacturing capacity constructed prior to launch (Myers and Howe, 1997, 33).

## 2.5 Summary

The cost estimates discussed in this section are summarised in Table 2. These should be compared with the latest figure of \$635 million suggested by Lehman Brothers (Lehman Brothers, 1995) for drugs that started clinical trials in the mid-late 1980s and were approved for market in the mid 1990s .

Out-of-pocket and opportunity costs increased substantially between products discovered in the 1960s and products discovered in the 1970s. The OTA and Myers and Howe estimates illustrate the sensitivity of the cost estimate to the choice of discount rate. Their studies did not, however, incorporate any new original cost data.

These estimates are pre-tax values. To illustrate how important tax savings are to net R&D costs, the OTA recalculated the R&D costs per NCE from DiMasi et al. using a 46 percent marginal corporate tax rate, assuming no other tax credits (OTA, 1993, 68). OTA assumed that the firms in the DiMasi et al. sample fell into the highest tax bracket (taxable income exceeding \$1.4 million). For the R&D period covered in DiMasi et al.'s study (1970-1986), the US corporate marginal tax rates for the highest income earners was 48 percent until 1992 when it was cut to 46 percent<sup>16</sup>.

*Table 3* After-tax R&D cost per NCE under different marginal tax rates (million \$ 1997)

<i>Study</i>	<i>Before-tax</i>	<i>After-tax (46%)</i>	<i>After-tax (35%)</i>
DiMasi et al.	312	168	203
OTA	431	233	280
Myers and Howe	459	248	298

*Sources:* OTA, 1993; Myers and Howe, 1997.

*Note:* OTA used a 46 percent marginal tax rate, the rate applied to companies with taxable income of more than \$100,000; Myers and Howe assumed a 35 percent tax rate.

<sup>16</sup> According to a later study, (DiMasi et al., 1995a) only 37 of the 93 NCEs in the sample were produced in what the authors defined as 'large firms' (firms with sales exceeding \$600 million in 1971-74 period). This suggests that a share of the NCEs may have fallen in a lower tax bracket. As of 1979, companies with taxable incomes less than \$100,000 were charged lower marginal tax rates. For companies with taxable incomes between \$50,000 and \$75,000, for example, the marginal tax rate was cut from 48 percent to 30 percent in 1979 where it remained through 1986. The OTA estimate should therefore be considered a lower bound for net after-tax cost.

Table 3 shows the tax savings US companies (investors) received for investing in pharmaceutical R&D in the 1970s and early 1980s. In their study, Myers and Howe (1997) used a 35 percent tax rate, the 1997 marginal tax rate for the largest companies.

Interpreting the implications of tax break savings on R&D costs for companies and health care providers is complicated. From the perspective of a profitable, integrated company, tax breaks on R&D costs mean the amount of cost incurred is reduced. But to get these tax breaks, the equivalent post-tax income must be earned. As a result, providers must pay enough to provide companies with the necessary pre-tax income to achieve the post-tax income stream.

Furthermore, in the 1990s, as some companies move to break up the process of R&D, small companies sub-contracted in to conduct various phases of the R&D process are not in a position to benefit from the R&D tax credits, having little or no profit against which tax savings can be offset. This means they have to incur the whole cost of their research or development assignment. Therefore, the total cost savings of R&D tax credits may be less now than it was in the past.

No one has conducted a detailed study to update DiMasi et al.'s estimate for products that started clinical testing after 1982 but there is anecdotal evidence to suggest that R&D costs have continued to increase. Figure 4a shows how aggregate worldwide R&D expenditures have grown at an increasing rate since 1981 while the number of new molecular entities (NMEs) introduced on the market has tended downwards (CMR International, 1998)<sup>17</sup>. Even after the lag between R&D expenditures and marketing approval is taken into account, these pieces of information together suggest that R&D costs per NME continue to increase over time<sup>18</sup> (DiMasi, 1995b). See Figure 4b.

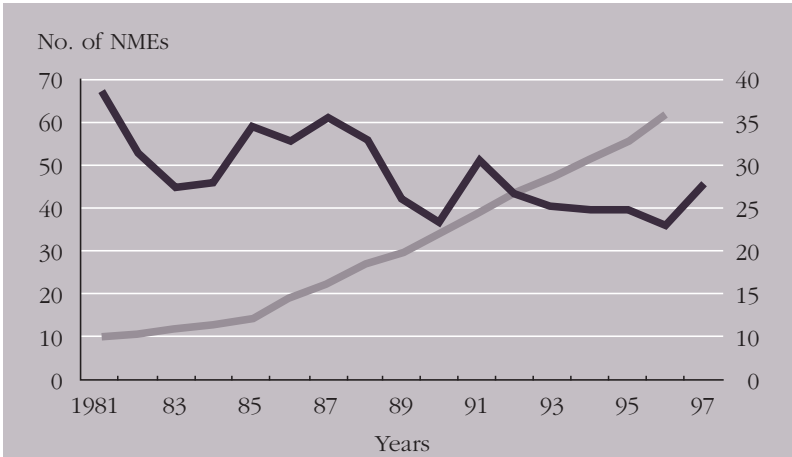
Lehman Brothers have suggested a total R&D cost per NCE estimate of over \$600 million for products entering development in the 1990s, a figure almost double that of DiMasi et al. (Lehman Brothers, 1995). This cost estimate is based on a spectrum of Zeneca products and includes research

17 NMEs include biological and biotechnology products while NCEs include only chemical based products.

18 The lag means that research expenditures that take place in the 1990s should be associated with numbers of NME approvals several years into the future.

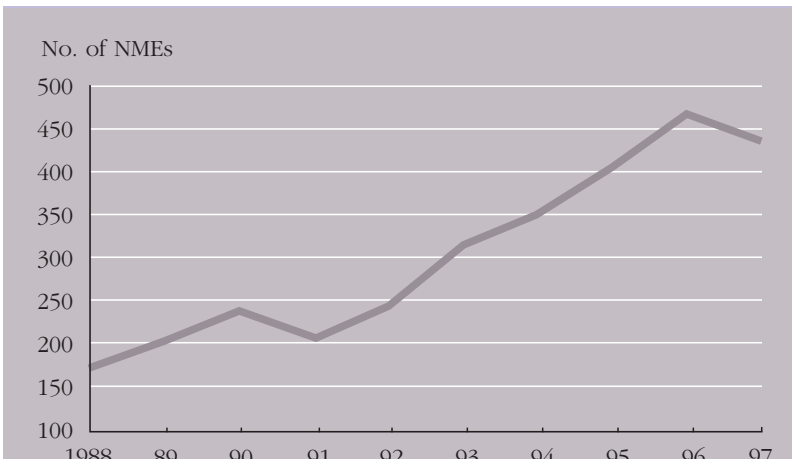


Figure 4a R&D expenditure and the number of NMEs launched, 1981-1997



Source: Halliday and Walker, 1997.

Figure 4b R&D dollars (1997, million) per NME



Source: Halliday and Walker, 1997.

Note: This graph is based on the illustrative assumption of a 10-year lag between R&D spend and consequent NME launch. Thus, for example, the 1995 cost per NME is approximated by R&D expenditure in 1985 divided by the number of NMEs launched in 1995.

*Table 4* A comparison of the DiMasi et al. and Lehman Brothers estimates (million \$ 1997)

	<i>% of NCEs entering phase</i>		<i>Cost per approved NCE</i>	
	<i>DiMasi</i>	<i>Lehman Brothers</i>	<i>DiMasi</i>	<i>Lehman Brothers</i>
Discovery			210	313
Phase I	100	100	24	58
Phase II	75	70	29	42
Phase III	36	36	37	177
Approval		23		46
Development			102	323
Total	23	21	312	635

*Sources:* DiMasi et al., 1991, Lehman Brothers, 1995, 43.

*Notes:* DiMasi's Clinical Trial Phases do not include costs of long term animal testing but these costs are included in the Development and Total cost figures. These tests are presumably incorporated into the Lehman Brothers Phase costs. DiMasi includes the costs of approval in the Phase III figure.

costs, capital costs and the cost of unsuccessful products. A comparison of the Lehman Brothers' estimate and DiMasi et al's estimate in Table 4 shows little change in attrition rates between the 1970s and the 1990s but dramatic increases in costs. Discovery costs increase 50 percent while development costs increase more than 200 percent. Phase III costs increase 3.8 times<sup>19</sup>.

DiMasi's estimate is twice that of Hansen's and the Lehman Brothers' estimate is twice that of DiMasi's. Few have questioned the accuracy of the magnitude of these increases. In the following section I analyse existing empirical evidence on how the components of total costs per NCE have changed over time to see if they support Lehman Brothers' proposition that costs have increased dramatically in the 1980s and early 1990s.

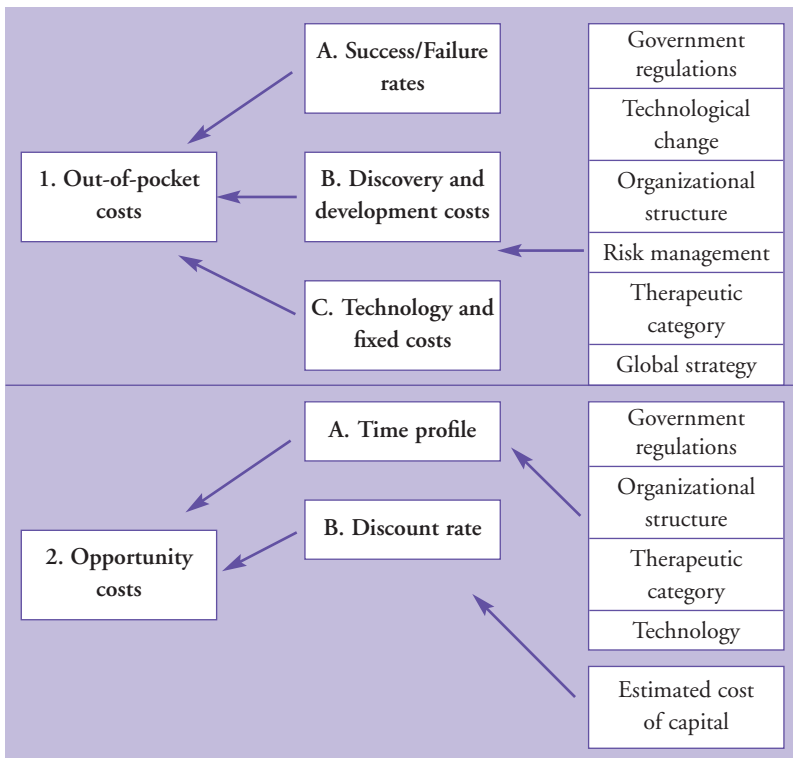
<sup>19</sup> According to Lehman Brothers, discovery's proportion of total capitalized costs, is fifty per cent as opposed to 66 per cent in the case of DiMasi et. al. An important question is whether DiMasi's estimate of discovery costs is too high or if, perhaps, the proportion of discovery to development costs has changed over time.

### 3 FACTORS INFLUENCING R&D COSTS FOR A NCE

Figure 5 identifies major factors driving out-of-pocket and opportunity costs for R&D. The middle column shows the components of DiMasi et al.'s cost calculation. The right column identifies factors that affect these variables.

In fact, the direction of influence flows both ways. Changes in costs affect decisions about what technologies to use, how to organize production, firm size, in which therapeutic groups to focus research, and so on; these decisions

Figure 5 Factors influencing the discovery and development costs of NCEs



in turn affect costs. In this section I focus only on how the factors in the right column affect the costs in the left columns. In the conclusion of the paper I return to the issue of how rising costs might in turn affect the producers' strategic decisions, i.e. how changes in the left affect factors on the right.

### 3.1 Out-of-pocket costs

Out-of-pocket costs depend on the success rate (the higher the percent of NCEs that enter clinical trials and obtain market approval the less that is spent on failed projects) and the quantity and quality of human and material resources and technologies used in the discovery and development phases. I examine the changes in each of these components in turn.

#### 3.1.1 Success rates

The cost of new drug development is critically dependent on the proportion of drugs that fail in clinical testing. For example, DiMasi et al.'s R&D costs per NCE estimate would fall by eight percent if the success rate were 25 percent rather than 23 percent. A decline in the success rate from 23 to 20 percent, by contrast, would mean a 15 percent increase in total R&D costs (DiMasi et al., 1991).

CSDD has examined changes in success rates for a sample of close to 2,000 NCEs that initiated clinical trials in the US between 1964 and 1989. Their data reveal time trends and highlight differences between licensed-in and self-originated products, between drugs in different therapeutic groups, and between drugs developed in companies of different size. Data from CMR International suggest that differences in attrition rates exist between companies from different countries.

In an examination of success rates (percent of products that initiate clinical trials and gain market approval) as of December 1993 for products entering clinical trials in four time intervals between 1964 and 1984, DiMasi (1995a) finds predicted success rates increased from 13.3 in 1964-69 to 22.9 in 1975-79 and then declined slightly to 20.5 in 1980-84<sup>20</sup>. To get a feeling for the

20 Not all INDs which entered clinical trials in a specific time period had been terminated or approved as of December 1993. DiMasi estimated a final success rate taking all products into account using a two-stage parametric model where times to termination of research (research abandonment or approval) are estimated and from there, the conditional probability of approval predicted (DiMasi, 1995a Table 1, 6 and Appendix).

trend in success rates for INDs initiating clinical trials late 1980s, given that too little time had passed to statistically estimate the success rate for these INDs, DiMasi looks at the observed success rates through 1993 and compares them with success rates for earlier periods at the same amount of time from IND filing. Cumulative success rates at 4 years from IND filings for 1980-84 filings, 1985 to 1986 filings, and 1987 to 1987 filings are 2.5%, 2.7%, and 1.4%. 'If the trend persists, then either success rates will have declined during the 1980s or development times will have increased, or both' (*ibid.*, 6).

Success rates vary by the kind of drug being developed, the kind of firm conducting the clinical trials, and where the firm was based. Throughout the 1980s, DiMasi (1995a) observed that success rates were significantly higher for licensed-in products and self-originated products first tested outside the US than for self-originated products first clinically tested in the US. The first two types of products benefit from having undergone testing in humans before the company filed an IND in the US. For the products entering clinical trials in the 1980-84 period, for example, the success rates of market approval as of 31 December 1993 were 16, 8.2, and 25.3 percent for all self-originated, self-originated tested first in the US, and licensed-in products respectively.

DiMasi also found that success rates vary by therapeutic class and that these rates change over time. In the 1980s, anti-infective and antineoplastic drugs' success rates of 34 percent and 33 percent were well above the total average rate of 18.2 percent for the NCEs in all eight therapeutic categories examined. Predicted success rates<sup>21</sup> for cardiovascular drugs were above the average for all the therapeutic groups in the early 1980s but much below average in the 1970s. Central nervous system (CNS) drugs had the lowest success rates of the eight categories for every time period.

According to the results from the sample of 2,000 NCEs, predicted success rate varied little between firms of different sizes<sup>22</sup> in the early 1980s. Predicted success rates were 19.5 percent, 20.9 percent and 19.4 percent for

21 See preceding footnote for definition of predicted success rates.

22 Company size is based on pharmaceutical sales. The DiMasi 1995a study used 1986 sales data. Pharmaceutical sales for small firms, medium-sized firms and large firms were: less than \$1.3 billion; between \$1.3 billion and \$2.1 billion; and more than \$2.1 billion; respectively (DiMasi, 1995a, Table IV, 11). The DiMasi et al., 1995b study used average annual sales over the 1970-74 period. In this case, small, medium, and large firms had average sales of less than \$500 million, \$500-600 million, and more than \$600 million respectively (DiMasi et al., 1995b, Table 1, 209).

small, medium, and large firms respectively (DiMasi, 1995a, 11)<sup>23</sup>. Thus, despite more research resources, large firms did not achieve a relative advantage. It could be that smaller firms pick less risky projects but DiMasi could provide no evidence of this.

For a smaller sample of 93 NCEs, DiMasi et al. (1995a) did find statistically significant differences between firms of different sizes but this time larger companies were more successful with success rates of 27.9 percent compared with 23.8 percent for small and 17.4 percent for medium. ‘This is suggestive of a more rational discovery by design approach on the part of larger firms, perhaps reflecting superior drug discovery programs’ (DiMasi et al., 1995a, 209).

DiMasi’s data are based on products developed in the US by US and international companies. CMR International uses information from a variety of sources to try and compare attrition rates of companies of different nationalities. The US companies see the highest failure rates at each phase and the Japanese the lowest but the difference is most pronounced in the early stages. The ratios of NCEs entering Phase III to those that get market approval are similar in US, European, and Japanese companies – about 2 to 1. See Figure 6.

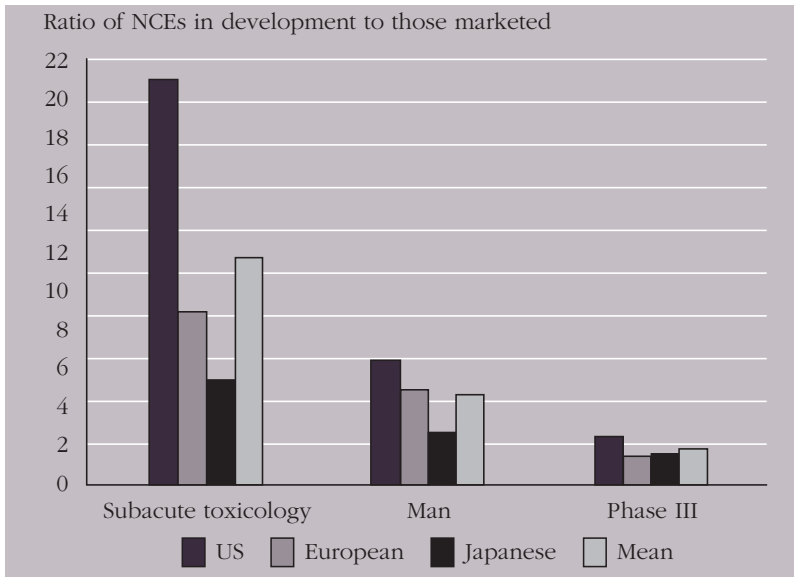
Discovery technology, the amount of pre-clinical testing, and the riskiness of the research process should all influence success rates. The advantage of improving success rates from the stand point of total R&D costs will depend, however, on how much additional time and money is involved in improving discovery and pre-clinical testing and on the acceptable balance between risk and return.

### ***3.1.2 Discovery and development costs***

The OTA (1993), PhRMA (1997), and DiMasi (1995b) provide different kinds of evidence to suggest that the costs of clinical trials and regulatory approval per NCE increased in the late 1980s and early 1990s, at least in the

23 The current success rates for products approved or terminated as of 1993 varied more significantly by size with 13.5%, 18.2% and 15.9% for small, medium, and large companies respectively. The difference between these and the predicted rates may reflect the fact a larger percent of NCEs in small firms were still active at the time of the study. DiMasi finds that the median survival time (products neither terminate nor approved) for small firms is 1.3 years longer than for large firms (.9 years longer than for medium firms) (ibid., 10-11).

Figure 6 Attrition rates – development to market



Source: CMR International, 1997.

US. Their findings are summarised in Table 5. Less empirical information pertaining explicitly to discovery costs for this time period is available, though clearly these costs are affected by increased hiring of scientists and researchers as well as the costs of toxicology studies with animals. As is discussed in Section 3.1.3, current (late 1990s) and future discovery costs as well as development costs are effected by investments in new technologies.

Costs are going up because companies have to conduct more clinical trials at each phase for each product. These trials have also become more complex. More patients are used in each stage and more procedures are conducted on each patient.

In the US, the changes in clinical trials are partly a function of more strict and extensive FDA regulatory requirements. DiMasi et al. (1991) and PhRMA (1997) both cite reports that the information required to support NDAs has increased dramatically. 'Clinical trials for one of the firm's anti-infective NCEs approved in 1970 used 1,493 patients; the trials for a related

*Table 5* Empirical evidence of increased clinical trial and regulatory costs

<p><b>1. Increase in research labour costs</b></p> <p>a. increase in the number of researchers, especially scientists and professionals, between 1980 and 1989; after 1993, the numbers levelled off (PhRMA, 1997, 73);</p> <p>b. little change in inflation adjusted salaries (OTA, 1993, 62).</p>
<p><b>2. Increase in animal research costs</b></p> <p>a. mixed evidence regarding trends in the number of animals used in research;</p> <p>b. significant increase in the cost of acquiring animals and the fees clinical research organizations (CROs) charge for conducting toxicological animal studies in the 1980s (OTA, 1993, 63-64).</p>
<p><b>3. Increase in human subject costs:</b></p> <p>a. increase in the number of humans enrolled in clinical trials. For three therapeutic groups the number increased 41 percent between 1978-1983 and 1986-1990 (DiMasi, 1995b, 379). PhRMA (1997) shows the number of patients in trials per NDA increasing from 1,321 in 1981-1984 to 3,567 in 1989-92 (20);</p> <p>b. increase in the average number of clinical trials per NDA from 30 in 1981-84 to 36 in 1985-88 to 60 in 1989-92 (<i>ibid.</i>,19);</p> <p>c. increase in the cost per patient. Mean costs per patient in 1997 US dollars for Phases I, II, and III increased steadily from \$5,504 in 1989 to \$6,217 in 1993 (DiMasi, 1995b, 378);</p> <p>d. increase in trial complexity. Measured as procedures per patient, complexity increased 69 percent from 1990-93 for Phase I, 118 percent from 1989-93 for Phase II, and 51 percent from 1989-93 for Phase III (DiMasi, 1995b, 379).</p>

anti-infective that the firm is currently developing will require testing on 10,000 patients' (DiMasi et al., 1991, 132).

The increased complexity of trials may also reflect a change in the therapeutic category mix of products going through the companies' pipelines in the 1980s and 1990s. A number of authors cite a move by companies towards developing treatments for chronic and degenerative illness away from acute illness. Treatments for these diseases are assumed to require longer and more expensive testing (DiMasi et al., 1991, 133; OTA, 1993, 65). Companies' R&D investment allocation choices are constrained in part by the demand pattern for new medicines (and thus the greater likelihood of a



profitable return). The shift towards diseases in which it is more expensive to conduct R&D reflects in part the saturation of markets for acute illnesses.

There is evidence of significant differences in R&D costs per NCE between therapeutic categories. Evidence of shifts in product mix and investment priorities towards the therapy areas where R&D is more expensive is less clear.

For the four therapeutic groups represented in the sample from the DiMasi et al. 1991 study, out-of-pocket costs per approved NCE for development and FDA approval (excluding discovery costs) ranged from \$49 million for anti-infective drugs to \$99.5 million for non-steroidal anti-inflammatory drugs (NSAIDs) (DiMasi et al., 1995b). See Table 6. Clinical trials for NSAIDs were more costly in each phase but the difference was most dramatic in Phase III where the average cost for all NCEs was \$5.8 million but the NSAIDs' trials cost \$11.2 million (*ibid.*, 159).

As DiMasi did not have access to discovery cost data by therapeutic group, it is not clear how total R&D costs differ between therapeutic groups. Nonetheless, the differences in clinical costs suggest that a company's average R&D cost per NCE will depend on its product portfolio.

The allocation of R&D expenditures gives some indication of company priorities, although it is not clear how much of an increase in the share of funds is prompted by a shift in priority and how much by changes in the

**Table 6** Uncapitalised out-of-pocket costs by therapeutic group (million \$ 1997, US data)

	<i>Expected costs (per investigational NCE)</i>			<i>Success rates (percent)</i>	<i>Total clinical costs (per approved NCE)</i>
	<i>Phase I</i>	<i>Phase II</i>	<i>Phase III</i>		
NSAID	4	5.3	11.2	22.2	99.5
Cardiovascular	3.1	3.8	6.5	26.2	62.2
Anti-infective	3.1	4.1	7.0	30.2	49.0
Neuropharm.	1.5	2.7	6.3	20.3	61.1
All (average)*	2.9	4.0	6.3	23.0	64.9

*Source:* DiMasi et al., 1995b, 159, 160, 162

*Note:* \*All includes all the drugs in DiMasi et al.'s 1991 sample, not just the ones in these four therapeutic groups.

relative cost of the specific therapeutic category. US R&D expenditure data between 1975 and 1988 suggest a shift in priority towards cardiovasculars (from 14.9 percent of total R&D expenditure to 25 percent) and neoplasm/endocrines (from 15.5 percent to 18.5 percent) and a shift away from anti-infectives (from 20 percent down to 14 percent) and CNS and sense organs (from 18 percent to 14.6 percent) (Mossialos, 1993, 54). According to DiMasi et al., cardiovascular products are relatively expensive while anti-infectives are relatively cheap. See above.

If, however, the cost of undertaking R&D in certain groups increased (decreased) over the time period, these total expenditure trends may not reflect change in priority. Data on number of approvals and development costs suggest that R&D for anti-infectives, for example, became more productive in the 1980s. So it is not clear whether companies gave it lower priority or were able to achieve their objectives at relatively lower cost.

DiMasi et al. (1994) show how the number and share of NCE's which filed INDs for eight therapeutic groups changed between 1963 and 1989. These numbers may provide a better indicator of the industry's product portfolio priorities over time. Three categories together account for more than half of the NCEs tested (cardiovascular 21 percent, CNS 21 percent, and anti-infectives 16 percent) but the relative magnitudes for different categories changed over time. In particular endocrine, analgesic-anesthetic, and anti-infectives all lost share while antineoplastic and cardiovascular gained share. Again, this provides some, albeit incomplete, evidence of a shift towards more expensive therapeutic categories.

The evidence about the importance of firm size on success rates is mixed (Section 3.1.1) but discovery and development costs per approved NCE do appear to vary significantly between firms of different sizes. For their 93 product sample, DiMasi et al. (1995a) found that development costs increased with firm size while discovery costs decreased with firm size. See Table 7.

Out of pocket costs per investigational NCE for the development stages were \$12.6 million for small firms compared with \$18.3 million for large firms. In particular, Phase III expenses per investigational NCE for large firms were 2.6 times those for small firms. Significant cost disadvantages in the discovery stage, and slightly lower success rates meant, however, that total uncapped out-of-pocket R&D costs for small firms were 25 percent larger than those for large firms.

*Table 7* Uncapitalised out-of-pocket costs per approved NCE  
(million \$ 1997, US data)

	<i>Discovery</i>	<i>Development</i>	<i>Total</i>
Small	143.9	53.0	197.0
Medium	93.1	93.9	187.0
Large	93.2	65.6	158.7

*Source:* DiMasi et al., 1995a, 210.

Henderson and Cockburn (1996) also found evidence of both scale and scope economies in the discovery phase of pharmaceutical R&D. Rather than sales data, they used total annual research expenditures to measure firm size and the number of research programs in which expenditure was more than \$500,000 per year. ‘Ceteris paribus, research programs located within larger firms are significantly more productive than rival programs located within smaller firms’ (ibid., 55).

To explain the positive relationship between firm size and development costs, DiMasi et al. speculated that smaller firms may have more efficient development processes or, alternatively, less ambitious objectives in terms of the innovativeness of their new drug candidates (DiMasi et al., 1995a, 208). Depending on how many investigational NCEs they are working on and where these medicines are in the pipeline, large, integrated firms may have problems with excess clinical trial capacity. It might, therefore be more cost effective for some to outsource parts of the development process to clinical research organizations (CROs) rather than do everything in-house.

Recent literature specifically concerning biotechnology companies seems to challenge DiMasi et al.’s and Henderson and Cockburn’s findings of an inverse relationship between discovery costs and firm size and a positive correlation between development costs and firm size. Simpson (1998) for example, argues that small companies that specialise in research have certain advantages in discovery, while large companies are in a better position to exploit scale advantages that exist in development. She suggests that the technological change in the way discovery takes place, which is characteristic of biotechnology, means that the advantages gained from specialising in discovery outweigh scale economies gained from large research facilities and staffs.

It is important to keep in mind that DiMasi et al.’s study looks at products

starting clinical trials between 1970 and 1982 and Henderson and Cockburn's studies looked at patents received between 1960 and 1989, periods before many companies started to use biotechnology methods. DiMasi et al. and Henderson and Cockburn were also, presumably looking at fully integrated companies of different sizes. Thus one must be careful in comparing the costs of the small research focused companies in Simpson's piece with the small fully integrated companies of DiMasi et al. and Henderson and Cockburn. Nonetheless, when thinking about R&D costs per NCE in the 1990s, it is important consider how the organization of production has changed with the development of new technologies.

The next section briefly explores how new technologies might affect total costs per NCE. As companies have only started to integrate them into their R&D processes relatively recently, however, the impact of these changes is more important for consideration of future rather than past costs.

### 3.1.3 The impact of new technologies on total costs per NCE

The integration of new technologies such as biotechnology, combinatorial chemistry, and genomics are expected to have a direct impact on the pace and cost of the drug discovery and development processes. 'The triumvirate of technologies (genomics, combinatorial chemistry and high-throughput screening) has the potential to create an explosion of new products over the next 10-20 years with the first products developed via this strategy potentially hitting the market within 5-7 years' (Lehman Brothers, 1997b, 6).

Morgan Stanley Dean Witter (1998) and Lehman Brothers (1997b)

*Table 8* The impact of new technologies on the pharmaceutical industry

<i>Technology</i>	<i>Influence on process</i>	<i>Influence on industry</i>
Combinatorial chemistry	Compound creation	Increased productivity of drug discovery
Rational drug design	Compound creation	Increased productivity of drug discovery
Genomics	Target identification	New drug categories
Signal transduction	Target identification	New drug categories
High throughput screening	Compound screening	Increased screening efficiency

Sources: Lehman Brothers, 1997b, 6.

provide thorough summaries of how the different technologies work and their likely impact on the pharmaceutical industry. Table 8 list some of the new technologies and their expected influence on the industry.

Much is made in the press about the expected positive effects: improved success rates, reduced discovery times for new targets and increased number of therapeutic targets. Morgan Stanley Dean Witter caution, however, that the net impact on costs is not easy to predict and it will depend on how and in what combination a company employs the new technologies.

Consider the example of combinatorial chemistry, the technology that companies are most rapidly integrating into their R&D process (see Table 9). It is used to generate large numbers of novel small molecules using medicinal chemistry. The two key advances of this technology are in terms of speed and diversity of chemical reactions. Combinatorial chemistry's roles in the R&D process are "the modification of existing drugs in order to improve therapeutic profile and reduce toxicology... and more fundamentally, to find molecules that block or activate targets emanating from the target identification process" (Morgan Stanley Dean Witter, 1998, 10).

The likely impact on the industry of combinatorial chemistry's ability to modify existing drugs is to decrease the time between the first and follower products in a therapeutic class, i.e., to reduce the period of exclusivity for first products. This does not mean lower costs for those developing the first-in-class drugs. It means greater success rates and perhaps quicker development times for the follower producers and so a shorter period during which the

*Table 9* Timing the commercial impact of new technologies

	<i>Expected years from 1998 until 80% implementation</i>
1. Combinatorial chemistry	2
2. Ultra high throughput screening	4
3. Genomics	5-7
4. Bio-informatics	3
5. Pharmacogenomics	7-8
6. Virtual drug discovery – integrating the platforms	7-9
7. Gene therapy	10-15

*Sources:* Morgan Stanley Dean Witter, 1998, 20.

leader can recover the high costs of innovation by taking advantage of its market exclusivity<sup>24</sup>.

High-throughput screening (HTS) and genomics-linked technologies are part of a more profound structural change in how research is done. HTS is the flipside of combinatorial chemistry: it is the facilitator in extracting the maximum value from the combinatorial libraries when applied to a new target. Genomics is aimed at identifying new targets for drug interaction. Though linked to greater leaps in drug discovery, these technologies also require significant up-front investments to integrate them into the R&D function, so increasing the costs for companies to be a competitor in drug discovery (*ibid.*, 19). Morgan Stanley Dean Witter suggest that it will be a number of years before HTS and genomics have a significant effect on the NCE approval rate.

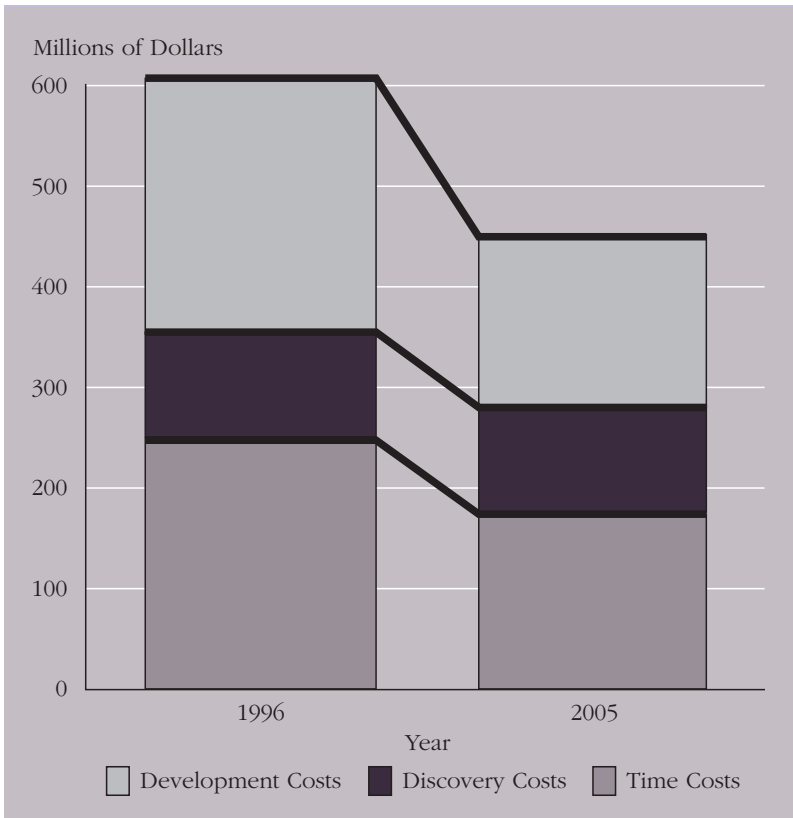
Lehman Brothers are nonetheless optimistic about the net effect of new technologies on costs. Acknowledging that they might increase absolute total R&D spending, these analysts still predict a reduction in the cost per NCE. In one scenario, total development spending would increase but the percent of INDs ultimately approved for marketing would increase from 20 percent to 45 percent while the total time required would fall from 11-14 years to 9-10 years (Lehman Brothers, 1997b, 4-5). This adds up to a decline in out-of-pocket development costs per NCE (as the costs of failures fall) and a decline in opportunity costs as the R&D period shortens. Figure 7 illustrates this impact on the cost per NCE (including capitalised costs). Lehman Brothers do not predict a significant change in discovery costs per NCE<sup>25</sup> but the total R&D costs per NCE would fall from \$635 million to \$468 million (in 1997 dollars).

The next section examines how R&D time profiles have changed and how they differ between therapeutic categories and between companies of different sizes. At the time of the DiMasi et al. 1991 study, opportunity costs already made up more than 50 percent of total capitalised costs. The observed

24 Morgan Stanley Dean Witter predict an increase in marketing costs as companies strive harder to differentiate their products from others to attain enough market share to cover costs.

25 Discovery costs per NCE will be affected, if, as Simpson (1998) and others have suggested, small biotechnology companies become increasingly cost-efficient at research and discovery (see above). By choosing to license-in investigational NCEs at one of the clinical trial phases rather than invest in the discovery research, companies might be able to reduce total R&D costs per NCE.

Figure 7 Expected impact of enabling technologies on the cost of a NCE



Source: Lehman Brothers, 1997a, 10.

increase in development and discovery times in the 1980s and 1990s implies that total capitalised costs are much higher in the 1990s than they were in the 1970s and early 1980s.

### 3.2 The impact of time on opportunity costs

#### 3.2.1 Trends in development times

Opportunity costs increased 140 percent between Hansen's 1979 and DiMasi et. al.'s 1991 studies, and their share of total costs increased from 48 percent to 51 percent (see Table 2 in chapter 2 above). These values and shares are

sensitive to the estimator's assumption about the discount rate, as the OTA's and Myers' work have illustrated (chapter 2)<sup>26</sup>. The influence of changes in the time profiles of the discovery and clinical phases on opportunity and total R&D costs are also substantial.

To illustrate the importance of time on the R&D costs, the OTA adjusted Hansen's and DiMasi et al.'s figures for different discovery and approval times. It found that increasing the duration of the discovery phase for DiMasi et al.'s study from three and a half years to five years, for example, would produce a 4.2 percent increase in costs, while an increase in the NDA review time from 2 years to 2.2 years produced a 0.9 percent increase in Hansen's estimate (OTA, 1993, 59)<sup>27</sup>.

The drugs included in DiMasi et al.'s study spent an average of 12 years in the discovery and development phases. By the early 1990s, according to CSDD's estimates, the average NCE took 15 years to obtain FDA approval in the US. See Table 10.

It is important to emphasise that these are the development times for obtaining US approval. CMR International's time profiles, which present the time from first synthesis to first launch anywhere in the world, not just the US, are shorter. See Figure 8. With first market launch as an end point, the time trend is also different from the CSDD figures. CMR International finds times levelling off in the late 1980s and declining after 1994 from 13 years to around 10 years in 1996. Figure 8 also shows the standard deviation of

*Table 10* Average development time from synthesis to FDA approval in the US (years)

	<i>1960s</i>	<i>1970s</i>	<i>1980s</i>	<i>1990-95</i>
Discovery	3.2	5.1	5.9	6.1
Clinical Trials	2.5	4.4	5.5	6.9
Approval	2.4	2.1	2.8	2.3
<b>Total</b>	<b>8.1</b>	<b>11.6</b>	<b>14.2</b>	<b>15.3</b>

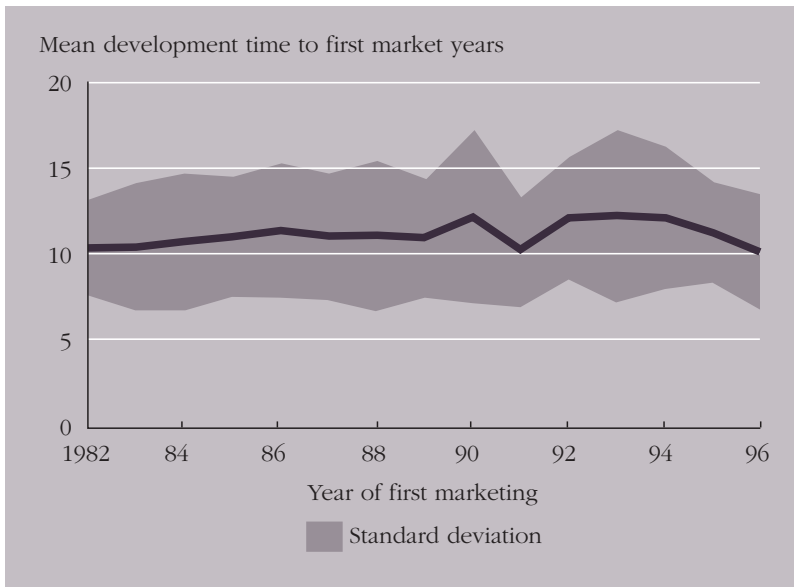
Source: CSDD, 1997, Figure 3.3, 19.

26 Combining DiMasi et al.'s out-of-pocket cost data and time profiles with larger discount rates, these studies produced significantly larger cost estimates (See Table 2).

27 It is possible to estimate the approximate impact of any time change on DiMasi et al.'s costs by recalculating capitalised costs (DiMasi's step two). To get an exact figure, however, one needs to know DiMasi et al.'s assumptions about time overlaps and gaps between phases.



*Figure 8* Mean development times for NMEs introduced onto a 20 country market (1982-1996)



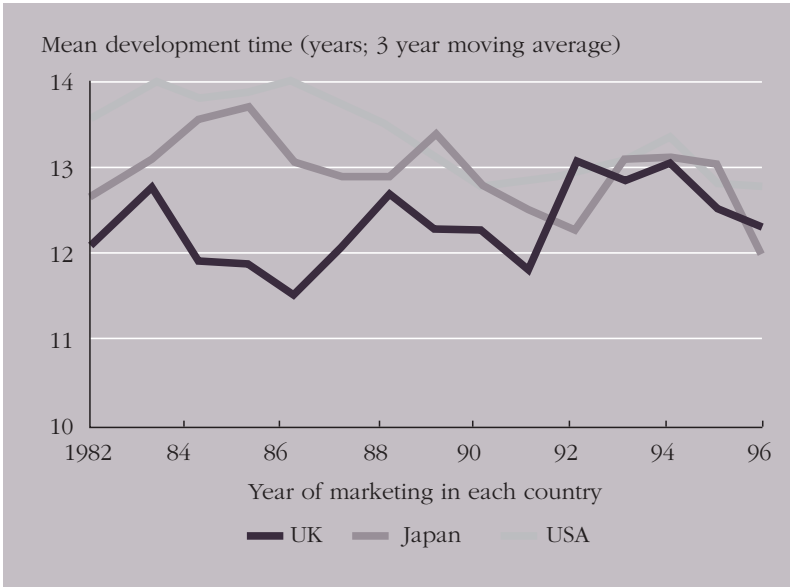
*Source:* CMR International, 1997.

development time about the mean which has not changed greatly over the period studied. Factors causing variations, including therapeutic group, company's product priority decisions, and firm size, are discussed below.

Figure 9 shows the difference in times from first synthesis to market between products in the US, the UK, and Japan. This figure shows the US and Japanese times declining throughout the 1980s with a slight increase in the early 1990s. The UK times, by contrast, increased steadily in the 1980s, peaking at 13 years in 1994. After 1994 times in all three countries fall together. Japan recorded the lowest at 12 years and the US, the highest at around 12.8 years.

According to the CSDD data, the largest increases in duration have occurred in the clinical trial phase, where average testing times grew 176% from 2.5 years in the 1960s to 6.9 years in the early 1990s (See Table 10). The

Figure 9 Mean development times to market in the USA, the UK and Japan (1982-1996)

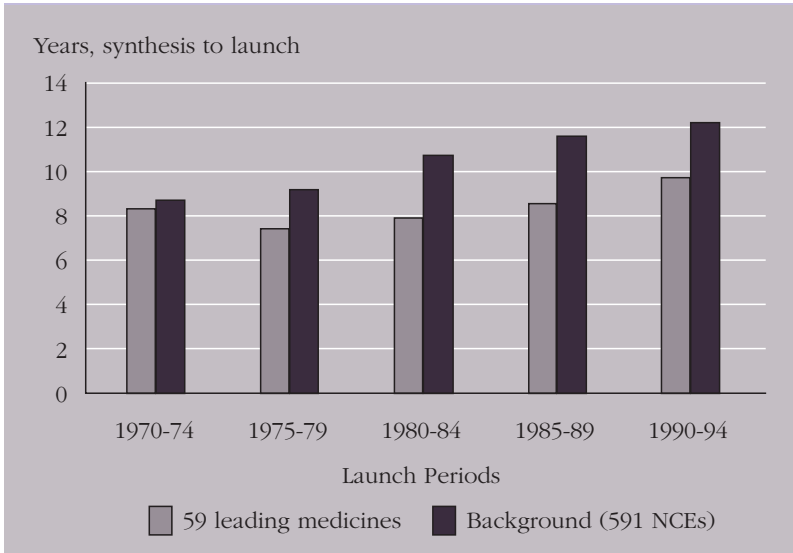


Source: CMR International, 1997.

average total time required to discover a drug almost doubled between the 1960s and the early 1990s from 3.2 to 6.1 years<sup>28</sup>. During this same time, approval times fell, a reflection, perhaps, of the FDA's renewed effort to speed up the approval phase (PhRMA, 1997, 20).

Not all of the increased duration in discovery and development times is due to external factors. Companies may choose to put lower priority projects 'on the back burner', thereby increasing the average duration measured by CSDD. Figure 10 compares the development times from synthesis to first market launch of leading medicines and all other medicines over the 1970-

28 DiMasi's discovery times for the same time periods are significantly lower, fluctuating between two and four years since the early 1970s (DiMasi, 1995b, 382). This difference may reflect different definitions of the pre-clinical period. DiMasi measures discovery time from first synthesis to first human testing. This may be a conservative estimate of time as it does not include basic research and early screening processes (OTA, 1993, 59).

*Figure 10* Mean development times for NCEs

Source: CMR International, 1997.

1994 time period. Leading medicines are defined as the top selling products in 1994 from the IMS Pharmaceutical World Review for which the CMR International had development time information. The average time for leading medicines increased from 8.4 years in 1970-74 to 9.5 years in 1990-94, while the time for all other drugs increased from 8.8 to 12.2 years. The gap between the two groups widened from three months to more than three years (Halliday and Walker, 1997, 33).

Reasons for the increased development times in the US are summarised in Table 11.

PhRMA sees changes in the scientific complexity of the products, government regulations, and in the companies' global strategies all playing a role. As an example of a change in global strategy, companies increasingly work to meet government safety and efficacy regulations in multiple countries, so as to enter many markets simultaneously. If the additional clinical studies are conducted in the US, this strategy can reduce the total global time to market, but may mean delays in applying for approval in the US relative to a single country approach.

*Table 11* Factors contributing to longer development times in the US

Pharmaceutical companies often design pre-clinical and clinical drug studies to satisfy requirements in multiple countries. Although this approach may reduce global time to marketing, it may also increase clinical development times reported in the US.
Increasing scientific complexity of new products that target persistent, degenerative, and life-threatening disease typically leads to longer development times.
Growth of pharmacoeconomic and market-oriented studies in the pre-registration phase are driven by the increasing need to demonstrate post-launch cost-effectiveness of new products over existing therapies.
There is an increasing burden of added FDA regulatory guidance and data requirements, such as the request for demographic analyses of clinical data.

Source: PhRMA, 1997, 20.

### ***3.2.2 Variations in development times across products***

Figure 8 showed significant variations in the product times around the mean. Factors attributed to these variations include: the product's therapeutic category, whether the product was discovered in-house or licensed-in from a different company, and the size of the firm undertaking the development (DiMasi et al., 1994; DiMasi, 1995b, DiMasi et al., 1995b). Existing empirical evidence of these influences is presented in the subsections which follow.

#### **Therapeutic category**

Just as there are differences in the out-of-pocket costs between therapeutic categories, there are also significant differences between these categories' time profiles. For example, for the products in DiMasi et al.'s 1995b study, the clinical and approval phase time profile for NSAIDs was 9.5 years, in comparison with 6.4 years for anti-infective drugs (DiMasi et. al, 1995b, 163)<sup>29</sup>. Phase III of clinical trials for NSAIDs was particularly long, lasting 4.5 years as compared with an average of three years for the whole sample.

<sup>29</sup> These profiles do not include discovery times because DiMasi could not get product specific data for the discovery phase.

Another sharp contrast is found in the NDA stage alone (time from NDA submission to NDA approval), where it took neuropharmacological drugs, on average, 3.5 years to get market approval as compared with two years for anti-infective drugs (*ibid.*, 162).

For a different sample, DiMasi et. al. (1994) found that the total time (drug synthesis to NDA approval) increased for all eight groups over the period of 1962-1992 but that the magnitude of the increase varied considerably across groups. 'Total time increased 10.7 and 9.1 years from the first decade to the third for the endocrine and central nervous system classes respectively.' (DiMasi et. al., 1994, 616). On the low end of the spectrum, anti-infective times increased less than four years over the same time period. See Table 12.

### **New biological entities vs. new chemical entities**

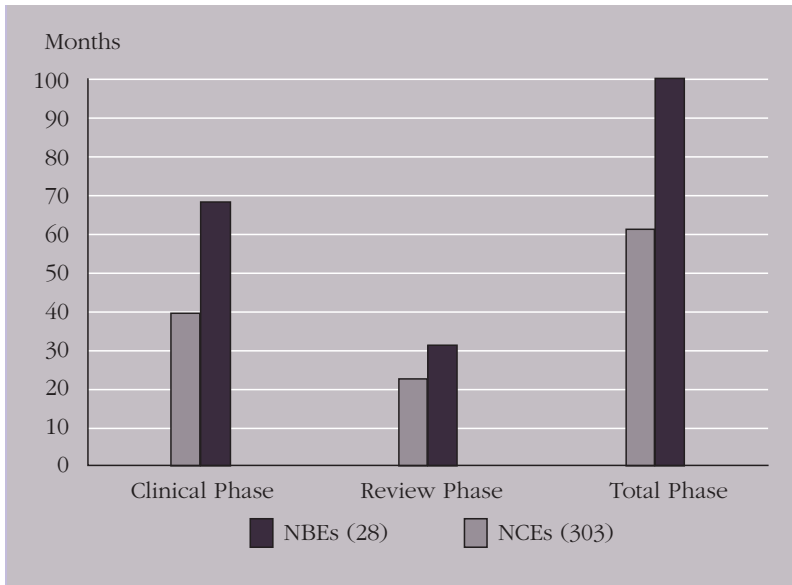
CSDD and the CMR International compare the development times for new biological entities (NBEs) and NCEs. In the CSDD study, for the sample of 28 NBEs approved in the US between 1980 and 1994<sup>30</sup>, the total time from the submission of the IND to market approval was 61 months, which is 39 months shorter than that for the 303 NCEs approved during the same period. See Figure 11.

*Table 12 Time from synthesis of NCE to NDA approval by therapeutic category (years)*

	1963-72	1973-82	1983-92
Analgesic/Anaesthetic	7.6	11.9	14.7
Anti-infective	7.8	10.0	11.4
Antineoplastic	11.5	16.8	14.7
Cardiovascular	5.4	13.9	11.0
Central nervous system	7.2	12.6	16.2
Endocrine	7.2	10.8	17.8
Gastrointestinal	N/A	7.4	11.5
Respiratory	4.5	11.6	16.7

Source: DiMasi et al., 1994, Figure 5, 616.

30 This includes NBEs developed by pharmaceutical and biotechnology companies.

*Figure 11* Comparing development times of NBEs and NCEs

Source: Gosse and Manocchia, 1996, 995.

Notes: Gosse and Manocchia, 1996, 995. Clinical phase – time from IND filing to product license application (PLA) for NBEs and NDA for NCEs

Review phase – time from PLA or NDA submission to approval

Total phase – clinical and review phase

The CSDD attributes some of the large difference to the type of NBEs approved in this period. About one quarter of the products were new recombinant versions (NRV) where the clinical profiles for these cases, both pharmacological and physiological, were already known. ‘In effect, the clinical trials of this subgroup of recombinant proteins were testing the new technology to manufacture existing products’ (Gosse and Manocchia, 1996, 999). These products took only 3.3 years on average to move through trials and gain approval versus 5.5 years for the other NBEs and 8.3 for the NCEs. Four of the seven of these NRVs were approved in the 1980s. This suggests that the gap between NCEs and NBEs might have been expected to narrow in the 1990s as the share of new recombinant entities (those not previously tested in humans) of total NBEs increases.

### Researching in-house vs. acquiring products

CSDD also finds differences in development and total time profiles between self-originated and licensed-in products. Table 13 summarises the average duration to approval in the US for self-originated and all NCEs (self-originated plus acquired NCEs). The findings show that up until the 1990s, clinical trials went faster with licensed-in products than with self-originated products. However, total times for all products including licensed-in products were longer than for just self-originated products. This implies that discovery takes longer for acquired products than self-originated ones.

‘The much higher IND phase for all NCEs during the 1990-92 period is a consequence of an unusually large proportion of very long IND phases for the *acquired* NCE group. Seven of the 34 *acquired* NCEs had IND phases that exceeded 11 years, whereas only two of the 39 self-originated NCEs had IND phases that high. The average IND phase time for acquired drugs was

*Table 13 Mean phase times up to FDA approval for self-originated and acquired NCEs (years)*

	1960s	1970s	1980s	1990-92
<b>Discovery times<sup>1</sup></b>				
Self-originated	1.5	2.3	2.8	2.6
All NCEs	N/A	N/A	N/A	N/A
<b>IND times<sup>2</sup></b>				
Self-originated	2.7	4.7	5.7	5.2
All NCEs	2.5	4.4	5.5	6.1
<b>NDA times<sup>3</sup></b>				
Self-originated	2.1	2	2.8	2.4
All NCEs	2.4	2.1	2.8	2.6
<b>Total times<sup>4</sup></b>				
Self-originated	7.9	11.1	13.8	12.8
All NCEs	8.1	11.6	14.2	15

Source: DiMasi et al., 1994, 615-616.

Notes: 1. Discovery Phase = time from first pharmacological testing of the compound to first human testing;

2. IND Phase = time from IND filing to NDA submission;

3. NDA Phase = time from NDA submission to NDA approval;

4. Total Time = time from synthesis of the compound to NDA approval.

7.1 compared with 5.2 years for self-originated ones' (DiMasi et al., 1994, 615 (emphasis added)).

Interestingly, there seems to be a link between the long IND phase times and whether a product was priority rated by the FDA for quick approval. For the 1988-92 period, the average total time from synthesis to market approval for priority rated products was 14 years compared with 13.5 for standard rated products (ibid., 617). All but one of acquired NCEs in DiMasi et al.'s study with long IND times (11 years or more) were priority rated by the FDA (ibid.). An interesting question is whether companies developing these acquired products choose to continue with difficult, and lengthy clinical trials because they were offered priority approval status, or if, in order to get this priority approval status, these companies were required to meet a set of more stringent and lengthy clinical requirements.

### **Firm size**

How the time profiles differ between self-originated and acquired products may be related to the size of the firms that conduct both discovery and development in-house, i.e., produce self-originated products, as compared with the firms that specialise in discovery and then license-out the product for clinical trials. In their study on R&D costs and firm size, DiMasi et al. (1995a) identified large differences in the time profiles for different sized firms for the 1970-82 period<sup>31</sup>.

Small firms took much longer to complete the discovery and NDA approval phases, while large firms generally had longer clinical trial phases. The total time profile from product discovery to market approval for a representative NCE from a small firm was 13.1 years as opposed to 10.7 years for a NCE from a large firm. See Table 14.

In sum, total time profiles appear to have lengthened since DiMasi's study but total time depends on where the product is marketed, as well as the companies' size, organization and drug profile. Large variations about the mean are observed. There is also evidence that in the past, NBEs were easier to test and approve than NCEs. If that was a function of the types of NBEs that were first introduced to market, however, the difference in times may have already narrowed in the 1990s.

31 For definitions of firm size, see footnote 22.



*Table 14* Phase lengths for NCEs by firm size, US data  
(years)

	<i>Small</i>	<i>Medium</i>	<i>Large</i>
Discovery	4.8	2.7	2.8
Phase I	1.2	1.6	1.2
Phase II	1.1	2.0	2.3
Phase III	2.3	2.6	2.3
NDA Review	3.7	2.4	2.2
Time Profile	13.1	11.3	10.7

Source: DiMasi et al., 1995a, 210.

CMR International's evidence suggest that development times have started to decline in the past few years. Times for the global industry peaked at 12 years in 1993 and declined to 10 years by 1996 (CMR International, 1998). This contrasts with CSDD's numbers which show continued increases. Where the product is launched makes a big difference. CMR International looks at the time to first launch anywhere in the world while CSDD looks at the time to first launch in the US. In another study, CMR International found important differences in times for leading products developed and brought to market in different countries<sup>32</sup>. Italy, UK, Swiss, and German medicines had development times less than the 8.5 year global mean (6.4, 7.2, 8.3, 8.4 years respectively), while US, Swedish, and Japanese medicines had longer development times (8.7, 9.8, 10.3 years respectively) (Halliday and Walker, 1997).

It is too early to accurately explain the observed declines in development times in the mid 1990s. The objective of a benchmarking project under way at CMR International since 1995, is both to monitor the changes in time profiles and to determine the influential factors. These factors could include: changes in the companies' organizational structures (more active use of outsourcing), the more efficient use of new technologies, and government regulators' efforts to approve products more quickly.

32 Time from synthesis to market approval in a specific country.

## 4 CONCLUSIONS

The cost of bringing a NCE to market is sensitive to the time to launch, the discount rate assumed, and the proportion of medicines that eventually prove successful.

Table 15 illustrates how the cost figure responds to changes in these three factors. Changing DiMasi et al.'s values to reflect changes observed in the 1980s, a figure such as the Lehman Brothers' \$635 million can quickly be arrived at. Holding all else constant, an increase in total time by 3.5 years would increase DiMasi et al.'s estimate by 50 percent from \$312 million per approved NCE to \$473 million (in 1997 US\$). This represents the upper bound in development times. Substitute a 10 percent discount rate in place of DiMasi's 9 percent and the cost increases to \$536 million per NCE. Finally, if aggregate success rates are lower than 23 percent, say 20 percent, costs would increase to \$615 million per NCE. This figure does not take into account reported increases in the complexity and number of clinical trials.

Another (crude) way to estimate the R&D costs for a NCE is to divide total R&D expenditure allocated to new medicines in one year by the number of NCEs entering the market in a subsequent year. Given the time lag between the drug synthesis and FDA approval of around 10-12 years, the most recent products that could be considered this way are products that were discovered in the late 1980s. Worldwide R&D expenditure was around \$15

*Table 15* The sensitivity of the NCE cost estimate to changes in time, discount rates and success rates  
(million \$ 1997)

	<i>Discovery</i>	<i>Development</i>	<i>Total<sup>(1)</sup></i>	<i>Total<sup>(2)</sup></i>	<i>Total<sup>(3)</sup></i>
Case 1	210	102	312	287	359
Case 2	330	143	473	435	545
Case 3	380	156	536	493	615

*Source:* Case 1: DiMasi et al., 1991, 126.

*Notes:*

Case 1 – 11.8 years; 9% discount rate

Case 2 – 15.3 years; 9% discount rate

Case 3 – 15.3 years; 10% discount rate

Total 1 – 23% success rate

Total 2 – 25% success rate

Total 3 – 20% success rate

billion in 1987 (1997 US\$). If we assume that 80 percent<sup>33</sup> went towards new products and use a 10 percent discount rate<sup>34</sup>, the 40 products coming on to the market in 1997 cost an average of \$770 million each including opportunity cost.

However, the cost per NCE is not an exogenously determined fact imposed on companies. Companies can use strategies to shape costs. I have provided evidence in this paper that costs will be affected by the company's product profile, the type of technology it uses, and the types of activities it chooses to conduct in-house and those it outsources. Depending on their choice of priorities for clinical trials, the company might also increase average development times beyond what is technically necessary by delaying the testing of some medicines in order to focus on others.

Significant differences exist in the costs of developing medicines in different therapeutic categories. The company's choice of drug categories is in part demand determined but companies are also constrained by their human capital skills and experiences. To bring consumer demand more in line with their capabilities, companies can use marketing and advertising.

More important than the question of the exact R&D cost per NCE today is the question of cost trends. Have R&D costs per NCE peaked? Many in the industry are betting that new technologies can produce dramatic improvements in pharmaceutical R&D productivity and reduce unit costs. But how these technologies will affect the industry's average cost per NCE will depend on companies' strategies to integrate them (Morgan Stanley Dean Witter, 1998) .

Related to this is the fact that companies of different sizes execute stages of the R&D process more or less effectively. In the past, large companies seemed to have had an advantage in the discovery stage, where economies of scale were important, while small companies could execute clinical trials more cheaply and quickly.

Studies of the biotechnology industry, suggest that the role of scale in

33 Total R&D spending includes spending not only on new drug products but also on modifications and extensions of existing products. Wiggins used 80 percent as an estimate of the proportion of total PhRMA spending devoted to NCE R&D (OTA, 1993, 61).

34 The OTA (1993) and Myers and Howe (1997) suggest that the cost of capital is higher than the 9 percent used in DiMasi et al.'s 1991 study. Later studies conducted by DiMasi et al. using this original data (DiMasi et al., 1995a and 1995b) include discussions of how the cost of capital should probably be higher than was originally assumed.

pharmaceutical R&D is changing. Small companies, armed with new technologies and motivated scientists, might be better able to discover drugs with efficiency comparable to large companies (Simpson, 1998). Large companies, on the other hand, can provide the resources to move products through clinical trials more quickly and with greater success, again, with the help of new technologies. That inter-firm collaborations, out-sourcing agreements, and licensing-in of products have become more frequent in the 1990s suggest the companies are seeking to take increasing advantage of these differences.

Given the difficulties in collecting adequate data, few serious attempts have been made to calculate the R&D costs per NCEs. This examination of how the R&D processes have changed over the 1980s and 1990s suggest that existing estimates are out of date. I have argued that the costs per NCE launched today may approach \$600 million, almost twice that of DiMasi et. al.'s 1991 figure adjusted for inflation. The main factors pushing up these costs include longer development and approval times, larger and more complex clinical trials, increased expenditures in new technologies, and shifts in product portfolio towards riskier, more expensive therapeutic categories. Whether costs per NCE have reached their peak or will continue to increase, will depend in particular on the ability of companies to use new technologies to reduce discovery and development times and increase success rates.

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