A Sensitivity Analysis of Expected Profitability of Pharmaceutical Research and Development

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An indirect effect of increased regulation of the pharmaceutical industry in the USA has been a reduction in the effective patent life for a new drug. The reason is that the average time to develop a new chemical entity and gain regulatory approval far exceeds the time necessary to obtain a patent. The period of patent protection now averages only 10 years compared to the legal life of 17 years. In this article we describe a sensitivity analysis which sheds some light on the relationship between product life and profitability. Based upon a number of important assumptions, we show, for example, that at a 10% real rate of return the average 1970–1976 new drug required 19 years to break even. At an 8% real rate of return, 12 years would permit the firm to break even.

The pharmaceutical industry has been one of the most innovative industries in the USA over the past 30 years. However, the rate of new drug introductions in the past decade has been significantly lower than it was in the earlier post World War II period. As a result, the reasons for and social significance of this decline have been the subject of considerable attention by both policymakers and academicians.

The decline in new drug introductions has been accompanied by strong upward trends in costs, time and risks associated with discovering and developing new drugs. As one would expect, studies of the rate of return to drug innovation have found relatively low returns.[1,2] It is also the case that US firms are increasing their Research and Development (R and D) expenditures in foreign countries at a faster rate than in the USA. In fact, in real terms, US R and D expenditures may be declining. One important explanation for these trends has been the increased regulatory controls of the Food and Drug Administration (FDA) which resulted from the 1962 Kefauver–Harris amendments to the Food, Drug and Cosmetic Act.[3] These amendments required a new drug's efficacy, as well as safety, to be demonstrated on the basis of well controlled scientific tests prior to marketing approval by the FDA.

An indirect effect of regulation has been a reduction in the effective patent life for a new drug. The reason is that the average time to develop a new chemical entity (NCE) and gain regulatory approval far exceeds the time necessary to obtain a patent. While the length of patent protection has been of secondary import historically in the drug industry, this situation appears to be changing with the repeal of antisubstitution laws.[4] That is, the antisubstitution laws made it possible for innovating firms, through strong brand loyalties, to maintain dominant market positions for their products even after patent expiration. Now, in many states, lower cost generic products that become available upon patent expiration can be substituted by pharmacists even though the physician prescribes the original brand name products.

The period of patent protection now averages only 10 years or so as compared to the legal life of 17 years. For this reason, legislative proposals have been made to restore part or all of the patent life lost during the chemical testing and FDA review period. The objective, of course, is to stimulate innovation by increasing the expected return to pharmaceutical R and D.

Given the current interest in patent policy and its impact on the expected return to pharmaceutical R and D, we have performed a preliminary sensitivity analysis which sheds some light on the relationship between product life and profitability. Of course, the results are inadequate to support any particular product life as being the 'socially optimal' patent life. Rather, the work here is intended as a first step in understanding the quantitative effects of various product lives on profitability as well as other related issues.

Based upon a number of important assumptions, we show, for example, that at a 10% real interest rate the average 1970–1976 new drug required 19 years to break even. At an 8% interest rate, 12 years would permit the firm to break even. 'Breaking even' means to cover all R and D discovery and development costs in addition to production and marketing costs.

While the above paragraph refers to the *average*

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investment in drug innovation, we also show that the variance in payoffs is great and highly skewed. For example, of the 37 NCEs discovered and introduced in the USA in the 1970–1976 period, only 13 were able to at least cover their costs (over a 20 year life). This is true despite the fact that the *average* payoff to the 37 NCEs was slightly in excess of the average cost.

An interesting finding for R and D strategic decisions is the variation of profitability across therapeutic classes. Although the small numbers of NCEs in certain classes make it dangerous to generalize, it appears that for the 1970–1976 period the anti-infective category was clearly the most profitable. The cardiovascular and anti-inflammatory drugs were apparently next in order of profitability, while the remaining classes failed, on average, to break even.

Another interesting result is the impact of reducing FDA approval time on profitability. Suppose there is no change in the amount of clinical testing performed; however, suppose the time taken by the FDA to approve a submitted New Drug Application (NDA) is reduced from the usual 24 months to 6 months. What is the impact of this shorter approval time on profitability? We show, for one set of assumptions, that the average drug's product life necessary to break even is reduced by about 5 years – from 19 years to 14 years. In other words, reducing NDA approval time by 18 months is equivalent in present value terms to adding on 5 years to the drug's life.

In the next section we shall review the data and assumptions used in the analysis. The concluding section consists largely of a set of figures which show our principal results.

DATA AND ASSUMPTIONS

The primary data used in the analysis are US sales and promotion expenses for NCEs introduced into the US market between 1970 and 1976, and R and D costs by therapeutic class estimated by Professor Ronald W. Hansen.[5,6] The sales and promotion data are Intercontinental Medical Statistics (IMS) data.

Two additional important types of data were not available – the cost of producing the NCEs after FDA approval and the net revenues resulting from sales in foreign countries. In both cases we have relied on estimates made by Celia Thomas as part of her PhD dissertation at Duke University. For example, her best estimate for production costs as a fraction of sales is 0.30. However, because of the uncertainty about this estimate, we have also examined the effect of estimates of 0.20 and 0.40. A similar approach was taken with respect to Thomas' estimate of 1.75 as the ratio of world-wide net revenues to US net revenues. That is, estimates of 1.5 and 2.0 were also used in a sensitivity analysis.

As noted above, the R and D cost estimates are based on a study by Hansen. He obtained survey data from 14 pharmaceutical firms on the R and D costs for a sample of NCEs first tested in man from 1963 to 1975. The average discovery cost was $19.6 million and the average development cost was $14.1 million, for a total of $33.7 million. The $33.7 million represents the capitalized value (at 10% interest and in 1967 dollars) at the date of marketing approval.[5]

At our request, Hansen estimated the costs per NCE on a therapeutic class basis. These are the cost estimates used in this analysis, and as will be shown, reveal a rather large variation across classes. We should also note that Hansen's estimates include the costs of NCEs that enter clinical testing but are not carried to the point of NDA approval.[6] Hence, the estimates should be interpreted as the average *expected* cost of discovering and developing a marketable NCE.

Of course, real R and D costs have probably been increasing over time. However, by restricting the analysis here to NCEs marketed between 1970 and 1976, we can assume that Hansen's estimates match our NCEs reasonably well without the need for further adjustments. We also note that our primary analysis pertains to 37 NCEs that were both discovered and introduced in the USA. Some 23 additional NCEs were discovered in foreign countries and introduced in the USA during this period. However, only limited use was made of these 23 NCEs because Hansen's R and D cost figures clearly do not apply to foreign discoveries.

As observed above, Hansen's estimates are expressed as capitalized values at the date of marketing. For example, the capitalized expected cost of discovering and developing a cardiovascular drug at the date of marketing is $30.6 million in 1967 dollars. Because he worked with constant dollars, Hansen used real interest rates; in the example

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above, the interest rate is 10%. The natural measure for comparison with Hansen's estimate is the present value of the net revenue stream resulting from the NCE. To be consistent, of course, the net revenue stream must be deflated to 1967 dollars and discounted to the date of marketing at the same real interest rate. The ratio of present value of net revenue to capitalized R and D cost is termed the profitability index (*PI*) in the finance literature, and it will be the measure of expected returns used here. Clearly, a $PI = 1$ implies a project that just breaks even.

The formula for the *PI* for a particular drug is

$$PI = \frac{1}{RD} \sum_{t=1}^{L} (S_t - P_t - mS_t) f e^{-r(t-1)}$$

where S_t = deflated sales revenue in year t; P_t = deflated promotion expenses in year t; m = production cost as fraction of sales; f = ratio of world-wide net revenues to US net revenues; r = real interest rate; L = product life; and RD = capitalized value of R and D costs by therapeutic class. Table 1 provides some general information about the data.

Actual sales and promotion data were available for 10 years for NCEs introduced in 1970, for 9 years for 1971 NCEs, and so on, so that data were available for only 4 years for 1976 NCEs.[7] Hence, projections into the future were necessary and were made in two steps. In step one, sales and promotion expenses were projected out to the tenth year after introduction for all NCEs, based on the average growth rate experience for a sample of 55 NCEs with introduction dates extending back into the mid-1960s. No projection was necessary for 1970 NCEs while 1976 NCEs required a 6 year extrapolation. In step two, sales and promotion expenses were projected beyond the tenth year, by assuming that nominal dollar increases would be exactly offset by inflation. In other words, real dollar sales and promotion were held constant at their tenth year values.

RESULTS OF THE ANALYSIS

The figures in this section are intended to be largely self-explanatory. The basic relationship is that between the *PI* and the Product Life. For the analysis here we have simply set the net revenue stream equal to zero at the end of the assumed Product Life. More reasonable assumptions about the time pattern of net revenues will be incorporated in later work. For example, we might assume that upon patent expiration there may be an immediate impact of generic competition, but that the market share diminishes gradually.

Figure 1 shows the *PI* versus Product Life relationship for four alternative real interest rates (cost of capital). As stated the *PI* variable is a weighted average *PI* for the 37 NCEs, where the weights applied are the R and D costs. The fraction of production cost to sales is held at 0.30 and the ratio of world net revenues to US net revenues is taken to be 1.75. If we assume that the appropriate real cost of capital (inclusive of a risk premium) is 10%, then the product life necessary to break even on average is 19 years. An 8% cost of capital reduces the break-even life to 12 years.

Since the assumptions about production costs and foreign sales are uncertain, Fig. 2 was prepared to reflect this uncertainty. Given the subjective probability distributions shown in Fig. 2, a band of one standard deviation in width about the weighted average *PI* is presented. The one standard deviation band brackets the break-even life between approximately 14 and 30 years.

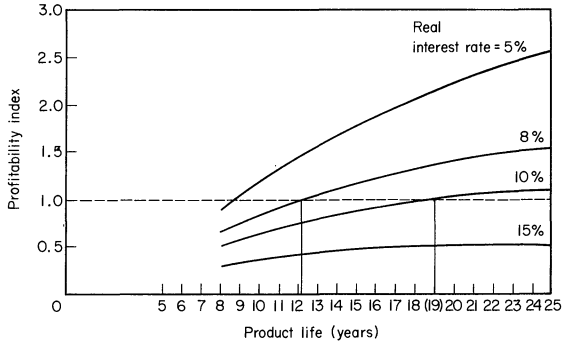


Figure 1. Weighted average *PI* versus life for various interest rates (weights are R and D costs). Assumptions: (1) 37 NCEs discovered and introduced in the USA between 1970 and 1976; (2) Hansen's R and D cost by therapeutic class; (3) ratio of production cost to sales = 0.3; and (4) ratio of world net revenues to US net revenues = 1.75.

Table 1.

Therapeutic class	Hansen's R and D cost (10%, 1967 dollars)	Number of US NCEs	Number of foreign NCEs
A. Cardiovascular	30.6	4	1
B. Neurologic, analgesic	36.3	6	2
C. Psycho-pharmacology	70.0	3	4
D. Metabolic, antifertility	65.3	5	4
E. Anti-infective	19.1	12	6
F. Anti-inflammatory	68.3	4	1
G. Gastro-intestinal, respiratory, surgery	28.5	3	5
Total		37	23

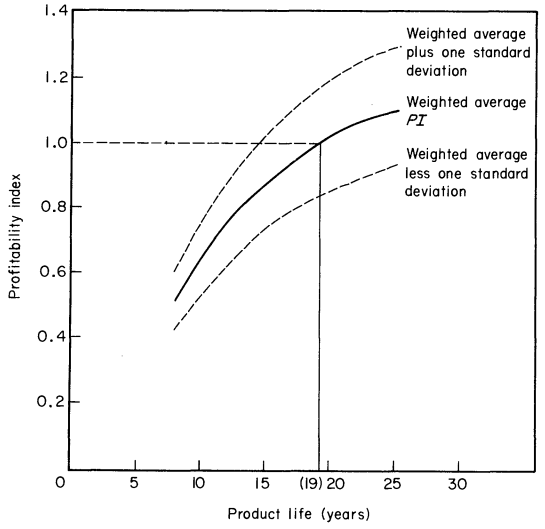


Figure 2. Weighted average *PI* versus life with uncertainty bands (uncertainty due to estimates of *m*, *f*). Assumptions: (1) 37 NCEs discovered and introduced in the USA between 1970 and 1976; (2) real interest rate = 10%; (3) Hansen's R and D costs by therapeutic class; and (4) ratio of production cost to sales, *m*, and ratio of world net revenues to US net revenues, *F*, have probabilities:

Probability	*m*	*f*
0.25	0.2	1.5
0.50	0.3	1.75
0.25	0.4	2.0

More specifically, we assume that there is a 50% chance that the ratio of production cost to sales is 0.3, and a 25% chance each that the ratio is 0.2 or 0.4. Similarly, we assume that the ratio of world net revenues to US net revenues is 1.75 with a 0.5 probability, and either 1.5 or 2.0 with probabilities of 0.25 each. These probability distributions give rise to a probability distribution of the weighted average *PI*, and the one standard deviation band for this distribution is shown by the dashed lines in Fig. 2.

Figure 3(a) focuses on a different type of uncertainty. It shows a frequency distribution of the *PI*s of the 37 NCEs. Clearly, the distribution is highly skewed – with only 13 of the 37 projects breaking even or better. The letters are codes for the innovating firms and indicate that firm 'A' had 3 'winners', while the remaining 10 were spread over 10 different firms. Figure 3(b) is the same figure except that the letters are codes for the therapeutic classes of the 13 NCEs that break even or better.

Of course, the 24 NCEs that have *PI*s of less than unity fail to break even only in the sense of not covering fully allocated discovery and development costs, including a share of the costs of drugs that never make it to the point of NDA submission. This is the nature of Hansen's R and D cost estimates. If we consider only the development costs of a single NCE (neglecting discovery costs and attrition costs), the capitalized R and D costs decline substantially.

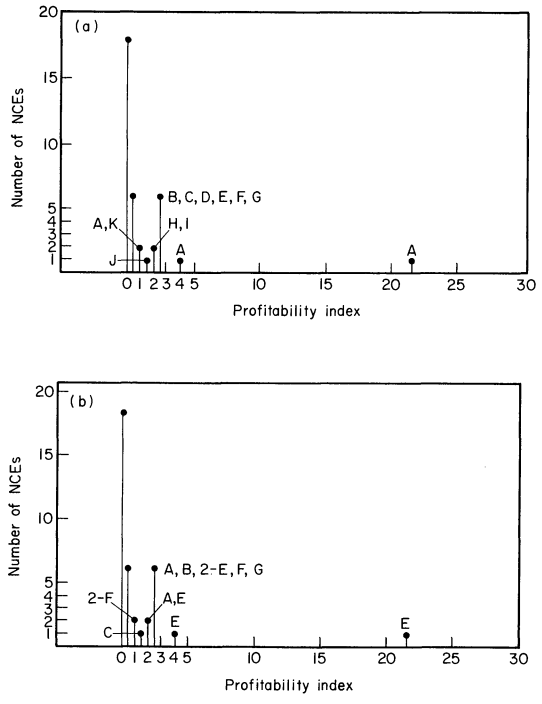
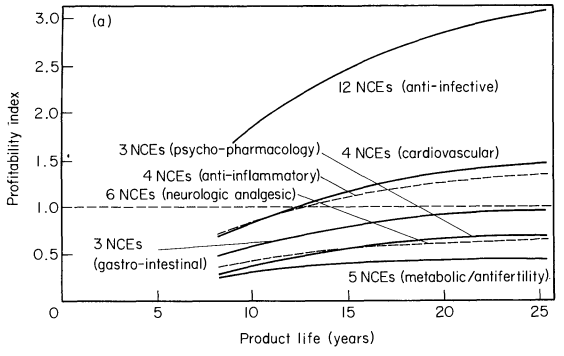


Figure 3. Distribution of *PI* of 37 NCEs 1970–1976. (a) Letters indicate firms introducing the 13 NCEs with $PI \geq 1$. Assumptions: (1) ratio of production cost to sales = 0.3; (2) ratio of world net revenues to US net revenues = 1.75; (3) Hansen's R and D costs by therapeutic class; (4) real interest rate = 0.10; and (5) product life = 20 years. (b) Letters indicate therapeutic classes of 13 NCEs with $PI \geq 1$. For identity of class, see Table 1. Assumptions: (1) ratio of production cost to sales = 0.3; (2) ratio of world net revenues to US net revenues = 1.75; (3) Hansen's R and D costs by therapeutic class; (4) real interest rate = 0.10; and (5) product life = 20 years.

For comparison with the values in Table 1, they range between $1 million and $2.3 million. As one would expect, substituting these lower R and D values into the *PI* calculations lead to a larger number of 'break-even' NCEs. In particular, the number of NCEs that fail to cover their own development costs is only 7. Hence, in only 7 of 37 cases were firms worse off by carrying through the projects to marketing.

Figure 4 indicates *PI*s by therapeutic class. Figure 4(a) shows the weighted average *PI*s while Fig. 4(b) shows the median *PI*s. One striking result is that the anti-infective class average *PI* is far above unity while the converse is true for the median *PI*. This is easily explained by reference to Fig. 3(b) which shows that one anti-infective NCE had a *PI* of about 22, far above that of any other NCE in the sample. The median *PI* is, of course, unaffected by this 'outlier' while the average is strongly affected.

Figure 5 is a comparison of the 37 US discoveries versus the 23 foreign discoveries. The incorrect assumption that the foreign NCEs had the same R and D costs as the US discoveries is made for



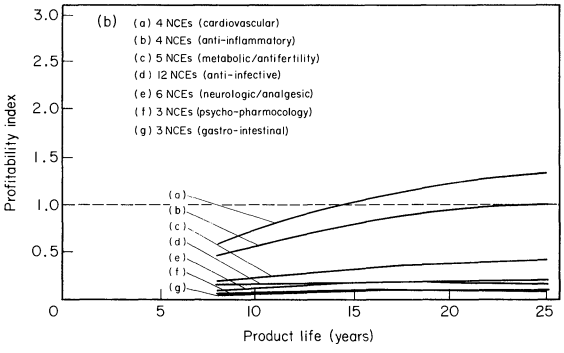


Figure 4. (a) Weighted average *PI* versus life for 7 therapeutic classes 1970–1976. Assumptions: (1) 37 NCEs discovered and introduced in USA 1970–1976; (2) Hansen's R and D cost by therapeutic class; (3) real interest rate = 10%; (4) ratio of production cost to sales = 0.3; and (5) ratio of world net revenues to US net revenues = 1.75. (b) Median *PI* of class versus life for 7 therapeutic classes 1970–1976. Assumptions: (1) 37 NCEs discovered and introduced in the USA 1970–1976; (2) Hansen's R and D cost by therapeutic class; (3) real interest rate = 10% (4) ratio of production cost to sales = 0.3; and (5) ratio of world net revenues to US net revenues = 1.75.

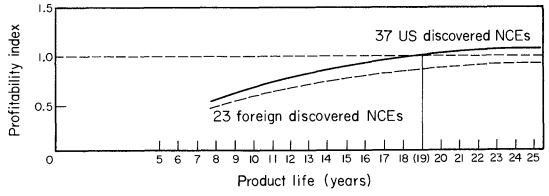


Figure 5. Weighted average *PI* versus life for US discoveries and foreign discoveries. Assumptions: (1) 37 US discoveries and 23 foreign discoveries introduced in the USA 1970–1976; (2) foreign discoveries assigned same R and D costs, production costs and foreign sales fraction as US discoveries; (3) real interest rate = 10% (4) ratio of production costs to sales = 0.3; (5) ratio of world net revenues to US net revenues = 1.75; and (6) Hansen's R and D costs by therapeutic class.

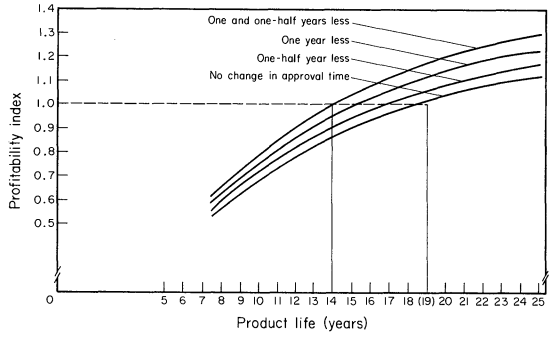


Figure 6. Weighted average *PI* versus life for alternative NDA approval times. Assumptions: (1) real interest rate = 0.10; (2) ratio of production cost to sales = 0.3; (3) ratio of world net revenues to US net revenues = 1.75; (4) 37 NCEs discovered and introduced in the USA 1970–1976; and (5) Hansen's R and D costs by therapeutic class.

purposes of the comparison. Perhaps the main message is simply that the average sales of US discoveries exceeds that of foreign ones.

The final figure, Fig. 6, shows the effect of reductions in NDA approval times. As discussed earlier, reducing NDA approval time by 18 months is equivalent in present value terms to adding on 5 years to the drug's life. That is, the break-even life with no change in approval time is 19 years, but with an 18 month reduction the life is reduced to 14 years.

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REFERENCES

1. D. Schwartzman, *The Expected Return from Pharmaceutical Research.* American Enterprise Institute, Washington (1975).
2. J. R. Virts and J. F. Weston, in *Drugs and Health,* edited by. R. B. Helms. American Enterprise Institute, Washington (1981).
3. H. G. Grabowski, J. M. Vernon and L. G. Thomas, Estimating the effects of regulation on innovation: An international comparative analysis of the pharmaceutical industry. *Journal of Law and Economics.* (April 1978).
4. H. G. Grabowski and J. M. Vernon, Substitution laws and innovation in the pharmaceutical industry. *Laws and Contemporary Problems,* (Winter–Spring 1979).
5. R. W. Hansen, in *Issues in Pharmaceutical Economics,* edited by R. I. Chien. Lexington Books, Lexington, USA (1979).
6. R. W. Hansen, *Pharmaceutical Development Cost by Therapeutic Categories.* University of Rochester Graduate School of Management Working Paper No. GPB-80–6 (March 1980).
7. The numbers of NCEs by year of introduction are as follows: 1970(4), 1971(7), 1972(3), 1973(3), 1974(7), 1975(7) and 1976(6).

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