ELSEVIER

Journal of Health Economics 13 (1994) 383–406

JOURNAL OF HEALTH ECONOMICS

Returns to R&D on new drug introductions in the 1980s

Henry G. Grabowski *, John M. Vernon

Duke University, Department of Economics, Box 90097, Durham NC 27708-0097, USA

Received July 1993; final version received September 1993

Abstract

This study finds that the mean IRR for 1980–84 U.S. new drug introductions is 11.1%, and the mean NPV is 22 million (1990 dollars). The distribution of returns is highly skewed. The results are robust to plausible changes in the baseline assumptions. Our work is also compared with a 1993 study by the OTA. Despite some important differences in assumptions, both studies imply that returns for the average NCE are within one percentage point of the industry's cost of capital. This is much less than what is typically observed in analyses based on accounting data.

Keywords: Pharmaceuticals; Drugs; R&D; Returns; IRR; Risk

JEL classification: L65

1. Introduction

The profitability of the pharmaceutical industry has recently become the subject of increased attention by public policymakers. Both the Clinton Administration and several legislators have called attention to the fact that the industry's return on stockholder equity has been more than double that of the median firm in the

* Corresponding author. Tel. (919) 660–1839, Fax (919) 684–8974. We would like to thank Judy Wagner of the Office of Technology Assessment for making available the work sheets from their analysis of the returns to R&D for 1981–83 NCEs. We would also like to thank Mike Scherer for his thoughtful comments on an earlier draft of this paper.

SSDI 0167-6296(94)00023-9

Fortune 500 Firms listings. Furthermore, there have been calls for price controls on pharmaceuticals as a strategy for health care cost containment.

While pharmaceutical profitability is a relevant subject of inquiry for both academics and policymakers, accounting measures of the return like those appearing annually in *Fortune* are not a very good basis to evaluate this industry s market performance. Stauffer (1971), Fisher and McGowan (1983) and other authors have demonstrated that accounting measures are a poor proxy for the underlying internal rate of return (IRR) of a firm or industry. The basic reasons are problems of bias due to both timing and aggregation. Furthermore, accounting measures of profitability are subject to significant distortion in industries with high rates of intangible capital investments like pharmaceuticals. The consensus from empirical studies is that the returns to equity for pharmaceuticals are overstated by at least 20 to 25% for this latter reason (Clarkson, 1977; Grabowski and Mueller, 1978; Megna and Mueller, 1991).

In the current paper, we present an alternative approach for evaluating pharmaceutical industry profitability. In particular, we focus on the cohort of new chemical entities (NCEs) introduced by drug firms in the first part of the 1980s. For these NCEs, we estimate annual cash flows over the product life cycle. Our basic objective is to compute IRRs and NPVs for the representative NCE introduction over this period. Our investment life cycle approach, using NCE cohort data, avoids the timing and aggregation problems associated with profitability studies based on income and investment data from corporate accounting statements [1].

Of course, our approach also has limitations. We must make forecasts of future sales revenues and cash flows that are necessarily somewhat uncertain. It is also true that the returns estimates that we obtain apply only to NCEs and not to profits resulting from existing, older products or non-pharmaceutical activities. Nevertheless, we think analyses of the returns to recent cohorts of NCE introductions are likely to shed more light on the pertinent policy questions facing legislators than aggregate accounting-based studies of profitability.

Our analysis builds on prior work on the returns on NCEs introduced in the 1970s (Grabowski and Vernon, 1990; Joglekar and Paterson, 1986). Our previous analysis found that returns over the full decade of the 1970s were generally in line with the industry's cost of capital, but that returns in the latter half of the period exhibited a significant upward advance. More recently the Office of Technology

[1] Baber and Kang (1991) in a recent paper have shown how the internal rate of return can be derived from an accounting approach (i.e., the cash flow recovery return) under very special assumptions. They have applied this approach to the pharmaceutical industry. However, it remains to be seen how sensitive their findings are to the special assumptions that are employed. In addition, in contrast to our approach based on individual innovations, their analysis uses aggregate corporate-level data which includes non-pharmaceutical businesses.

Assessment has conducted an analysis of the profitability of 1981–83 NCEs (OTA, 1993). Their study utilizes an approach similar to our earlier analysis, but they change some of the primary assumptions. A major finding of the OTA study is that 1981–83 NCEs had a positive present value of 36 million dollars or surplus revenues above break-even values of approximately 4%. These findings have been cited by one of the study's sponsors, Representative Henry Waxman, as evidence that competition does not work in the prescription drug market [2].

Aside from the OTA report, a number of industry developments make an analysis of the 1980s NCE returns especially interesting at this time. First, both R&D costs for new drug introductions and prescription prices have significantly increased in real terms during the 1980s. In addition, important legislation was passed in 1984 that significantly altered both the effective patent terms in this industry and the ease of entry by generic competitors after patent expiration (Grabowski and Vernon, 1992). There is also evidence suggesting that the rapid growth of managed care during the past decade is beginning to have significant effects on price competition among pharmaceutical firms (Ito, 1992; Chinburapa and Larson, 1991).

This paper is organized as follows. In the next section, we present a description of the data samples and methodology for the returns to 1980–84 NCEs. The primary results are given in Section 3, which includes a comparison of returns in the 1980s with our prior findings on returns to 1970s introductions. Section 4 then compares the assumptions and findings of our analysis to those in the OTA study. The final section offers a summary and concluding remarks.

2. Data samples and methodology

2.1. Overview

The objective of this section is to explain the key assumptions and methodology used in estimating the returns to the 1980–84 NCEs. At the outset we should note that a detailed discussion of the methodology is provided in our 1990 paper; hence, we will give a fairly brief treatment here – emphasizing areas in which the present study differs materially from the 1990 study. The basic sample is 67 NCEs

[2] Congressman Waxman's comments, however, contained major distortions in the OTA findings on drug industry profitability. In particular, he asserted that the OTA study implied there is two billion dollars in excess drug industry profits (New York Times, Feb. 26, 1993, p. C1). However, this two billion dollar figure is based on an extrapolation of OTA's small estimated surplus for 1981–83 NCEs to the full universe of pharmaceutical sales revenues (including those of older NCEs, generic drugs, etc.). By contrast, the OTA report emphasizes the fact that "dollar returns on R&D are highly volatile over time," and hence its findings are applicable only to the period and NCEs investigated in the study.

approved by the Food and Drug Administration (FDA) and introduced into the United States between 1980 and 1984. Our sample includes all NCEs originating from and developed by the pharmaceutical industry, except those in a few therapeutic classes where the R&D process is likely to be non-representative [3]. For each NCE, annual cash flows are estimated over the drug's projected product life. Industry mean values are then constructed for this portfolio of NCEs and compared to mean R&D costs per NCE obtained from an analysis by DiMasi et al. (1991). The R&D costs include discovery costs common to all NCEs and the costs associated with R&D failures. From these estimated values, we compute after-tax IRRs and net present values for the industry's total portfolio of new drugs for the 1980–84 period [4].

2.2. *Cost of capital*

In our earlier study, we employed a 9% real cost of capital based on our own capital asset pricing model (CAPM) analysis of the cost-of-equity capital in the 1970s for pharmaceuticals. A more comprehensive study by Myers and Shyam-Sunder (1990) has recently been completed of the real cost of capital for the pharmaceutical industry during the 1980s. Their study was commissioned by the Office of Technology Assessment. They found that the real after-tax cost of capital on equity plus debt for the pharmaceutical industry, varied between 10 and 11% during the 1980s.

Relying on the findings from the Myers and Shyam-Sunder study, we use a 10.5% rate for the cost of capital for our sample of 1980–84 NCEs. However, it should be borne in mind that their cost of capital estimate is based on all the business activities of drug firms, while we are focusing here on investment in new prescription drugs. As Myers and Shyam-Sunder indicate in their analysis, investments in new drugs would be expected to have a higher cost of capital, ceteris paribus, than investment in less research-intensive businesses activities of pharma-

[3] In particular, we omit new drugs in the cancer area because they were typically developed jointly with NIH. In addition, we excluded two drug approvals for schistomasis, one for malaria and one for tapeworm because these drugs are also likely to have non-representative R&D costs. Similarly, drugs discovered by universities and non-profit institutions are excluded because the R&D costs of these compounds may not be representative of drugs originating in industry. The group of excluded drugs have significantly smaller mean sales than the 67 NCEs in our sample.

[4] Because of the length of the innovative process in pharmaceuticals – 12 years of R&D and clinical testing and then 20 years or so of market life – there is always a judgment call as to the most current vintage of NCEs that one can meaningfully evaluate. The 1980–84 vintage, for example, permits 12 years of actual sales data for the NCEs introduced in 1980 and fewer years for the 1981–84 vintages. Sales data for remaining years of commercial life must be forecast. NCEs introduced after 1984 would require significantly more forecasting of sales data than we believe to be feasible.

ceutical firms such as proprietary drugs, generic drugs, and basic chemicals [5]. Hence, from this perspective, the 10.5% value estimated in their analysis is a conservative estimate of the cost of capital for investment in new drugs.

Our approach to the cost of capital may also be compared to that of the OTA (1993). They utilize a variable cost of capital (COC) over the investment period for new pharmaceuticals. In particular, they employ a COC of 14% for the initial stages of the research process, which then steadily decreases to a COC of 10% for the later phases of development. They use a 9.8% COC on investments in plant and equipment and cash returns from market sales. By contrast, our COC of 10.5% is based on the average riskiness of drug industry investment over the whole product life cycle.

While a plausible theoretical case can be made that earlier-stage R&D is riskier and warrants a higher COC when a firm considers projects sequentially in the R&D decision-making process, (Myers and Shyam-Sunder, 1990), no empirical studies currently exist that allow one to quantify the structure of risks by R&D phase [6]. Hence, we think it is preferable to employ a single benchmark COC value when evaluating returns on the representative NCE introduction from the industry's total portfolio of NCEs. In fact, our approach utilizes a lower COC than the blended rate implicit in the OTA analysis. This is discussed in Section 4 below.

2.3. R&D costs

While we do not have R&D specific data for each of the NCEs in our sample, a major study of R&D costs for pharmaceuticals is now available. The study, by DiMasi et al. (1991), is based on a representative survey of U.S. drug firms, and utilizes cost data on a random sample of 93 drugs first tested in humans between 1970 and 1982. These drugs had an average introduction date of 1984. The DiMasi study also performed a cross check of the findings on R&D costs using publicly available aggregate industry data on R&D expenditures and NCE outputs.

Based on the data given in the DiMasi study, we were able to calculate the out-of-pocket R&D costs for a typical new drug introduction in each of the twelve years prior to marketing. It should be noted that these costs are the average costs

[5] A recent analysis by Conroy, Harris and Massaro (1992) finds support for this hypothesis in terms of a multiple regression analysis of shareholder risk. Specifically, they find the beta coefficient measure of equity risk commonly derived from the CAPM is positively and significantly related to a firm's research intensity. Their work is based on an analysis of a sample of firms from four industries including pharmaceuticals.

[6] OTA uses CAPM stock market analyses of biotechnology firms as a rough way to gauge the riskiness of discovery research in pharmaceuticals. They also assume a linear decline in the cost of capital over later stages of the R&D process. The riskiness of pharmaceutical R&D by phase is currently being studied by Professor Myers and his colleagues at MIT.

per NCE, and that they include the costs of failures [7]. Expressing these R&D costs in 1990 dollars and capitalizing them to the date of marketing at a real cost of capital of 10.5% gives $280.5 million as the mean R&D investment cost per '80–'84 NCE introduction. Because we compute cash flows on an after-tax basis, R&D costs should be after tax as well. R&D investments can be expensed for tax purposes. Based on empirical analysis of major U.S. pharmaceutical firms discussed further below, we use an effective tax rate of 33%. Hence, on an after-tax basis, the relevant R&D investment cost per '80–'84 NCE becomes $187.9 million (i.e., 67% of $280.5 million).

In addition to the R&D costs described above, R&D costs are undertaken by firms during the marketing period to modify and improve the particular NCE. These improvements include new indications, new product formulations, and new dosage levels of the originally approved NCE. All of these product changes require separate data submissions and approval by the FDA, usually in terms of a supplemental NDA. Since these product improvements can be thought of as spillovers from the original NCE introduction, it is appropriate to incorporate them into both the R&D costs and sales revenues for NCEs.

Based on a separate analysis by DiMasi, we estimated out-of-pocket R&D costs per NCE for product improvements of $31.8 million (before tax) [8]. We allocated these ongoing R&D costs equally over the first eight years of marketing. The discounted present value of R&D costs for product improvements are then equal to $20.8 million (pre-tax) and $14 million (after tax). Adding these costs to the ones for the originally approved NCE given above, yields a figure of $201.9 million for total R&D costs on an after-tax basis. This is the number we compare with the present value of post-launch returns per NCE introduction.

2.4. U.S. sales revenues

The first step in estimating the returns stream of cash flows was to assemble data on the U.S. sales for each NCE. Annual drugstore and hospital sales were obtained from audit data sources (IMS America) for the period 1980 through 1991. This provided up to 12 years of actual sales data for the drugs in our sample.

[7] The uncapitalized R&D outlays expressed in 1990 dollars (millions) from year $t-11$ to year 0 (market introduction is year 1) are 16.5, 20.9, 20.9, 17.8, 8.1, 8.1, 9.6, 10.9, 8.2, 7.5, 0, 0.

[8] The R&D cost data collected as part of DiMasi et al. study allows one to make a rough estimate of average R&D for product improvements. In particular, data were supplied on the annual aggregate R&D expenditures for both NCEs and for product improvements by the 12 firms in the participating survey. Using this information, and allowing for an average lag of 10 years between R&D expenditures on existing products and NCEs, it was estimated that out-of-pocket R&D expenditures for existing products were 24.9% of those incurred for NCEs. Applying this percentage to our estimate of out-of-pocket expenditures per approved self-originated NCE yields 31.8 million in 1990 dollars as the cost per approved NCE for ongoing R&D (DiMasi, private correspondence, 1992).

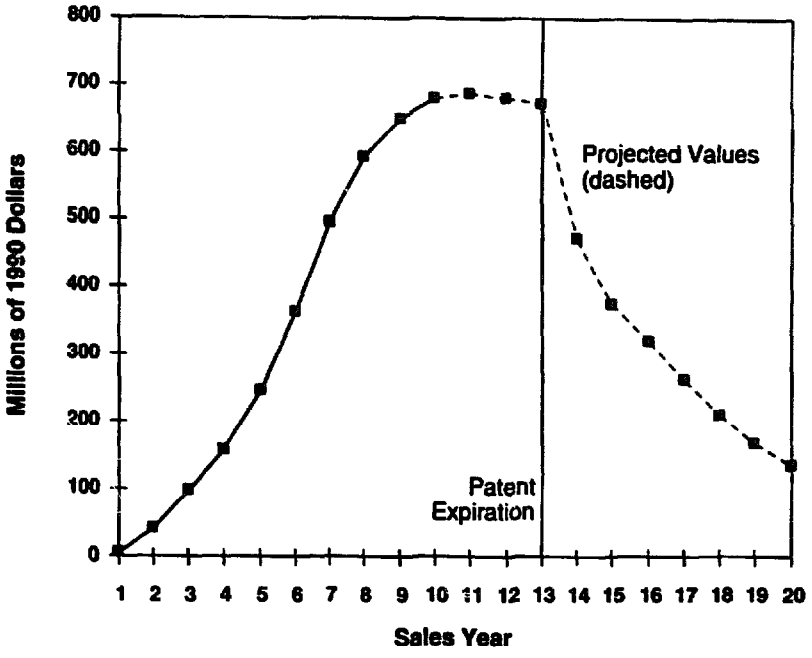

Fig. 1. Extrapolation procedure.

The next task was to extrapolate future sales over the market life of each product. Twenty years was selected as the market life for the 1980–84 cohort. We utilized a standard life-cycle curve for prescription drug sales, in conjunction with information on the NCE's patent expiration date, to extrapolate sales over the assumed 20-year life [9]. Most of the drugs in our sample have effective patent lives between 9 and 13 years. Our extrapolation procedure is illustrated in Fig. 1.

Sales data and projections are presented in Fig. 1 for a particular product from the top sales decile. This product has 10 years of actual sales data and 13 years of patent protection. By year 10, this product was in the mature portion of its product life cycle. Using our representative life-cycle curve, the product is projected to have relatively stable sales to year 13. A significant decline in sales is then projected after year 13 due to generic competition and product obsolescence.

The estimated sales loss upon patent expiration for this and the other leading NCEs in our sample is derived from a recent study of generic competition in the

[9] The standard product life cycle utilized in this analysis is based on the representative sales pattern for past NCE introductions (Grabowski and Vernon, 1990). In our prior analysis, we employed a market life of 25 years. Since the rate of sales decline after patent expiration is expected to be significantly greater for 1980s NCEs compared to 1970s NCEs, we felt that a 20 year life was a more plausible assumption in the present analysis. Given the fact that any returns realized after year 20 are heavily discounted in present value terms, the results for the baseline case are not very sensitive to whether a 20- or 25-year market life is assumed.

period after the 1984 Waxman–Hatch Act was passed (Grabowski and Vernon, 1992) [10].

Specifically, we were able to compile total sales on 14 NCEs from our previous study for four years after patent expiration. The average percentage declines in the first four years following patent expiration were 30%, 21%, 12% and 12%, respectively. [11] Thereafter a 10% decline is employed in our sales projections until the final four years of market life (where a 20% decline rate is utilized) [12].

In our prior work on the 1984 Waxman–Hatch Act, we found that this law greatly facilitated generic entry and contributed to a much more rapid sales decline by brand name firms in the post-patent period. However, since patent expiration for most drugs in this study will not occur until the mid 1990s and beyond, the experience of past introductions provides only a rough benchmark for future projections. Nevertheless, we think that the erosion of sales to generic competitors is likely to intensify in future periods. This is because the market is still adapting to the greater availability of generics. Furthermore, managed care programs, which are extensive users of generics, are growing rapidly over time (Ito, 1992). The potential effect on industry returns of faster sales erosion for future patent expirations is examined in terms of the sensitivity analysis.

Fig. 2 shows the resulting U.S. sales profiles (in 1990 dollars) for the top two deciles (ranked by tenth-year sales) as well as for the mean and median drug. These curves exhibit a life-cycle pattern frequently observed in pharmaceuticals. In particular, sales increase rapidly in the years after market introduction, reach a peak in year 10 or 11, and then decline steadily over the remaining years of market life.

Fig. 2 also illustrates the highly skewed distribution of sales which exists for new product introductions in the pharmaceutical industry. In this regard, peak sales of the top decile are several times that of the next ranked decile. Further-

[10] The actual patent lives for the 30 largest selling NCEs were obtained in order to incorporate the impact of generic competition at patent expiration using the approach outlined above. This sample of products corresponds well with those used in our 1992 analysis of generic competition (discussed below). We neglected generic competition for the smaller selling NCEs because they are unimportant empirically and also because it is uncertain whether generic competitors will emerge for these less profitable drugs.

[11] In contrast to the approach used in our published study of the 1984 Act (Grabowski and Vernon, 1992), the sales erosion rates used for this study are based on total prescription drug sales (rather than the most frequently prescribed dosage size) and are computed from the year of patent expiration (rather than the date of first generic entry).

[12] Using our prior study of returns to 1970s NCEs as a guide, the amount of error introduced into the current present value analysis from extrapolated sales values should be minimal (Grabowski and Vernon, 1990). This is because we have actual sales data for most compounds through their peak sales period, and the last segment of the sales life cycle for major products is subject to intensive competition from both new drug introductions and generics. In addition, sales and cash flow after year 10 are heavily discounted in present-value terms.

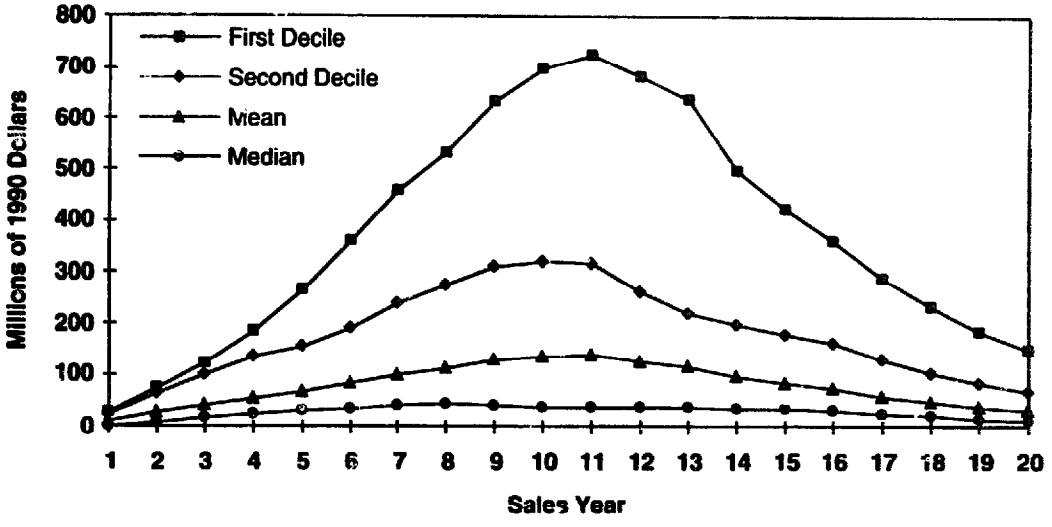

Fig. 2. U.S. sales profiles for different sample groupings.

more, mean sales are significantly greater than the median. This same pattern of skewness was observed in the sales of 1970–79 NCEs (Grabowski and Vernon, 1990, p. 811).

2.5. Global sales

The revenues discussed so far refer to U.S. sales revenues only. As in the earlier study, we use a foreign sales "multiplier" to estimate global sales. Our baseline value for the ratio of global sales to U.S. sales is 2.0. This multiplier was determined by examining domestic and worldwide sales in 1991 for the top 25 products in our sample of NCE introductions (the tenth-year sales of these products accounted for 90% of total tenth-year sales for our sample). As in our earlier work, we perform a sensitivity analysis to examine the impact of alternative values.

2.6. Pre-tax contribution margins and other assumptions

To obtain cash flows from sales, sales are multiplied by the pre-tax "contribution" margin (i.e., pre-tax profits plus R&D costs as a percent of sales). In our 1990 study, we used margins derived from income statement data from the pharmaceutical divisions of several major health oriented firms. In that analysis we found that margins increased throughout the 1980s from about 33% in the late 1970s to just under 40% in the late 1980s. More recent data suggests that margins have increased moderately in the 1990s. Based on this analysis, we think that 40% is a reasonable mean value to use in the baseline case for 80–84 introductions [13].

[13] This margin value is net of depreciation charges. As discussed in Section 2.7, depreciation charges are added to after-tax profits in each period to obtain cash flows in the post-launch period.

However, as for other important parameters, we examine alternative values in a sensitivity analysis.

We also followed the assumptions used in our 1990 study for promotional expenditures in the first three years of product launch (promotion equals sales in year 1, declines to 50% in year 2, and falls to 25% in year 3). Because of these heavy product launch expenditures in the first three years, contribution margins are less than 40% over this three-year period. However, as a product matures, promotional and administrative costs decline, and margins increase over time. Our model is set up so that margins average 40% over the full product life cycle [14].

We estimated capital expenditures for plant and equipment to be equal to 40% of tenth year sales [15]. Half of these outlays were assumed to occur in the first two years before marketing and the other half during the first 10 years after marketing. For working capital, it was assumed that accounts receivable represent 1.3 months of annual sales and inventories are 5 months of sales (valued at manufacturing cost). Working capital is recovered at the end of the final year of product life.

2.7. Tax rates

An analysis of income tax data on eight major pharmaceutical firms yielded an average effective rate of 35% during the 1970s (1970–1981). The average effective tax rate for these same firms was 32% during the 1980s (1981–91). Looking forward in time, it is reasonable to expect that effective tax rates for pharmaceutical firms in the 1990s will be at least equal to those of the 1980s. Average effective rates in pharmaceuticals have been below the statutory corporate tax rate historically because of various tax credits and deferrals [16]. The difference between the average and statutory rates was particularly large in the 1970s and early 1980s. (The corporate tax rate was 46% over this period while the average effective rate was in the mid-30s.) The 1986 Tax Reform Act lowered the statutory

[14] Specifically, we employed above-average margins in years 11 through 20 of market life. This is the mature phase of the life cycle. Promotional and administrative costs are much lower in this phase of the life cycle, contributing to higher than average margins. In addition, we found in our generic pricing study that drug firms facing generic competition tend to increase or maintain price on older drugs while unit sales decline, in accordance with a segmented market model (Grabowski and Vernon, 1992). However, with the growth of managed competition, price discounting of older drugs is now becoming prevalent. This could constrain the margins realized on older drugs in future periods.

[15] This value is based on analysis of the incremental change in gross fixed assets to the incremental change in sales for a sample of pharmaceutical firms over the relevant period. Our prior work on 1970s NCE introductions used a larger ratio of capital expenditures to tenth-year sales (50%). The lower value for 1980 NCEs, which emerged from our analysis of aggregate balance sheet data, is consistent with the significant increase in average sales per unit of output of 1980 NCEs compared to 1970 NCEs.

[16] These include the fact that pharmaceutical firms have extensive sales and manufacturing operations outside the United States. This has allowed these firms to obtain tax deferrals and credits which have lowered their average effective corporate income tax rate.

corporate rate from 46 to 34%, but it also curtailed the ability of firms to utilize particular credits. As a consequence, the gap between effective and statutory rates for pharmaceutical firms has narrowed considerably since 1986 [17]. The 1993 Budget Reconciliation Act is likely to contribute to a further convergence in these rates [18].

Based on our empirical analysis of average effective rates in the pharmaceutical industry, a 33% tax rate is utilized as a representative baseline tax rate for our analysis of 1980–84 NCE introductions. (This is the mean average tax rate over the 1971–91 period.) As in the case of other parameters, this rate is subjected to a sensitivity analysis.

2.8. Cash flow

Cash flow in each year is equal to after-tax profits plus depreciation charges. It should be noted that after-tax cash flows are affected by differences in book and tax depreciation. In particular, book depreciation is based on the straight-line accounting method, while tax depreciation is based on an accelerated schedule, as specified in the U.S. tax code. Accelerated depreciation for tax purposes results in deferred taxes and positive cash flow in the early years of market life in our model, which then reverses in later years.

3. Empirical findings

3.1. Mean industry performance

Using the above data and assumptions, the representative NCE for the 1980–84 period has the pattern of cash flows over the life cycle shown in Fig. 3. In particular, there are 12 years of investment in R&D and capital investment in which cash flows are negative in value. Product introduction occurs in year 1. Cash flows are negative in the first few years of market life due to the heavy launch expenditures in this period. After turning positive in year three, cash flows

[17] Since 1987, the differences in the average effective rate and the statutory rates for our sample has been less than 5%, while it was over 10% in the period 1970–85.

[18] OBRA 93 significantly reduces the possession or Section 936 tax credit. This is a provision of the tax code that has been extensively utilized by pharmaceutical firms with manufacturing plans in Puerto Rico (GAO, 1992). While firms continue to calculate this tax credit as before, they are now subject to one of two alternative limitations. The first alternative limits the credit to a percentage of employee compensation and depreciation deductions in Puerto Rico. The second alternative limits the amount of credit on a fixed percentage basis over time (60% of prior benefits in 1994 down to 40% by 1998). An analysis of this new tax provision by Arthur Andersen (1993) indicates that pharmaceutical firms are expected to elect the second option.

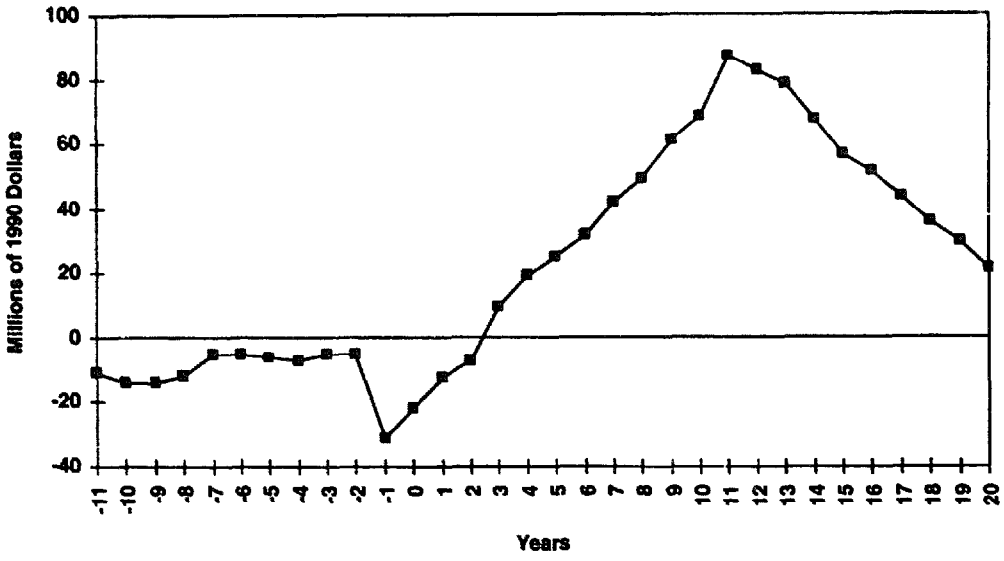

Fig. 3. Cash flows over the life cycle for the baseline case.

grow rapidly to a maximum in year 11 (the year in which sales revenues peak). They then decline in value until the final year of market life, year 20 [19].

The internal rate of return for the baseline case shown in Fig. 3 is 11.1%. This can be compared directly with our real cost-of-capital estimate of 10.5% for investment in pharmaceutical industry activities. While these results indicate positive economic returns to investment in new drug R&D, profitability is much less than what might be inferred from a naive comparison of aggregate accounting returns data.

The first row of Table 1 further shows that the capitalized value of R&D investment costs in the baseline case is 201.9 million dollars. The discounted value of post-launch returns emanating from this R&D investment is 224.1 million dollars. Hence, the NPV for the representative 1980–84 NCE introduction is 22.2 million in 1990 dollars.

To put this result in perspective, in our 1990 paper, we reported the analysis of the returns to NCEs introduced in the United States in 1970–79. This analysis employed the same sample selection criteria. Our focus was on the mean returns for this entire period (the IRR averaged a little over 9%), but we did some analysis of the two sub-periods 1970–74 and 1975–79. We found that the NPV and mean IRR in the later sub-period were significantly greater than those for the earlier one. In particular, the IRR was estimated to be 10.0% for the 1975–79 period, compared to 7.1% in the 1970–74 period.

Our findings for the 1980–84 cohort of NCEs suggest that the IRR has increased moderately over the 1975–79 period (11.1% versus 10.0%), but the

[19] Not shown in the figure is the recovery of working capital that occurs at the beginning of year 21. In present value terms, the working capital recovery amounts to only $2.3 million.

Table 1
Returns to 1980–84 NCEs

Case	Present Value Cash Flows (after tax)	Present Value R&D Costs (after tax)	NPV	IRR
Baseline	224.1	201.9	22.2	11.1
at 35% margin	187.6	201.9	(14.3)	10.1
at 45% margin	260.6	201.9	58.8	11.9
at 1.8 international multiplier	201.7	201.9	(0.2)	10.5
at 2.2 international multiplier	246.5	201.9	44.6	11.6
at 0.25 tax rate	257.1	226.0	31.2	11.2
at 0.40 tax rate	195.2	180.8	14.4	10.9
at 25% greater sales decline after patent life	214.7	201.9	12.8	10.8
at 50% greater sales decline after patent life	205.2	201.9	3.4	10.6
at 10% cost of capital	238.2	195.3	42.9	–
at 11% cost of capital	210.7	208.7	2.1	–
at 1-year reduction in regulatory review time	224.1	184.0	40.1	11.6

Baseline case assumes 10.5% cost of capital, international multiplier of 2.0, tax rate of 0.33, and margin of 0.40.

NPV in the two periods remains essentially unchanged in value (both are approximately 20 million in 1990 dollars). (This latter result reflects a somewhat higher cost of capital for the 1980s compared to the 1970s.) Thus, the major upward shift in observed pharmaceutical returns that occurred in the later 1970s has continued into the 1980s.

As we noted in our earlier work, the latter half of the 1970s corresponded to the first introduction of several commercially important new drug therapies, based on the innovative principles of rational drug design. Breakthrough drugs like Tagamet (an anti-ulcer compound introduced in 1977) were not only large commercial successes, but also created a new period of optimism about technological opportunities and the ability of firms to exploit accumulating knowledge emerging from basic biomedical research. The 1980s also witnessed a significant change in the domestic economic environment with rising domestic drug prices and profit margins. All of these developments contributed to the upward shift in the IRR that

was first observed for the 1975–79 cohort of NCEs and which has been maintained for the 1980–84 cohort.

Our findings do indicate a moderately lower NPV for 1980s NCEs than that found by the OTA in their recent work (22 million versus 36 million dollars). However, they utilize a shorter interval for their NCE sample period (1981–83) and also make some different assumptions. The findings of the two studies are compared in Section 4 below.

3.2. Sensitivity analysis

Of course, there is uncertainty about certain parameters. For this reason we also show in Table 1 how the NPV and IRR performance measures vary with these parameters. For example, changing the contribution margin from 35% to 45% causes significant changes in the IRR – the IRR varies from 10.1% to 11.9%. As discussed above, average profit margins have been in the neighborhood of 40% in the late 1980s. The relevant issue then is whether changes in real drug price or costs will occur throughout the 1990s – leading to significantly different margin values over future periods. The movement toward managed care would suggest more price discounting and lower margins in the 1990s. But this could be offset, at least in part, by lower marketing and distribution costs in this new environment.

The results are also sensitive to changes in the international multiplier. At the present time cost containment efforts toward pharmaceuticals appear to be intensifying in several European countries (Burstall, 1991; Munnich, 1993; Mattison, 1993) [20]. A more detailed model of the international sector is probably appropriate. It might be feasible in future work, for example, to allow for different sales profiles and margins in foreign and domestic markets, if such data can be obtained.

The third sensitivity analysis in Table 1 involves variations in the effective tax rate. This results in only modest changes in the baseline values for the NPV and IRR. This outcome reflects the fact that the present values of R&D expenditures and cash flows are affected in offsetting ways by changes in the tax rate variable.

The next issue considered is post-patent sales losses. Our baseline case embodies assumptions on the sales erosion of pioneer brands consistent with what we observed in the first several years after the 1984 Hatch-Waxman Act was passed. However, as noted above, most of the drugs in our sample face patent expiration

[20] The most drastic changes have occurred in Germany. This country now reimburses pharmaceuticals based on a system of reference prices with drugs grouped by common therapeutic classes. In addition, beginning in January 1993 Germany also implemented global budget caps on pharmaceutical expenditures. Furthermore, if overruns occur in the budget for pharmaceuticals, physicians' incomes are partially at risk for funding the shortfall. This has caused some marked changes in physician prescribing behavior with significant declines in total pharmaceutical expenditures (Munnich, 1993).

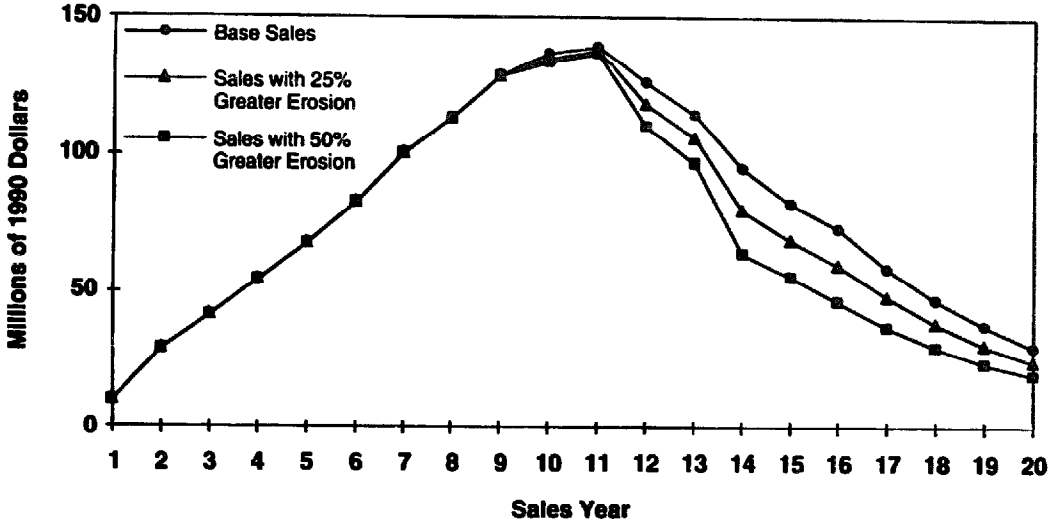

Fig. 4. Alternative sales erosion patterns in the post-patent period.

in the mid 1990s and beyond where there is the prospect of increasing generic competition.

In order to test the sensitivity of our results to increased generic competition, some alternative scenarios were examined. In these scenarios, pioneer sales losses after patent expiration are 25% and 50% lower than what was assumed in the baseline case. The effect of these changes is shown in Fig. 4. Under the 25% greater decline in post-patent sales the NPV drops from 22 million to 13 million dollars in value. In the 50% decline case, NVP is only 3.4 million dollars, just barely above break-even value. These changes are illustrative of the fact that evolving developments in the health care system could have a material effect on the returns to new drug introductions.

The next set of sensitivity analyses in Table 1 shows the change in NPVs associated with a change in the cost of capital. This is a parameter which can have a substantial effect on net returns. A 10% cost of capital would result in a net present value of over 40 million, while an 11% cost of capital would cause the NPV to be approximately break even in value. We noted above that Myers and Shyam-Sunder's cost-of-capital estimates are based on all pharmaceutical firm activities, while we are focusing here on investments for prescription drugs. Given this fact, a 10.5% cost of capital for pharmaceutical activities is probably on the conservative side.

The final sensitivity analysis in Table 1 analyzes the effect on NPVs of changes in regulatory review time. This is an interesting issue to consider, given the recent passage of a user fee on new drug applications (HR 6181). The user fee is to be dedicated to hiring additional FDA reviewers with the objective of speeding up the review process. Currently the average new drug takes two and one-half years to obtain regulatory approval. The goal of the FDA under the new user fee scheme is to reduce this by at least one year.

The results in Table 1 indicate that NPVs are sensitive to regulatory review

time. In particular, a one-year shortening in review time would have permitted the average NCE in our sample to increase its NPV from 22 to 40 million dollars [21]. The user fee on a new drug application is only a small fraction of this amount. However, the schedule of user fees includes charges for supplemental NCEs as well as annual fees for all registered products and manufacturing facilities) [22]. An analysis of the private and social benefits of drug user fees is an interesting issue for further research. The sensitivity analysis presented in Table 1 suggests that if user fees are indeed successful in substantially shortening review times, this could have significant incentive effects for pharmaceutical R&D.

3.3. Distribution of returns

In Fig. 5, the decile distribution of present values of post-launch returns for our sample of 1980–84 NCEs is presented. These are gross of R&D costs. Clearly, this is a highly skewed distribution. The top decile has an estimated present value of $1 billion. This is more than five times the present value of average R&D costs ($202 million). Note also, however, that only the top three deciles exceed the average R&D cost. The fourth decile at $177 million is significantly below average R&D costs [23].

[21] In this analysis, we only consider the effect of shorter review times on the capitalized value of R&D costs. We abstract from any benefits in terms of additional revenues from increased effective patent lives. With the passage of the 1984 Hatch–Waxman Act, most drugs are eligible for compensatory increases in effective patent life equal to time lost in regulatory review (Grabowski and Vernon, 1992). Hence, only for those drugs for which patent restoration is constrained under the Act would there be an increase in patent life from reductions in regulatory review time. We abstract from an analysis of any benefits of this kind in the present study.

[22] Congress authorized user fees on pharmaceuticals in October 1992 (HR 6181). This act mandates a $100,000 NCE application fee in the 1993 fiscal year, rising to $233,000 in five years. Supplemental NCE applications for new indications, dosage forms, etc. cost $50,000 each, with a similar rise in fees over time. In addition, there is an annual fee for each currently registered product ($6,000 initially) and on each manufacturing plant ($60,000 initially). The legislation stipulates that these fees shall only be collected and available for increases in resources allocated for the review of human drug applications. The FDA must report annually to Congress on how it utilizes the fees and on its progress in achieving time approval goals. (It may be noted that in early 1993, OMB proposed a big increase in FDA user fees to replace existing budgetary appropriations for the FDA, but this was not accepted by Congress.)

[23] We do not have R&D costs by each drug in our sample so it is possible that these costs are also correlated with sales. The analysis of average R&D costs by DiMasi does indicate significant variance in development costs across drugs, but there is no evidence of the extreme skewness that is observed here for both NCE sales and post-launch returns. Furthermore, it is not clear how R&D costs vary with NCE sales. In this regard, both our analysis and that of the OTA's indicate that top-selling 1980s NCEs had longer than average effective patent life, which is indicative of shorter development periods. Ceteris paribus, this would cause R&D costs to be negatively correlated with sales performance. However, if firms can anticipate which products are likely to be important commercially, they have incentive to increase out-of-pocket R&D costs in order to accelerate development (i.e., through parallel clinical trials, etc.). It is not obvious how these different forces balance out. This is an important issue for further empirical research.

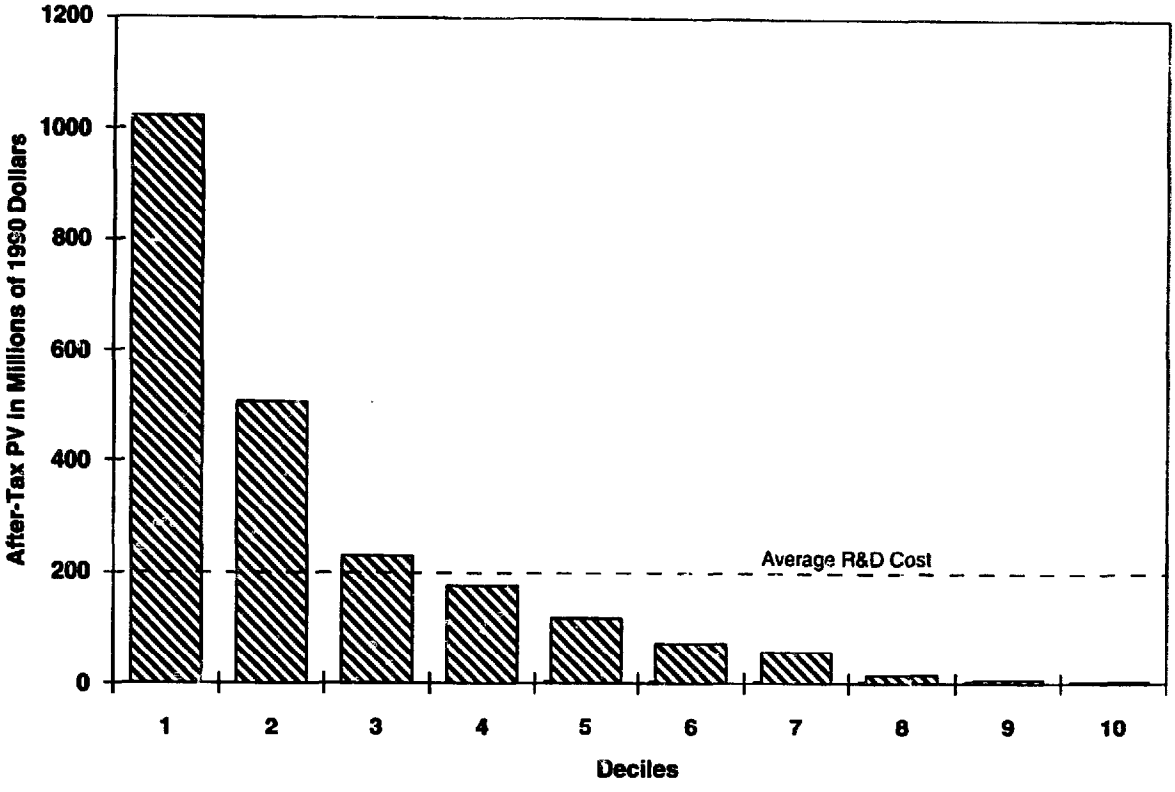

Fig. 5. Decile distribution of present values of post-launch returns for the sample of 1980–84 NCEs.

A very skewed distribution was also observed in the case of 1970s NCE introductions. In both that analysis and the current one, the top two deciles accounted for a dominant share (over 70%) of the total present value generated by these NCEs. In our prior analysis of NCEs for the entire decade of the 1970s, it was also true that only the top three deciles had present values in excess of average R&D costs.

The importance of top-ranked drugs to drug industry performance can be further illustrated by excluding Zantac, the top-ranked compound in our sample, in order to see how average present values are changed. Zantac, an anti-ulcer drug, was introduced in 1983 and has since achieved worldwide sales in excess of 3 billion dollars. If we exclude this one "blockbuster" compound from the sample, the average present value of post-launch returns declines by 33 million dollars, and the average NPV for the remaining 66 compounds is estimated to be −$10.7 million. Hence, if the top-ranked compound for the 1980–84 cohort of drugs was never introduced, the representative drug would fail to achieve break-even status.

It is important to note that while the majority of the 67 NCEs have present values substantially below the fully allocated average R&D cost, it is still true that many of these "unprofitable" drugs do contribute to firms' profits. That is, in many cases an "unprofitable" drug more than covers its own incremental development and capital costs. However, as discussed above, the average R&D

cost also includes an allocation for drugs that drop out along the development path and are never marketed. The R&D costs of these unsuccessful drug candidates, as well as common discovery costs, must be covered from the sales of successfully marketed drugs. Hence, with such a skewed distribution, it is critical that a firm have an occasional big winner or drug in the top few deciles, if it is to cover all costs of R&D over the long run.

4. Comparison with OTA report

In early 1993, the OTA published an analysis of returns on R&D to 1981–83 NCEs. Their principal finding was that the average NCE had an NPV of 36 million dollars (in 1990 dollars). This may be compared to the 22 million dollar average NPV for our sample. The OTA did not compute IRRs since they used a variable cost of capital over the R&D investment period.

Some general observations may be made about these results. First, the differences in the two studies are not that large if one considers the average pre-tax R&D investment for the typical NCE is in the neighborhood of 300 million dollars. Second, the findings of both studies are at odds with claims that there are large excessive returns in pharmaceuticals, an inference frequently made from simple accounting rate comparisons across industries. In particular, our work implies that realized returns are within one percentage point of the industry's cost of capital, and this result is implicit in the OTA's findings as well. (Increasing their various costs of capital by one percentage point each, the OTA's NPV becomes −6 million dollars.)

Table 2 provides a comparison of the main assumptions employed in the two studies. There are a number of dimensions in which the two studies are the same, but there are also significant differences. With respect to the R&D cost values, both studies rely on the estimated values from the DiMasi et al. study. Both studies also rely on the same audit data source to generate sales over the first half of sales life cycle. However, OTA uses a smaller sample (1981–83 NCEs) and a more aggregative approach for projecting future sales values.

Fig. 6 shows a plot of OTA's global sales revenue curve compared to the one utilized in our analysis. Despite some differences in sample selection procedures, the sales values are quite close for the first nine years [24]. These initial years are

[24] The sample period used by the OTA results in higher average sales per NCE. In particular, our analysis indicates that mean sales values in years 1980 and 1984 are less than those in each of the years 1981 through 1983. Hence, the shorter sample period chosen by the OTA leads to significantly higher sales than for our analysis. However, this effect is essentially offset by other differences in sample selection. Specifically, we exclude all compounds discovered in the universities and government laboratories, and those in certain therapeutic categories like cancer. (We exclude these NCEs because they could have different R&D costs. See footnote 3.) OTA includes these NCEs which tend to have smaller sales than the sample mean

Table 2
Comparison of our assumptions with OTA's analysis

	OTA	G&V
Sample	1981–83 NCEs	1980–84 NCEs
R&D Cost Data	Based on DiMasi et al.	Based on DiMasi et al.
Cost of Capital		
R&D Investment	10–14%	
Returns	9.8%	10.5%
Tax Rate		
R&D Investment	46%	
Returns	32%	33%
Sales Life Cycles		
Patent Exclusivity	9 years	NCE Specific
Sales Loss after Patent Expiration (Initial 3 years)	18%; 8.5%; 6.0%	30%; 21%; 12%
Product Life	20 years	20 years
Global Sales Multiplier	2.0	2.0
Contribution Margin	40.8% (plus adjustment for depreciation)	40% (plus adjustment for depreciation)
Capital Expenditures	25 million	40% of tenth-year sales

based on audit data in the two studies. However, our sales curve peaks later (year 11), and our sales values significantly exceed the OTA's in years 10 through 13. This results from the more disaggregate approach utilized in our analysis where each NCE's patent life and life cycle is separately considered [25].

It is clear that the higher NPV for OTA's baseline case does not result from the basic input values on R&D costs or sales values. The R&D costs values used in the two studies are the same, and our sales values yield higher rather than lower NPVs. Similarly, the average contribution margins used in the two studies are close in value, and this is not a significant factor in explaining the higher NPV of the OTA study.

[25] The OTA uses the mean patent life (9 years) to establish their sales curve peak. However the largest selling drugs typically have longer effective patent lives than the average NCE. Hence, on a sales-weighted basis, the average effective patent life is longer than 9 years. In addition, some commercially important drugs have been successful in extending patent life through product line extensions. The OTA attempts to capture the latter phenomenon strictly through a slower average rate of sales erosion after patent expiration. By contrast, we incorporate new patent life information for those products with major product line extensions. As a consequence of these factors, our sales curve peaks later and exceeds the OTA's in years 10 through 13.

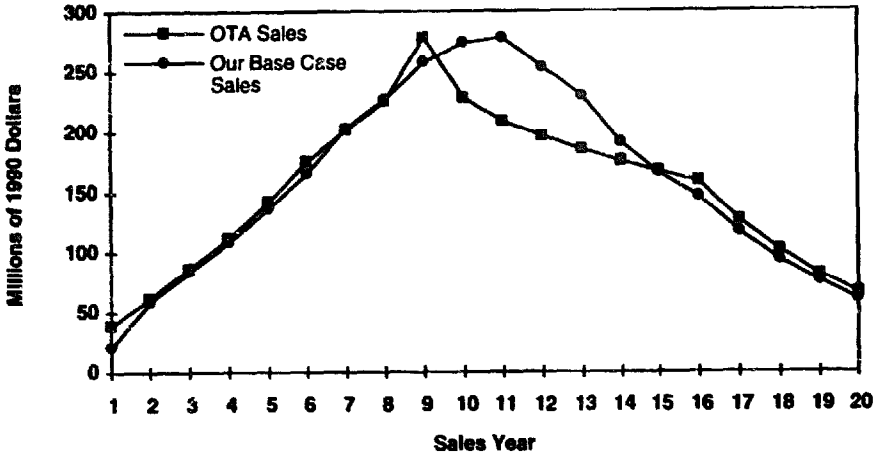

Fig. 6. Plot of OTA's global sales revenue curve compared to the one utilized in the analysis.

In looking at the other assumptions presented in Table 2, we see that the two studies utilize quite different approaches with respect to the cost of capital and tax rates. Specifically, OTA uses very different values for these two parameters in its treatment of R&D investment and post-launch returns. This asymmetry plays an important role in understanding the differences in the two studies.

To demonstrate that the assumptions on the COC and effective tax rates were a major source of the different findings in the two studies, we performed the following experiment. We substituted the OTA's assumptions on the COC and tax rates into our model while holding all other factors the same as in our baseline model [26]. We found that the NPV in this modified baseline case increased to $40 million (when both parameters were changed) and to $57 million (when only the effective tax rate parameter was changed).

Hence, the higher estimated baseline NPV for the OTA study can be largely explained in terms of these parameters [27]. Moreover, the single most important factor leading to a higher NPV in the OTA analysis is the large differential in tax rates utilized for R&D versus post-launch returns [28]. In particular, OTA's tax rate on revenues – 32% – is based on an analysis of the *average effective tax rate* for

[26] The OTA compounds R&D costs on a monthly basis and post-launch returns on an annual basis, while we utilize annual compounding for both series. In the experiments discussed above, we also adopt the OTA conventions on compounding in conjunction with its variable cost of capital and effective tax rates.

[27] Other differences between the two studies include the sales life cycle curve (discussed above) as well as differences in the level and timing of the capital investment and promotional expenditures. However, these tend to work in offsetting ways. On balance, they have a small effect on the difference in NPVs.

[28] The importance of OTA's assumptions on taxes is also illustrated by the fact that the mean NCE in their analysis has a negative *pre-tax* NPV of −18 million dollars, compared to a positive *after-tax* NPV of 36 million dollars.

drug firms during the 1980s, while their rate on R&D costs is based on the *statutory corporate tax rate* – 46% – during the 1970s. Although statutory corporate rates changed significantly in 1986, the effective tax rates for drug firms have not changed greatly over the past two decades (Section 2.7).

We believe that one must be consistent in the tax concept employed on both sides of the investment equation and that effective rates are analytically more appropriate here than statutory ones. From a historical perspective, the principal tax benefits enjoyed by research-intensive multinational drug firms – foreign – source income deferrals [29] and the possession tax credit [30] – have lowered the effective marginal tax rate for both R&D costs and revenues. Furthermore, the OTA assumptions on taxes are not appropriate for prospective policy analyses of R&D investments given the present corporate tax rate structure. Considering all these factors, we think the most reasonable proxy measure to use in our analysis is the average effective tax rate for pharmaceuticals [31].

In any case, while there are important differences in the assumptions of two studies, the resulting differential in baseline NPVs is not large. Furthermore, the findings can be generally reconciled in terms of the assumptions about the

[29] Multinational firms are taxed under the U.S. code on the basis of their worldwide income. However, income from foreign sources with lower tax rates can result in a tax benefit to U.S. firms, at least until this income is repatriated. But R&D performed in foreign countries with low corporate income taxes (like Switzerland) must be offset against foreign income. More importantly, under a 1977 Treasury Department Regulation (Section 1.861.8) a portion of a multinational's *domestic* R&D expenditure must be allocated to its foreign revenues. This regulation was suspended in 1981 by Congress and then reinstated on a less onerous basis after 1986. Hines (1993) provides a good discussion of the changes in this regulation over time and an analysis of their impact on multinational firm R&D behavior.

[30] As discussed earlier, the possessions tax credit has been utilized by pharmaceutical firms to shelter income associated with their Puerto Rican manufacturing subsidiaries. But under rules devised by Congress in 1982, a fraction of the parent firm's worldwide R&D must be allocated to the income sheltered in Puerto Rico under both the cost-sharing and income splitting options (U.S. Joint Committee on Taxation, 1982; pp. 79–96). Prior to that time, some pharmaceutical firms had transferred the patent rights emerging from their worldwide R&D to their Puerto Rican manufacturing subsidiary at little or no cost in order to increase the sheltered income on products produced there. But these practices were challenged by the IRS and subjected to subsequent tax liabilities by the U.S. tax court (e.g., *Eli Lilly and Co. vs. Comr.*, 84 T.C. 996, 1985; *G. D. Searle and Co. vs. Comr.*, 88 T.C. 252, 1987).

[31] In a prospective analysis of R&D expenditures, one would ideally model the specific incentive effects arising from the R&D tax credit. This credit, which is based on the growth of R&D expenditures, was first instituted in 1981 and has been modified several times since then by Congress. It may be noted that Altshuler (1988) and other researchers have found that the marginal effective R&D tax credit rate is quite small for the representative U.S. firm (i.e., typically only a few percent). With regard to pharmaceutical firms in particular, data compiled by the U.S. Treasury indicate that total R&D tax credits for the industry in the mid 1980s were small relative to total industry R&D expenditures, and also small relative to the values for the possessions and foreign tax credits (OTA, 1993, p. 196).

corporate tax rate and cost of capital, which work in offsetting ways. The reconciliation of these two independent studies lends strong support, in our view, to the general results presented here.

5. Summary and conclusions

The estimated mean return on pharmaceutical industry NCE introductions for the first half of the 1980s was 11.1%. This may be compared with the estimated (real) cost of capital of 10.5% over the same period. This corresponds to an NPV of 22 million dollars in 1990 dollars. As in our earlier work, the distribution of present values on post-launch returns for new drug introductions is highly skewed, with the top few deciles accounting for a very large share of total present values. Furthermore, only three of ten drugs had present values for post-launch returns in excess of average R&D costs.

We performed an extensive sensitivity analysis of our main results. We found that our results are generally robust to plausible changes in the baseline values. This analysis also can be used to gain insights into the potential effects of several evolving policy developments, such as cost containment programs and user fee requirements. Our analysis suggests that returns on NCE introductions are especially sensitive to government policies influencing R&D times and the margins realized on new drug sales.

Our work is also compared with a recent study by OTA. Although there are some important differences in assumptions, both studies find modest positive returns to the average NCE introduction of the early 1980s. In each case, realized returns are within one percentage point of the cost of capital.

Our findings do not provide general support for the assertion frequently made by policymakers on the basis of accounting data, that returns on pharmaceutical R&D are large and persistent compared to the financial risks involved. It is true that the returns distribution in pharmaceuticals is highly skewed, and that top-ranked decile drugs have earned very large returns. It does not follow, however, that this group of drugs should be subjected to price controls or profit constraints. Our analysis indicates that expected returns are highly sensitive to the performance of the top decile drugs. Imposing constraints on this class of drugs would significantly lower the average expected returns on future NCE introductions, and especially, make R&D on high-risk, high-return compounds subject to greater uncertainty.

References

Altshuler, R., 1988. A dynamic analysis of the research and experimentation credit, National Tax Journal 41(4), 453–466.

Arthur Andersen, 1993. Tax Act of 1993 (Arthur Andersen and Co., SC, 93–5056, Washington, DC).

Baber, W.R. and S.-H. Kang, 1991. Accounting-based measures as estimates of economic rates of return: An empirical study of the U.S. pharmaceutical industry, 1976–87. OTA working paper.

Burstall, M.L., 1991. European policies influencing pharmaceutical innovation, in: A. C. Gelijns and E. A. Halm, eds., The changing economics of medical technology (National Academy Press, Washington, DC), 123–140.

Chinburapa, V. and L.N. Larson, 1991. The availability of new drugs in health maintenance organizations, Journal of Research in Pharmaceutical Economics 3(1), 91–110.

Clarkson, K.W., 1977. Intangible capital and rates of return, (American Enterprise Institute, Washington, DC).

Conroy, R., R. Harris and T. Massaro, 1992. Assessment of risk and capital costs in the pharmaceutical industry, Darden School, University of Virginia.

DiMasi, J.A., R.W. Hansen, H.G. Grabowski and L. Lasagna, 1991. Cost of innovation in the pharmaceutical industry, Journal of Health Economics 10, 108–142.

Fisher, F.M. and J.J. McGowan, 1983. On the misuse of accounting rates of return to infer monopoly profits, The American Economic Review 73(1), 82–97.

Grabowski, H. G., 1989. An analysis of U.S. international competitiveness in pharmaceuticals, Managerial and Decision Economics, Special Issue, 27–33.

Grabowski, H. G. and D. C. Mueller, 1978. Industrial research and development, intangible capital stocks, and firm profit rates, The Bell Journal of Economics 9(2), 328–343.

Grabowski, H. G. and J. M. Vernon, 1977. Consumer protection regulation in ethical drugs, American Economic Review 67(2), 359–364.

Grabowski, H. G. and J. M. Vernon, 1990. A new look at the returns and risks to pharmaceutical R&D, Management Science 36(7), 804–821.

Grabowski, H. G. and J. M. Vernon, 1992. Brand loyalty, entry and price competition in pharmaceuticals after the 1984 Act, Journal of Law and Economics 35(2), 331–350.

Hansen, R. W., 1979. The pharmaceutical development process: Estimates of current development costs and times and the effect of changes, in: R.I. Chien, ed., Issues in pharmaceutical economics (Lexington Books, Lexington, MA), 151–187.

Hines, J.R., 1993. On the sensitivity of R&D to delicate tax changes: The behavior of U.S. multinationals in the 1980s, in: A. Giovannini, R.G. Hubbard, and J. Slemrod, eds., Studies In International Taxation, National Bureau of Economic Research Project Report (University of Chicago Press, Chicago), 149–187.

Ito, S. M., 1992. Prescription decisions in a managed care environment, Journal of Research in Pharmaceutical Economics 4, no. 1, 79–101.

Joglekar, P. and M. L. Paterson, 1986. A closer look at the returns and risks of pharmaceutical R&D, Journal of Health Economics 5, 153–177.

Mattison, N., 1993. Health care systems and methods for controlling pharmaceutical expenditure in eight OCCD countries, (F. Hoffman-La Roche Ltd., Basel, Switzerland) March.

Megna, P. and D. C. Mueller, 1991. Profit rates and intangible capital, Review of Economics and Statistics 73(4), 632–42.

Munnich, F., 1993. Reference pricing and the impact of recent legislative change in Germany, Paper presented to Tufts University European Center Conference on Pricing and Reimbursement of Pharmaceuticals, July, Talloires, France. Forthcoming in Pharmaco Economics, 1994.

Myers, S.C. and L. Shyam-Sunder, 1990. Cost of capital estimates for investment in pharmaceutical research and development, OTA working paper.

Stauffer, T.R., 1971. Measuring rates of return, Bell Journal of Economics and Management Science 2(2), 434–469.

United States Congress, General Accounting Office, 1992. Pharmaceutical industry: Tax benefits of operating in Puerto Rico, Briefing Report to the Chairman, Special Committee on Aging, U.S. Senate, GAO/GGD–92–72 BR.

United States Congress, Joint Committee on Taxation, 1982. General explanation of the revenue provisions of the Tax Equity and Fiscal Responsibility Act of 1982. (U.S. Government Printing Office, Washington, DC).

United States Congress, Office of Technology Assessment, 1993. Pharmaceutical R&D: Costs, risks and rewards, (Washington, DC: U.S. Government Printing Office).