Patents and New Product Development in the Pharmaceutical and Biotechnology Industries

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Abstract

This paper examines the rationale for intellectual property protection in the development of new pharmaceutical products. Prior survey studies of R&D executives have found that patents play a more critical role in appropriating the benefits of innovation in pharmaceuticals compared to other high tech industries. This paper considers why this is so based on an analysis of the economic characteristics of R&D costs and returns in the pharmaceutical and biotechnology industries. The final section examines recent policy developments and issues surrounding patent lifetime and generic competition in this industry.

I. Introduction

Grilliches, in a 1992 survey paper found that high social returns to R&D are a major factor underlying the growth in per capita income and consumer welfare during the twentieth century.[1] Many of the studies done by economists on this topic have found that the social returns to R&D are more than twice the private returns to R&D.[2] A primary reason for this finding is the positive externalities generally associated with industrial innovations. As F.M. Scherer stated in his leading graduate text in industrial organization, "Making the best use of resources at any time is important. But in the long run it is dynamic performance that counts."[3]

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[1] Zvi Grilliches, "The Search for R&D Spillovers." 94 *Scandinavian Journal of Economics* (1992 Suppl.): 29-47.

[2] Ibid., Table 1.

[3] F.M. Scherer, *Industrial Market Structure and Economic Performance* (Chicago: Rand McNally, 1980), 407.

The pharmaceutical and biotechnology industries, which are among the most research intensive industries, have been the focus of several benefit cost and social return on R&D studies. Elsewhere in this symposium, Frank Lichtenberg has reported on his finding concerning the impact of new drugs on increased longevity, worker productivity, and savings in other types of medical expenditures.[4] He finds significant aggregate net benefits to society from new drug introductions. His analysis is consistent with more microeconomic analyses targeted to specific medical conditions such as cardiovascular disease, depression, and infectious disease. These studies have also found high incremental social benefits from new drug innovation.[5]

Another general finding of the academic literature is that public policy actions can have a significant influence on the rate of innovation in particular industries. Among the key industrial policies influencing the innovative process in pharmaceuticals are the public support of biomedical research, patents, FDA regulatory policy, and government reimbursement controls.[6] The focus of this paper is on the role and impact of patents and intellectual property protection in the discovery and development of new pharmaceutical and biotechnical products.

The importance of patents to pharmaceutical innovation has been reported in several cross-industry studies by economists. In particular, Richard Levin, et al, and Wes Cohen, et al, have undertaken surveys of U.S. R&D managers in a large cross-section of

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[4] Frank Lichtenberg, paper on Social Returns to Pharmaceutical R&D presented at April 19, 2002, Federal Reserve Bank of Dallas Conference.

[5] See for example David M. Cutler and Mark McClellan, "Is Technological Change in Medicine Worth It?" 20 *Health Affairs* (Sept/Oct 2001): 11-29; Jack E. Triplett, editor, *Measuring the Price of Medical Treatments* (Washington: Brookings Institution, 1999).

[6] Adrian Towse, editor, "Industrial Policy and the Pharmaceutical Industry" (London: Office of Health Economics, 1995).

industries to identify which factors are most important and necessary in appropriating the benefits from innovations.[7] These factors included the competitive advantages of being first in the market, superior sales and service efforts, secrecy and complexity of productions and product technology, as well as patents. Both studies found that the pharmaceutical industry placed the highest importance on patents. By contrast, many other research-intensive industries, such as computers and semiconductors, placed greater stress on factors like lead-time and learning by doing efficiencies in production accruing to first movers.

The findings of these studies are in accordance with an earlier study performed by the British economists Taylor and Silberston. Based on a survey of UK R&D managers, they estimated that pharmaceutical R&D expenditures would be reduced by 64 percent in the absence of patent protections. By contrast, the corresponding reduction was only 8 percent across all industries. Similar findings were reported by Edwin Mansfield from a survey of the research directors of 100 U.S. corporations.[8]

In the sections of this paper which follow, we examine the economic characteristics of the R&D process in pharmaceuticals that make patents so critical. The next two sections consider the costs of innovation relative to imitation in this industry.

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[7] Richard D. Levin, et al., "Appropriating the Returns from Industrial Research and Development," *Brookings Papers on Economic Activity* (1987): 783-820; Wes Cohen, et al., "Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector," Working Paper (Pittsburgh: Carnegie-Mellon University, 1997).

[8] C.T. Taylor and Z.A. Silberston, *The Economic Impact of the Patent System* (Cambridge, England: Cambridge University Press, 1973); In a follow on study, Silberston categorized three groups of industries for when patents are essential, very important or less important based on both survey responses and objective analyses (patent and R&D intensity). He concluded that "the first category consists of one industry only, pharmaceuticals." Z.A. Silberston, "The Economic Importance of Patents" (London: The Common Law Institute of Intellectual Property, 1987); Edwin Mansfield surveyed the R&D directors of 100 U.S. corporations on what fraction of the inventions they introduced between 1981 and 1983 would not have been developed without patent protection. For pharmaceuticals, the value was 60 percent, while the average across all industries was 14 percent. Edwin Mansfield, "Patents and Innovation: An Empirical Study," 32 *Management Science* (1986): 175.

Section IV considers whether the biotech industry is different than the pharmaceutical industry in terms of R&D costs. Section V considers the distribution of returns on R&D in these industries. The final section presents conclusions and policy considerations.

II. R&D Costs for a New Drug Introduction

The explanation for why patents are more important to pharmaceutical firms in appropriating the benefits from innovation follows directly from the characteristics of the pharmaceutical R&D process. In essence it takes several hundred million dollars to discover, develop and gain regulatory approval for a new medicine. Absent patent protection, or some equivalent barrier, imitators could free ride on the innovator's FDA approval and duplicate the compound for a small fraction of the originator's costs. In essence, imitation costs in pharmaceuticals are extremely low relative to the innovator's costs for discovering and developing a new compound.

One of the reasons R&D is so costly in pharmaceuticals is that most new drug candidates fail to reach the market. Failure can result from toxicity, carcinogenicity, manufacturing difficulties, inconvenient dosing characteristics, inadequate efficacy, economic and competitive factors, and various other problems. Typically, less than 1 percent of the compounds examined in the pre-clinical period make it into human testing. Only 20 percent of the compounds entering clinical trials survive the development process and gain FDA approval.[9] Furthermore, the full R&D process from synthesis to FDA approval involves undertaking successive trials of increasing size and complexity.

[9] Joseph A. DiMasi, "Success Rates for New Drugs Entering Clinical Testing in the United States," 58 *Clinical Pharmacology and Therapeutics* (1995): 1-14.

The pre-clinical and clinical testing phases generally take more than a decade to complete.[10]

In a recently completed study, Joe DiMasi, Ron Hansen and I have examined the average R&D cost for drugs introduced into the market in the late 1990s. Data were collected on R&D costs for a randomly selected sample of 68 investigational drugs from 10 multinational firms. We found the representative new product approval incurred out of pocket costs of over $400 million.[11] This includes money spent in the discovery, pre-clinical and clinical phases as well as an allocation for the cost of failures.

Figure 1 shows a breakdown of total R&D costs per approved drugs that are incurred during the pre-clinical and clinical R&D phases. As shown in this figure, expenditures in the clinical period account for roughly 70 percent of total out of pocket expenditures. This reflects the fact that clinical trials are very expensive on a per patient basis, many drugs must be tested for every one approved, and drugs that do make it to the final testing phase and FDA submission typically require pre-market testing on thousands of patients.

Figure 1 also shows R&D costs capitalized to the date of marketing at a representative cost of capital for the pharmaceutical industry of 11 percent. The average capitalized R&D cost for a new drug introduction during this period is $802 million, or nearly double the out of pocket expenditure. Capital costs are high in this situation

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[10] Joseph A. DiMasi, "Trends in Drug Development Costs, Times and Risks," 29 *Drug Information Journal* (1995): 375-384; Kenneth I Kaitin and Joseph A. DiMasi, "Measuring the Pace of New Drug Development in the User Fee Era," 34 *Drug Information Journal* (2000): 673-680.

[11] Joseph A. DiMasi, Ronald W. Hansen and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs" (Boston: Tufts University Center for the Study of Drug Development, 2002); For an earlier study using the same methodology for 1980s new drug introductions, see Joseph A. DiMasi, et al., "The Cost of Innovation in the Pharmaceutical Industry," 10 *Journal of Health Economics* (1991): 107-129.

because of the long time periods involved in pharmaceutical R&D. More than a decade typically elapses from initial drug synthesis to final FDA approval. Since pre-clinical expenditures occur several years prior to FDA approval, these costs are subject to greater compounding at the industry cost of capital of 11%. Therefore they account for a greater proportion of total capitalized compared to total out of pocket costs (42 percent versus 30 percent).

R&D costs per new drug approval were observed to have increased at an annual rate of 7.4% above general inflation when compared to the costs of 1980s introductions. A major factor driving this increase is the size, complexity and number of clinical trials, which have increased significantly in the 1990s compared to the 1980s.[12] One important factor underlying this trend is the increasing focus of the pharmaceutical industry on chronic and degenerative diseases. These conditions require larger trial sizes to establish their efficacy and longer time periods for effects to be observed.

A number of factors could operate to alter the growth pattern for future R&D costs. Emerging discovery and technologies may have profound effects on R&D productivity in the next decade. The mapping of the genome, and related advances in fields like proteomics and bioinformatics, has led to an abundance of new disease targets. Nevertheless, some industry analysts have hypothesized that these developments may actually cause R&D costs to rise in the short run.[13] The basic reason is that these new technologies require substantial up front investments, and to date they have generated many disease targets that are not yet well understood. Eventually this expansion in the

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[12] Ibid.

[13] Lehman Brothers, "The Fruits of Genomics: Drug Pipelines Face Indigestion Until the New Biology Ripens" (New York, January 2001).

scientific knowledge base should lead to substantial efficiencies in the R&D process for new pharmaceuticals.

III. Generic Entry and Competition

In contrast to new product introductions, the development costs of generic compounds are relatively modest. In the United States, since the passage of the 1984 Hatch-Waxman Act, generic products need only demonstrate that they are bio-equivalent to the pioneering brand to receive market registration. Generic firms can file an Abbreviated New Drug Application (or ANDA). The ANDA process only takes a few years and typically costs a few million dollars.[14] The probability of success is also very high, as reflected by the fact that many generic firms file to receive FDA approval and enter the market within a short time window around patent expiration of the pioneer brand.

John Vernon and I have completed studies of generic competition during the 1980s and 1990s.[15] A distinctive pattern of competitive behavior for generic and brand name firms has emerged in the wake of the 1984 Act. First, commercially significant products experienced a large number of generic entrants within a short time after patent expiration. This was in sharp contrast to what occurred in the pre-1984 period. In the post-1984 period, we also observed a strong positive relation between the size of the

[14] U.S. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry" (Washington, DC: U.S. Government Printing Office, 1998); U.S Department of Health and Human Services, Theodore Goldberg, et al., "Generic Drug Laws: A Decade of Trial: A Prescription for Progress (Washington, DC: NCHSR, 1986).

[15] Henry Grabowski and John Vernon, "Effective Patent Life in Pharmaceuticals," 19 *International Journal of Technology Management* (2000): 98-100; This paper summarizes and extends our analyses of generic competition published in the *Journal of Law Economics* Oct. 1992, and Pharmco-Economics, vol. 10, supplement 2, 1996.

market and the number of generic competitors in accordance with expectations from economic theory.

Second, generics exhibited a high degree of price competition. The initial generic product entered the market at a significant discount to the brand name firm, and this discount grew larger as the number of generic competitors for a particular brand name product expanded over time. For our 1984 to 1989 sample of commercially significant products, generic prices averaged 61 percent of the brand name product during the first month of generic competition. This declined to 37 percent by two years after entry.

Third, we observed a more rapid rate of sales erosion by the brand name products in the case of more recent patent expirations. This is illustrated in Figure 2. This figure shows the growth in generic market shares during the first year on the market for four successive time cohorts. Market share are measured in terms of pills sold for the most popular dosage size. The more recent time cohorts in Figure 2 are characterized by much more intensive generic competition. The observed trend is particularly striking for the 1994-97 cohort of brand name products. In particular, generic drugs captured a 64% share of total units sold after one full year on the market. This increased to 73% after the second year. Recently Prozac was subject to its first generic competition in September 2001. Prozac lost over 80 percent of its U.S. sales to generics within the first month after their entry.

In sum, price competition and generic utilization have increased dramatically since the Waxman-Hatch Act was passed. In the mid-1980s, generic products accounted for approximately 19 percent of all prescriptions. By 1999, the figure was 47%.[16] The

[16] PhRMA, Pharmaceutical Industry Profile 2000: Research for the Millennium (Washington, DC, 2000), 69.

growth of managed care and other related demand-side changes also have been important factors underlying the rapid increase in generic usage that has taken place during the last decade. However, the passage of the 1984 Act played a major role in relaxing the regulatory hurdles for generic firms and facilitating higher levels of generic entry.

IV. Are the Innovation and Imitation Costs of New Biotech Entities Different?

Most of the analyses of R&D costs for new drug entities and their generic imitators have focused on small molecule new chemical entities. This reflects the fact that the biotech industry is relatively young. New biologic entities were first introduced in the 1980s. By 1994, only 29 new biologic entities had been introduced into the U.S. market, but this number has increased dramatically since then. In this regard, 41 new biological introductions occurred between 1995 and 2001.

The newest R&D cost study by DiMasi, et al, does include 7 biotech compounds in the sample of 69 entities for which data were obtained from 10 major pharmaceutical and biopharmaceutical firms.[17] While this sample of biological entities is too small to say anything definitive about the cost of biotech drug development, the clinical phase costs in the DiMasi, et al, study were similar for the biotech and pharmaceutical projects.

As discussed in Section II, capitalized R&D costs per new drug introductions are influenced by a number of factors. These include out of pocket costs at the preclinical and clinical phase, the probability of success for new drug candidates at different stages of the R&D process, and the length of time that it takes to move through all the stages of the R&D process and gain FDA approval. Recent studies of the probability of success and

[17] Joe DiMasi, et al., "The Price of Innovation," *op. cit.*, footnote 11.

length of the R&D process for biotech drugs indicate a convergence in these parameters toward the values observed for small molecule pharmaceuticals.

Two initial studies of success rates for biotech drugs were performed by Bienz-Tadmor, et al, and Struck.[18] Both studies found that success rates for biotech drugs were substantially higher than success rates for new chemical entities. In particular, both studies projected success rates for biopharmaceuticals in excess of 50 percent. However, a basic assumption implicit in the methodology of both studies is that success rates for biotech drugs that entered development in the late 1980s and early 1990s are the same as for the biotech drugs that entered development in the early to mid 1980s. This was a very strong, and potentially hazardous, assumption given that 90 percent of the drugs in their samples were still under active testing.

Subsequently, Gosse, et al,[19] analyzed a comprehensive sample of U.S. biopharmaceutical drugs and compared the success rates of older and newer biotech entities. They found dramatic differences in the time pattern of success rates observed for early versus later biotech drug cohorts. In particular, for the investigational new drugs (INDs) filed in the early 1980s, the success rater for new recombinant entities is 38%. For the INDs filed during the late 1980s the success rate was only 10% based on approvals to date (i.e., six years after testing). At a comparable point in time, the new recombinant entities of the early 1980s had a success rate of 26%. In fact, the success curve of the

[18] Brigitta Bienz-Tadmor, Patricia A.D. Cerbo, Gilead Tadmor, and Louis Lasagna, "Biopharmaceuticals and Conventional Drugs Clinical Success Rates," 10 *BioTechnology* (May 1992): 521-525; M.M. Struck, "Biopharmaceutical R&D Success Rates and Development Times," 12 *BioTechnology* (July 1994): 674-677.

[19] Marilyn E. Gosse, Michael Manocchia and Toben F. Nelson, "Overview of U.S. Pharmaceutical Development, 1980-1994," Tufts University Center for the Study of Drug Development, May 1996.

recent recombinant entities more closely resembles that of new chemical entities rather than that for the early biological entities.

This result is consistent with the history of biotech research in the U.S. The first biological entities introduced into the market were naturally occurring proteins that replaced purified non-recombinant formulations already in general use as established therapies (e.g., insulin and human growth hormone). It is reasonable to expect that recombinant versions of established therapies would have high success rates, once the technology to manufacture these products was proven. Other earlier targets for biotechnology were naturally occurring proteins with well-known and defined physiologic activity (e.g., erythropoietin and filgrastim). As the biotech drugs moved to targets for which limited knowledge existed about clinical and pharmacological profiles, it is reasonable to expect that success rates would fall back toward those of conventional drug entities. This is consistent with the findings of the recent Gosse, et al, study.

The prospect of a long and uncertain discovery and development period for a new drug is another factor affecting costs and risks in the drug R&D process. The longer the development and approval process, the higher the interest and opportunity costs and the overall capitalized R&D costs of a new drug introduction. Recently Janice Reichert of the Tufts University Center for the Study of Drug Development has done a historical analysis of clinical development time for successive cohorts of new biopharmaceuticals.[20] The results are presented in Figure 3. This figure shows that the earliest biopharmaceuticals had much shorter total clinical development times than more recent introductions. In particular the cohort of 2000-2001 new biopharmaceutical introductions had a total

[20] The data in figure 3 were provided by Janice Reichert of the Tufts University Center: April 2002.

clinical development time (including FDA approval) of 86 months, versus 53.2 months for 1982-1989 biopharmaceutical introductions.

Hence the experience with respect to development times parallels the experience observed with respect to success rates. In particular, there has been a convergence in clinical trial period times observed for new biological and new chemical entries. Of course, the biotech industry is still in the early stages of evolution. It may eventually produce higher success rates and shorter development times as a result of new technologies currently emerging in the discovery period. However the best evidence at the current time is that biopharmaceuticals, like new chemical entities, are subject to very high rates of attrition and long gestation periods in the clinical development stage.

One aspect in which biopharmaceuticals may be different than small molecule new chemical entities concerns the ease of generic entry when patents expire. To date there have only been a few patent expirations involving biopharmaceuticals. One case in which there has been entry after patent expiration is human growth hormone. However, all the entry to date has been by other big pharma firms that have had experience supplying this product in Europe and Japan (Pharmacia, Novo Nordisk and Ares Serono). There are greater hurdles in manufacturing biopharmaceuticals at an efficient scale compared to new chemical entities, and in addition there are greater regulatory requirements for biologicals associated with the manufacturing process.[21] These factors may moderate the degree of imitative competition for biopharmaceuticals compared to small molecule chemical entities. Whether or not this is the case will become more

[21] Henry Grabowski and John Vernon. *The Search for New Vaccines: The Effects of the Vaccines for Children Program* (Washington: American Enterprise Institute, 1994), 13-35.

apparent when some of the commercially important biopharmaceuticals are subject to patent expiration and potential competitive entry during the current decade.

V. Returns on R&D for New Drug Introductions

John Vernon and I have examined the distribution of returns for new drug introductions.[22] This work builds directly on the R&D cost analysis of DiMasi, et al, and considers the sales and net revenues realized over the product life of new drug introductions during the 1970s, 1980s, and 1990s. A finding of this work is that the distribution of returns to new drugs introductions is highly variable. This is another source of risks for firms developing new drug introductions.

Figure 4 shows the distribution for present value of net revenues (revenues net of production and distribution costs but gross of R&D investments outlays) for 1990 to 1994 new drug introductions. The distribution shows very strong skewness. Roughly one half of the overall present value from this sample of 118 compounds is accounted for by the top ranked decile of new drug introductions. The top decile of new drug introductions have an estimated after-tax present value that is more than five times the present value of average after-tax R&D costs per approved introduction. Furthermore, only the top three deciles have present values that exceed average R&D costs.

A major factor underlying the skewed distribution observed in Figure 4 is the level of sales realized by new drug introductions. Figure 5 shows sales profiles for the top two deciles and also for the mean and median drug introduction for the 1990 to 1994

[22] Henry Grabowski and John Vernon, and Joseph DiMasi, "Returns on R&D for New Drug Introductions in the 1990s," forthcoming in *Pharmco-Economics*, 2002; For earlier studies of new drug introductions in the 1970s and 1980s, see "Returns to R&D on New Drug Introductions in the 1980s," 13 *Journal of Health Economics* (1994): 383-406; "A New Look at the Returns and Risks to pharmaceutical R&D," 36 *Management Science* (1990): 804-821.

period. This figure illustrates the highly skewed nature of the sales distribution for new drug introductions. The sales peak of the top decile drugs is several times greater than the sales peak of the next decile. In addition the mean sales curve is much higher than the median one. This latter result is also reflective of a highly skewed distribution. John Vernon and I have investigated other periods and time cohorts of new introductions and found that they are characterized by similar patterns.[23]

Our returns to R&D analyses confirm the fact that the search for blockbuster drugs is what drives the R&D process in pharmaceuticals. The median new drug does not cover the R&D costs of the average compound (including allocations for the cost of discovery and the candidates that fall by the wayside). A few top-selling drugs are really key in terms of achieving economic success in pharmaceutical R&D over the long run. This result implies that larger firms, which have the resources to develop a diversified portfolio of drugs simultaneously, will have lower overall risk of failure (e.g. bankruptcy) than small firms. The large fixed costs of pharmaceutical development and the skewed distribution of outcomes helps to explain the clustering of biotech firms at the research stage of the R&D process and the large number of alliances between biotech and big pharma firms at the development and marketing stages.

In Figure 6, the distribution of worldwide sales in 2000 is presented for 30 new biological entities introduced into the U.S. market between 1982 and 1994. This includes new biological entities at different stages of their life cycle. However, all these compounds have been in the market at least 7 years, and therefore they have progressed beyond the initial rapid growth phase of their life cycle. The sales data presented in

[23] Ibid.; see in particular Figure 8.

Figure 6 indicates that new biopharmaceuticals also exhibit a high degree of skewness, similar to the much larger cohort of new drug introductions.

The high degree of skewness in the outcomes of pharmaceutical R&D projects indicates that there are substantial risks in this endeavor, both for big pharma firms as well as smaller biotech enterprises. Even though many big pharma firms spend billions of dollars per year on a diversified portfolio of in house and out-sourced projects, this does not guarantee a stable set of outcomes. In particular, the law of large numbers does not work very well in the case of skewed distributions.

If a firm invests in a large diversified portfolio of projects that are normally distributed, we expect that returns can be predicted with some confidence. When returns are highly skewed, however, individual companies experience highly volatile outcomes even when they invest in large numbers of independent projects. To illustrate this point, John Vernon and I examined the new product sales for the U.S. drug companies that spent between 300 and 500 million dollars on their global R&D in the mid-1980s (the top tier group in that period). We found subsequent new product sales emanating from these R&D efforts varied between 100 million dollars and 3 billion dollars (after 7 years of market life).[24]

Finally, it is important to note that the distribution of outcomes from pharmaceutical R&D projects has similar characteristics to many other innovation samples, including venture capital funding of high tech start-ups. In this regard, Scherer, et al, has examined the size distribution of profits from investments in innovation projects

[24] Henry Grabowski and John Vernon, "The Distribution of Sales from Pharmaceutical Innovation," 18 *Pharmco Economics* (2000, suppl. 1): 21-32.

using a diverse set of data samples.[25] His analysis included two large samples of high technology venture capital investments, as well as a comprehensive sample of venture backed start-up firms that had their initial public offering in the mid-1980s. A common finding was that the size distribution of profit returns from technological innovation is strongly skewed to the right. As in the case of new drug introductions, the most profitable cases contribute a disproportionate fraction of the total profits from innovation.

Table 1 summarizes the results from three data sets employed in Scherer's analysis. The first two data sets, assembled by Venture Capital Incorporated and Horsley Keough Associates involve an analysis of several hundred venture capital firm investments in high tech start up companies. Scherer's analysis indicates that roughly 60 percent of the returns, measured at the time of the final distributions to investors, are realized by the top decile of venture capital projects. At the same time roughly half of the projects in these samples failed to earn positive returns. Similarly, an analysis of the stock market performance of the universe of high tech companies that went public in the mid 1980s found that the top decile of companies realized 62% of the sample's total market value ten years later. The corresponding value for our sample of 1990-94 new drug introductions is 52 percent. Hence these samples of risky, high tech start-up companies exhibit similar skewed distributions of returns to the pharmaceutical industry.

VI. Conclusions and Policy Considerations

Economic analyses of the R&D process in pharmaceuticals indicate that it is a very costly and risky process, even for large established firms. Most compounds in the

[25] F.M. Scherer, D. Harhoff and J. Kukies, "Uncertainty and the Size Distribution of Rewards from Innovation," 10 *Journal of Evolutionary Economics* (2000): 175-200.

R&D pipeline never reach the marketplace. The process takes a long time, and the distribution of profits among those that are marketed is highly skewed. A few blockbuster successes cover the losses on many other R&D investment projects.

Overall then a key implication of my work with John Vernon and Joe DiMasi is that the returns of research-intensive pharmaceutical firms are positive, but are highly dependent on a relatively few highly successful new products. One important implication for public policy is that reimbursement, regulatory or patent policies that target the returns to the largest selling pharmaceuticals can have significant adverse consequences for R&D incentives in this industry.[26]

Many of the compounds in the top decile of the returns distribution involve the first mover, or other early entrants, in a new therapeutic class. The family of medicines in a given therapeutic class passes through a well delineated life cycle. There is dynamic competition involving breakthrough, as well as incremental advances, among the branded products within that class. This dynamic competition, in turn, produces substantial consumer surplus and social returns as discussed in Section I. When the patents for established products expire, consumers also benefit from imitative competition from generic entrants, which provide social benefits in terms of significantly lower prices.

The patent system is the public policy instrument designed to balance the trade-offs inherent between these dynamic and generic forms of competition. Without a well structured system of global patent protection, neither the research pharmaceutical industry nor the generic industry would be able to grow and prosper, as the rate of new product introductions and patent expirations would decline significantly.

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[26] Henry Grabowski and John Vernon, "Prospects for Returns to Pharmaceutical R&D Under Health Care Reform," in Robert Helms, editor, *Competitive Strategies in the Pharmaceutical Industry* (Washington: AEI Press, 1996).

Effective patent life (EPL), defined as patent time at a product's market launch date, is an important variable influencing R&D incentives in this industry, because it takes many years to recoup the R&D costs and earn a positive return for a typical new drug introduction. Because firms apply for patents at the beginning of the clinical development process, significant patent time is lost by pharmaceutical products by the time of FDA approval. This implies a significant reduction in the effective patent life of drugs relative to the nominal life of 20 years.[27] In light of this, the United States, the European Community and Japan have all enacted patent term restoration laws.

The U.S. law in this regard, the Waxman-Hatch Act, has been in existence since 1984. This law provides for patent term restoration of time lost during the clinical development and regulatory approval periods up to a maximum of 5 years additional patent life.[28] This is also the law that facilitates generic entry by allowing generic firms to file abbreviated new drug applications, in which generic firms only have to demonstrate bioequivalence to the pioneer's products to obtain FDA approval. Prior to the passage of the Act, generic firms had to submit their own proof of a compound's safety and efficacy, as well as show bioequivalence.[29]

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[27] For data on effective patent time, see the 1998 CBO stud cited in footnote 14, as well as my work with John Vernon cited in footnote 15.

[28] Title II of the Waxman-Hatch Act provided for partial restoration of the patent time lost during the clinical testing and regulatory approval periods. A formula for patent term restoration was embedded in the law. In particular, new drugs were eligible for an extension in patent life equal to the sum of the NDA regulatory review time plus one-half of the IND clinical testing time. The law capped extensions at five years and also constrained extensions to a maximum effective patent lifetime of 14 years. Drugs in the pipeline at the time the Act was passed, in September 1984, were limited to a maximum extension of 2 years.

[29] For new drug products with little or no effective patent life, generic firms are prohibited from filing an abbreviated new drug application within the first 5 years of the product life. Most European countries prohibit such filing within the first 10 years of market life.

John Vernon and I have investigated the effects of the 1984 Act on both generic competition and effective patent lifetimes.[30] In Section III of this paper, I have summarized our analysis of the significant increases in generic competition that has taken place since the Act's passage. We have also examined the impact of the law on effective patent lifetimes. Figure 7 shows the trends in EPLs by approval year for the new drugs introduced in the first half of the 1990s. This figure indicates that the average EPLs in the 1990s center around an 11- to 12-year range.[31] The mean for all 126 new drug introductions in the 1990-1995 period is 11.7 years with an average Waxman-Hatch extension of 2.33 years. In the last two years of this period, when virtually all of the drugs involve compounds that entered clinical testing after 1984, the average extension is close to three years in length. The mode of the frequency distribution of EPLs for this sample of annual new drug introductions is in the interval of 12 to 14 years.

We also found that relatively few NCEs are marketed with effective patent lifetimes of less than 10 years. The effective patent life on the top decile of compounds is particularly critical given the highly skewed nature of the outcome distribution and the vital role that the top compounds play in sustaining the viability of the entire R&D enterprise. We found that effective patent life for these compounds tend to be a few years above the mean for the full sample as a whole. This suggests that firms are able to accelerate the development of commercially promising compounds by doing R&D in

[30] Grabowski and Vernon, "Effective patent Life in Pharmaceuticals," cited in footnote 15.

[31] This includes any benefits from the international GATT Agreement passed by Congress in 1994 which harmonized U.S. patent laws with foreign countries, including setting the nominal patent life to 20 years from the date of patent application rather than 17 years from the date of patent grant. It does not include any potential benefits of a 6-month extension granted under the FDA Modernization Act in 1997, which can be awarded if the firm does additional testing and gains FDA approval for a pediatric indication.

parallel and by undertaking other cost increasing activities to marginally speed up the development process.

The Congressional Budget Office (CBO) has also done an analysis of the economic effects of the Act.[32] As in our analysis, they found that generic competition has been a powerful force for price competition since 1984. The CBO estimated annual savings of 8 to 10 billion dollars to consumers by the mid-1990s. In terms of R&D incentives, however, they found that the 1984 Act has had negative consequences on the expected returns on R&D. In this regard, they estimated that the Act, together with the increased demand side incentives promulgated by managed care organizations to utilize generic products in the 1990s, has resulted in steadily accelerating erosion in pioneer-brand's sales over time.

The CBO found that from the perspective of R&D returns, the much more rapid loss of sales in the period after patent expiration has dominated the patent term restoration aspects of the law. In particular, they estimated a 12 percent lower expected value for the after tax profits from R&D for the mean new drug compound as a consequence of the 1984 Act. While the mean compound is still profitable in their analysis, the increased generic competition since 1984 can have adverse R&D incentives for compounds of above average riskiness or ones with shorter than average effective patent life.

Overall, the Waxman-Hatch Act has provided a relatively balanced approach to the trade-offs between pharmaceutical R&D and generic competition. Improvements on the margin could be considered by policy makers, such as a longer minimum exclusivity

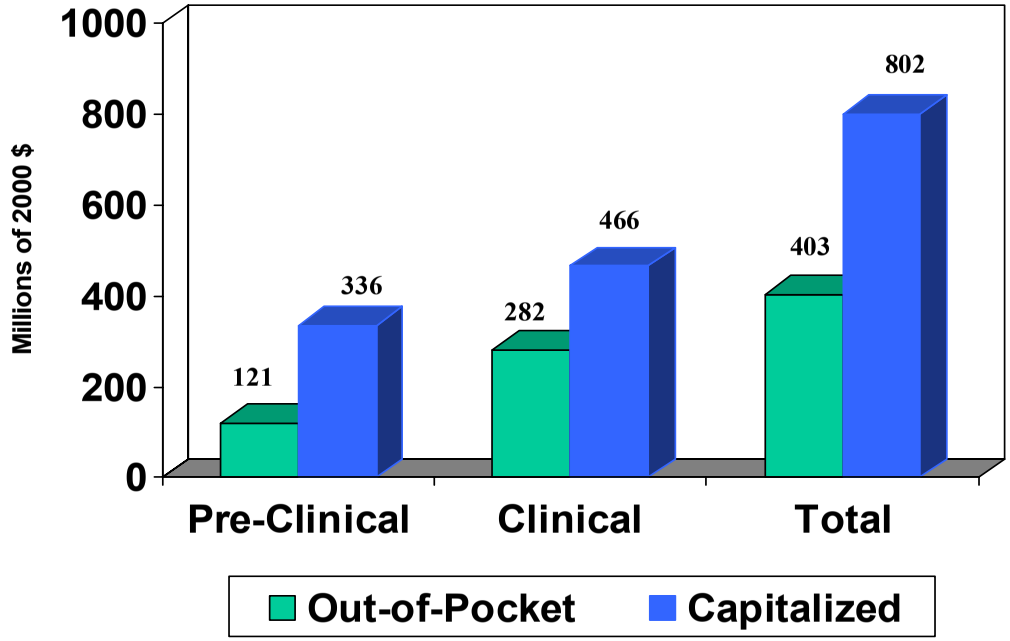
[32] See the CBO study, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," cited in footnote 14.

period before an ANDA could be filed for new drug introductions (currently 5 years in the United States but longer in Europe and Japan). Nevertheless, the law has provided a reasonably well structured system of incentives for both innovative and generic firms. Both R&D activities and generic utilization have increased dramatically in the period since the passage of the 1984 Act. Some groups have suggested that Congress consider changing the patent restoration aspects of the law in order to further increase generic competition in pharmaceuticals.[33] Given the critical role that patents and effective patent life play in terms of R&D incentives for this industry, this would not appear to be a desirable course of action on social welfare grounds.

[33] See for example, National Institute for Health Care Management Foundation, "Prescription Drugs and Intellectual Property Protection," NICHM Foundation Issue Brief, Washington, DC, August 2000.

Figure 1

Out-of-Pocket and Capitalized Costs per Approved Drug



Source: Tufts University Center for the Study of Drug Development

Figure 2

Generic Market Shares
One Year After Entry

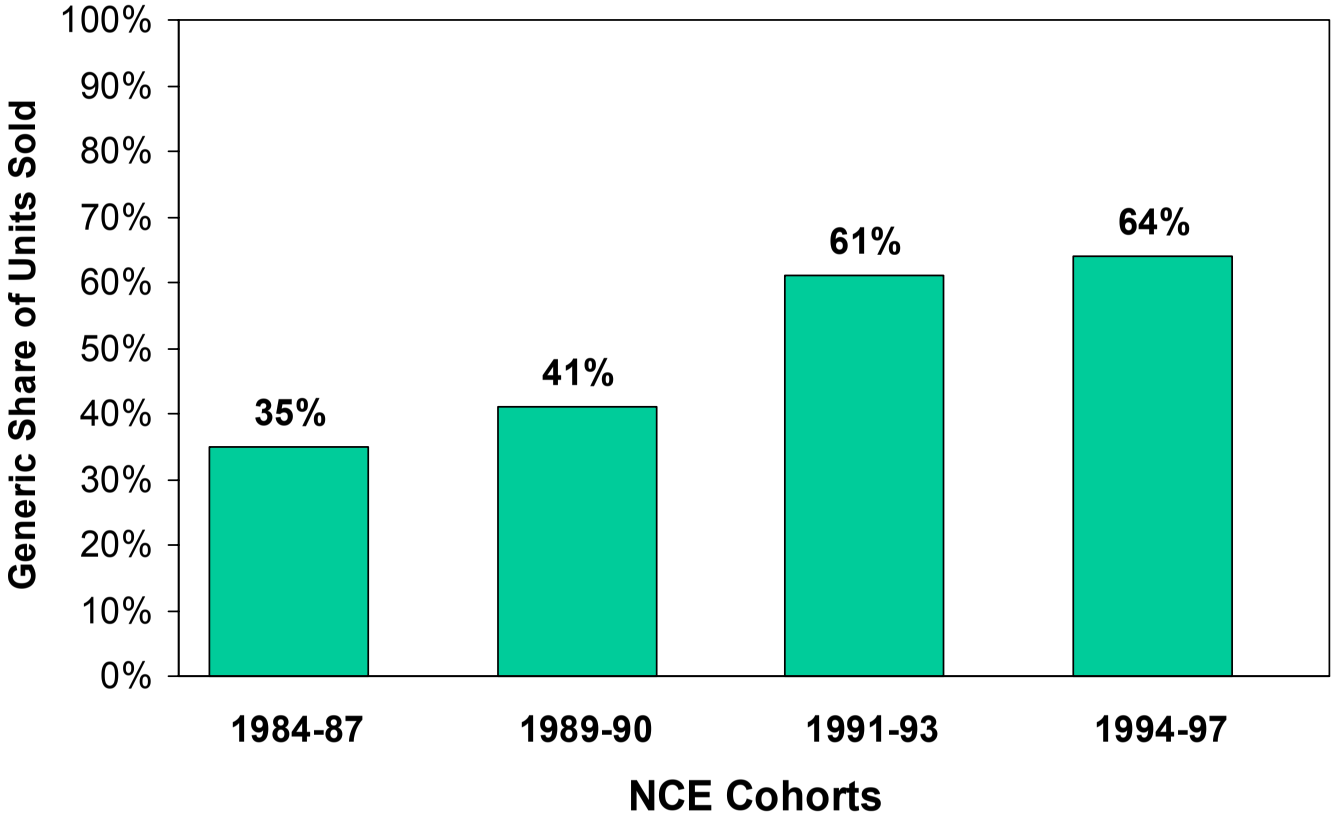
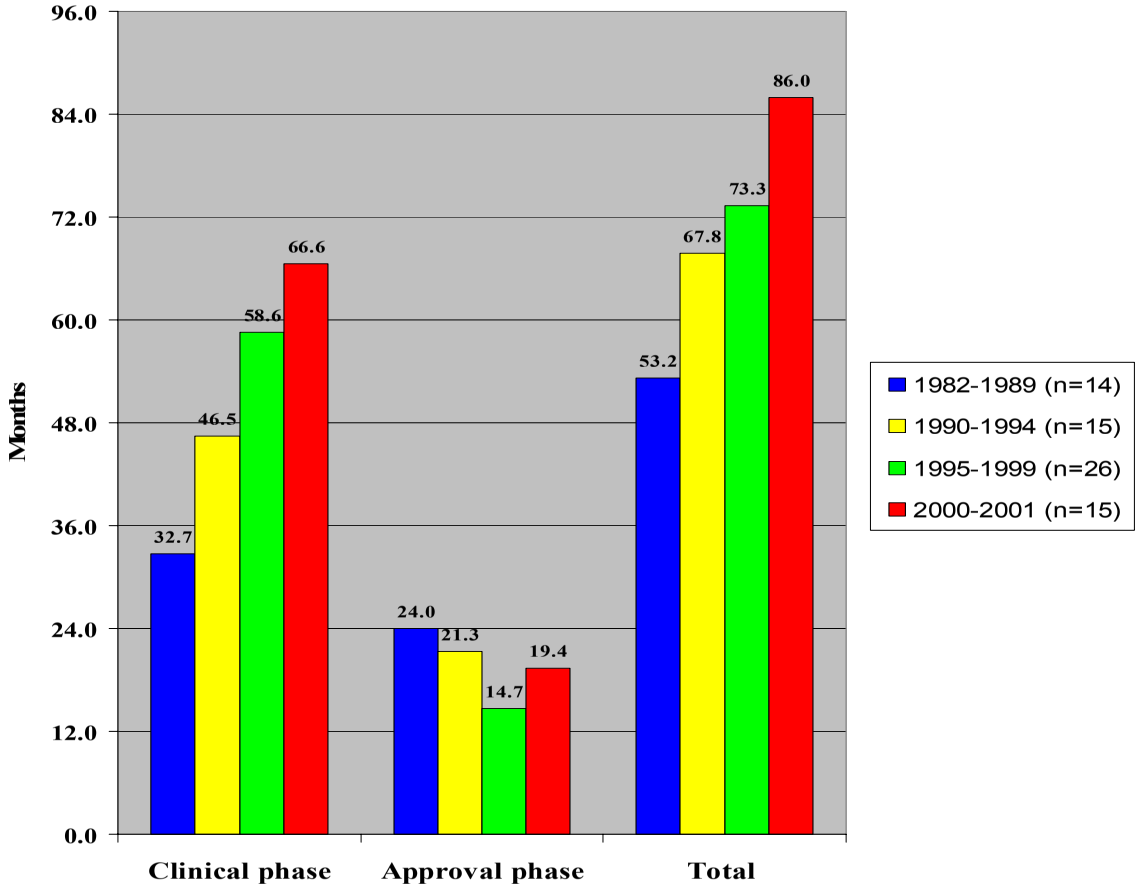


Figure 3

Historical comparison: biopharms



Source: Tufts Center for the Study of Drug Development Outlooks 2002

Figure 4

Present Values by Decile: 1990-94 NCEs

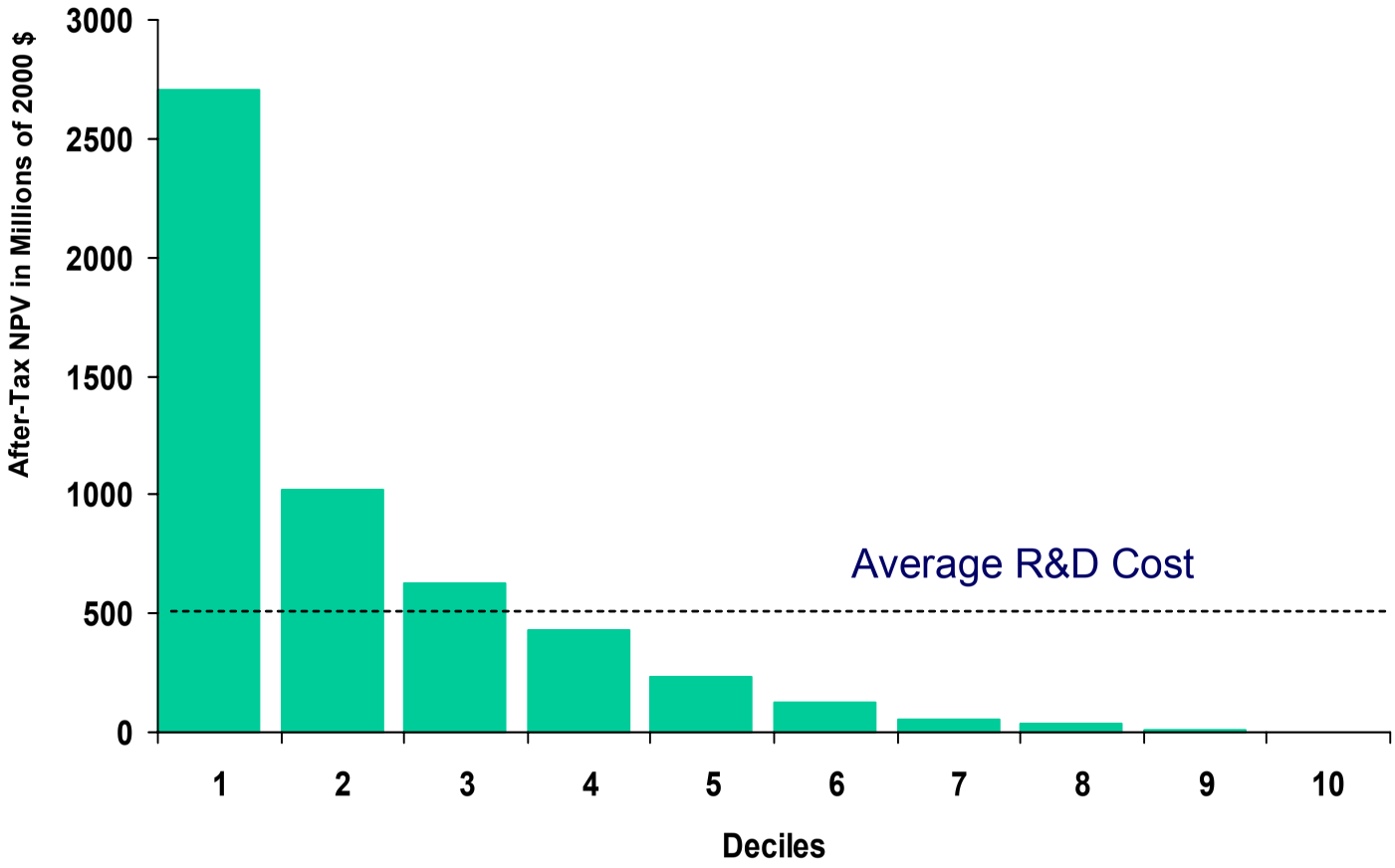


Figure 5

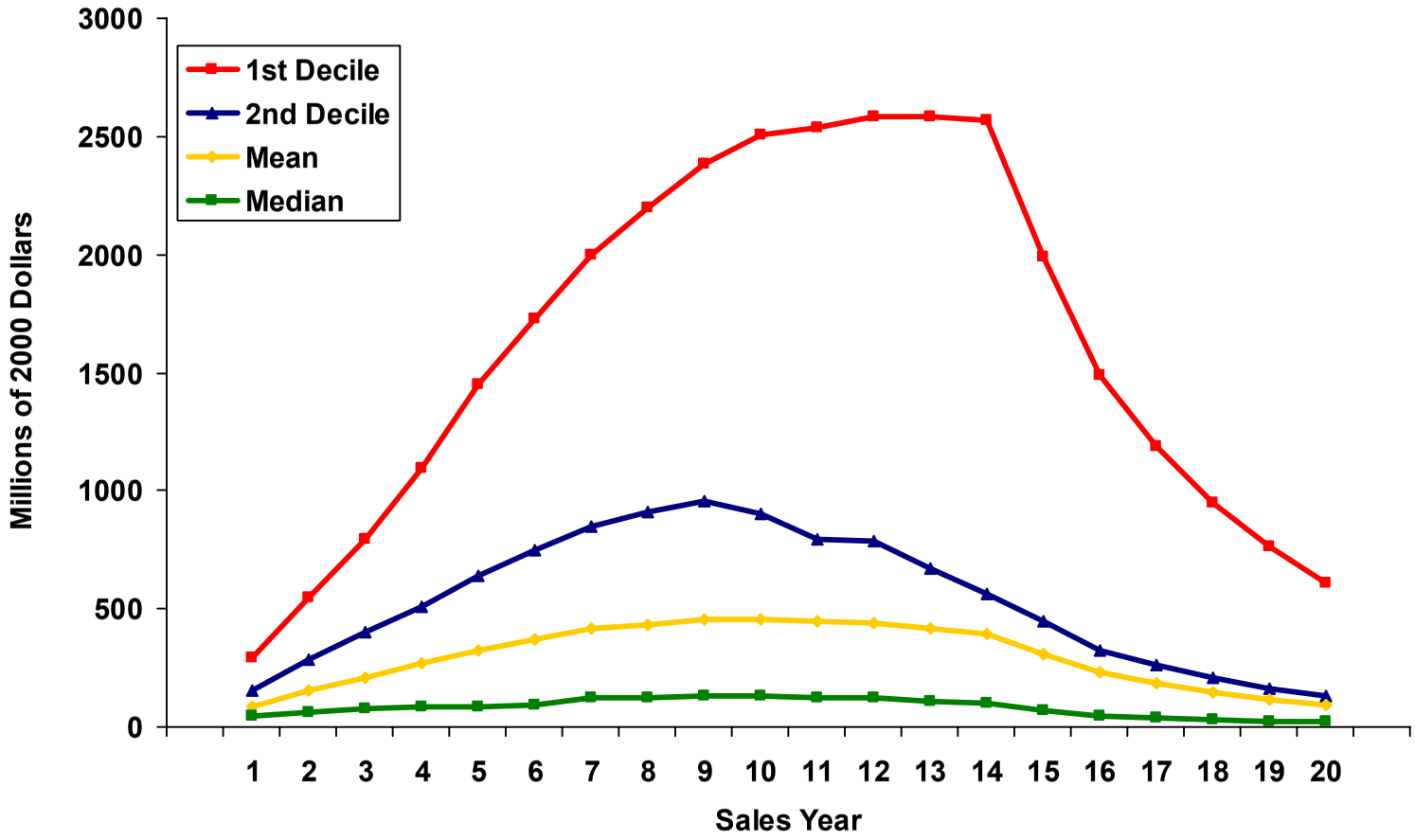

3000
2500
2000
1500
1000
500
0
Millions of 2000 Dollars
1st Decile
2nd Decile
Mean
Median
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Sales Year

Figure 6

New Biotech Introductions 1982-1994
Worldwide Sales in Year 2000

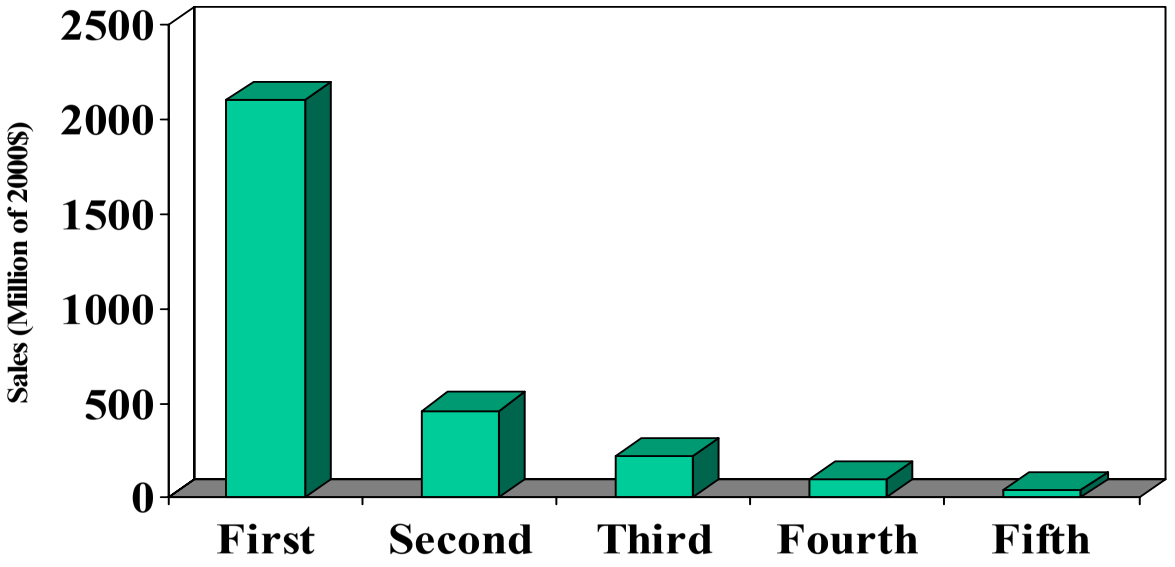


Figure 7

Effective Patent Life for 1991-1995 NCEs

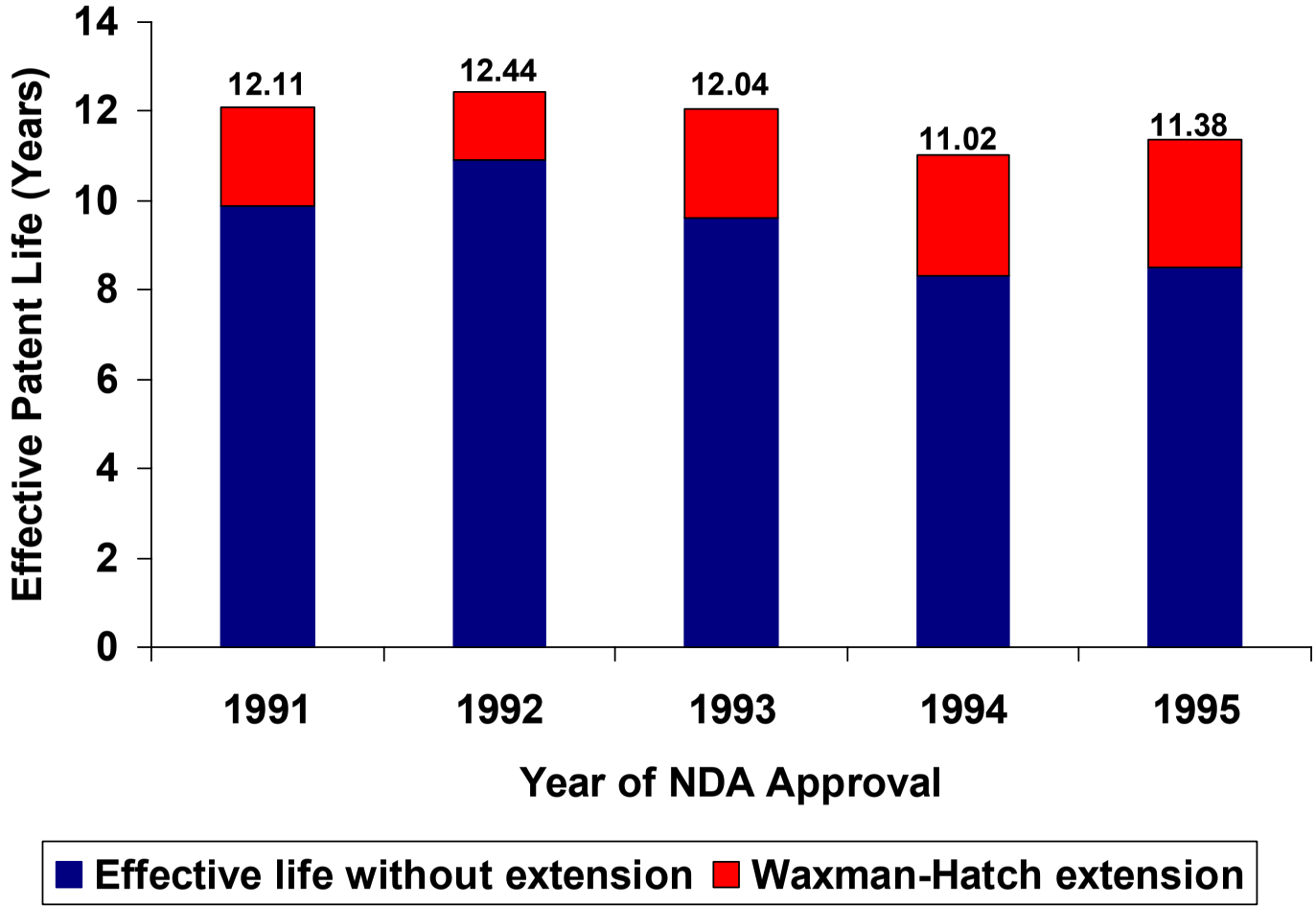


Table 1

Returns Distribution for Selective Innovation Samples

Date Set	Percent of Value From Top Decile
• Venture Capital (Start-Ups)	62%
• Horsley-Keough (Start-ups)	59%
• 1980s IPOs— (1995 Value)	62%
• 1990s New Drugs (Grabowski-Vernon)	52%