

HEALTH REFORM AND PHARMACEUTICAL INNOVATION

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I. INTRODUCTION

The basic objectives of the Clinton Administration's proposed Health Security Act (the Act) for pharmaceuticals, as for other health care services, are universal coverage and cost control.¹

Pharmaceuticals are currently the least insured element of basic health care in the United States. This situation would change dramatically under the Administration's plan. Prescription drugs would be part of the basic package of insured health care benefits guaranteed to all individuals. In addition, the elderly population would be insured for outpatient prescription drugs under Medicare, which currently covers only drugs consumed under inpatient settings.

While mandating universal coverage for drugs, the Act would simultaneously impose significant cost controls on drug therapies. The most stringent of these controls target new drugs, especially major therapeutic advances. In particular, the legislation sets up an Advisory Council on Breakthrough Drugs that would evaluate the reasonableness of prices for important new therapies. Furthermore, the Secretary of Health and Human Services (HHS) would be empowered to negotiate supplementary rebates to Medicare on any new drugs marketed at a lower price in twenty-one reference countries or those deemed to have "excessive" prices. Where HHS and manufacturers are unable to agree on a new drug's price in the Medicare program, it could be excluded from coverage.

The Clinton Administration has not addressed the effect of these proposed measures on research and development (R&D) investments for new drugs. R&D investment activity in pharmaceuticals is fundamentally a risky investment decision governed by expected returns. It is relevant to ask whether pharmaceutical firms will be willing to pursue lengthy and uncertain R&D projects

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¹ The Health Security Act was introduced in the Senate by Senator George Mitchell and in the House of Representatives by Representative Richard Gephardt on November 20, 1993. S. 1757, 103d Cong., 1st Sess. (1993); H.R. 3600, 103d Cong., 1st Sess. (1993). All references to the Act are based on S. 1757 and H.R. 3600.

if government controls on new drugs significantly constrain their expected future profits.

The U.S. pharmaceutical industry has been the acknowledged world leader in drug innovation, accounting for nearly half of the significant therapeutic advances since 1970.² New technologies based on biotechnology and other concepts have emerged in recent years with the capacity for striking advances in a number of disease areas. There is great optimism at the present time about these expanding opportunities. However, the rate of technological progress in pharmaceuticals is linked to long-term economic expectations. The Clinton Administration's health care plan could influence these expectations in unintended and undesirable ways.

The consequences of the Administration's health care plan for pharmaceutical innovation is the major issue addressed in this Article. In the next section, the characteristics of this plan are examined in more detail. Subsequent sections discuss the innovation process in pharmaceuticals and the various effects of the Act on this process.

II. MAJOR PROVISIONS OF THE ACT AFFECTING PHARMACEUTICALS

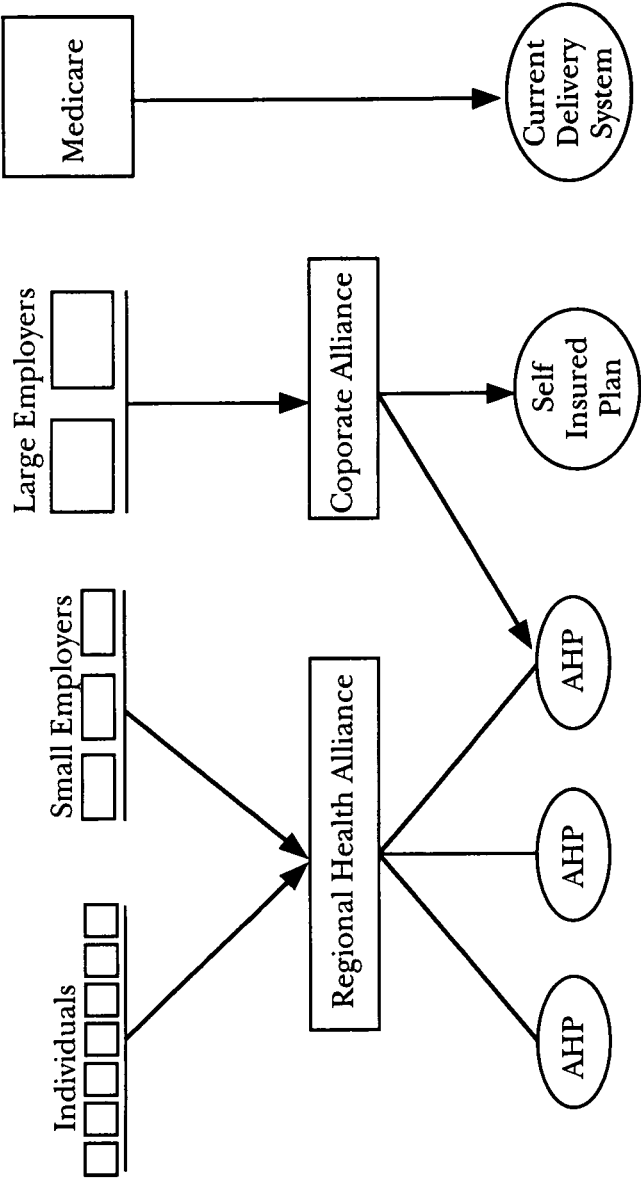
A simplified picture of the health care system under the Health Security Act is presented in Figure 1. Everyone would be insured for a minimum level of health care benefits (the basic benefit package), and this would be financed primarily through employer mandates. Government would subsidize unemployed individuals with low incomes as well as many small businesses. The Medicare Program would remain largely intact with the addition of outpatient prescription drugs as the major new benefit.

At the core of the health care insurance and delivery system would be regional health care alliances. These would be government-appointed organizations whose basic function would be to spread risks and reduce administrative costs. These organizations are envisioned as efficient local purchasing agents of health care, but also would have regulatory powers over physician fees and other market decisions. All unemployed individuals and businesses with less than 5,000 employees would obtain their medical care benefit plan through a regional health alliance.

Regional health alliances would in turn certify alliance health plans (AHPs), which would be the actual health care providers.

² Henry G. Grabowski, *An Analysis of U.S. International Competitiveness in Pharmaceuticals*, MANAGERIAL & DECISION ECON., Spring 1989, at 27; Heinz Redwood, *New Drugs in the World Market* (American Enterprise Institute) Aug. 1993, at 72-80.

Figure 1
The Clinton Administration's Health Care Plan



Providers would have to offer annual open enrollment, as well as continuous and portable insurance coverage. Premiums would be determined independently of pre-existing health conditions (community rating). Each health alliance would have to provide its members with at least three AHP options: a low cost sharing or "HMO type" option, a high-cost sharing or "fee for service" type option, and a combination plan. Eventually, limits will be placed on the federal tax preferences for enrollment in plans that provide richer benefits than the basic benefit package.

Businesses with more than 5,000 employees could offer enrollees a self-insured plan or buy insurance directly from the AHPs (i.e., through "corporate alliances") or utilize regional health alliances. However, all self-insured plans and AHPs offered through corporate alliances would be subject to the same basic terms as those certified by the regional health alliances (community rating, open enrollment, etc.).

Overseeing the whole system would be a federally appointed National Health Board. This board would have global budgetary responsibilities. In particular, the board would set annual budget caps on the growth in insurance premiums and ensure that the regional alliances implement these caps. The board would also determine changes in the basic benefit package on an annual basis. In addition, the board would have a number of other responsibilities, such as the standardization of accounting forms and paperwork, formulation of practice guidelines, and data requirements on outcomes measures, risk adjustments procedures, and so forth.

A. Universal Coverage for Pharmaceuticals

Outpatient pharmaceutical prescriptions would be included in the basic benefit package guaranteed to all individuals. These benefits would be subject to various deductibles and co-payments. Table 1 shows the proposed schedules in this regard. Enrollees in the low-cost sharing plan would have a five dollar co-payment per prescription in the network (or twenty percent co-insurance out of network), and a \$1,500 limit on all of their out-of-pocket health care expenditures (or \$3,000 per family). Enrollees in the high-cost sharing option would be subject to a \$250 deductible for pharmaceuticals and would pay a twenty percent co-insurance rate on expenditures above this deductible. There would be a \$1,500 limit on out-of-pocket health care expenditures. The combined plan would be subject to identical deductibles and co-payments,

TABLE 1
Prescription Drug Benefits Under the Health Security Act

	LOW COST-SHARING	HIGH COST-SHARING	COMBINATION	MEDICARE
DEDUCTIBLE	None	\$250	None within network, \$250 out of network	\$250
CO-PAYMENT/ CO-INSURANCE	\$5/Rx in network or 20% out of network	20% after deductible	\$5/Rx in network or 20% out of network after deductible	20% after deductible
ANNUAL LIMIT—OUT OF POCKET	\$1,500 (all expenditures)	\$1,500 (all expenditures)	\$1,500 (all expenditures)	\$1,000 (drugs only)

depending on whether patients use the cost-sharing network or go out of the network.

Outpatient prescription drug coverage would be extended to the Medicare patients under part B of the Medicare program. As shown in Table 1, Medicare prescription drug benefits would be subject to a deductible of \$250, twenty percent co-insurance, and an out-of-pocket annual limit of \$1,000 (on drug expenditures only). Medicare recipients would pay a monthly premium, which is designed to have enrollees pay for one-quarter of the benefits received under outpatient prescription drug coverage (similar to other part B health care benefits).

The Act, therefore, provides universal insurance coverage for the elderly and under-65 population under comparable benefit schedules and co-insurance provisions. One key issue for evaluating the impact on the research-based pharmaceutical industry is how much extra prescription drug usage would be induced as a result of universal coverage. The Administration has taken the position that a substantial increase in demand can be expected, and this will be a major benefit to the research-based industry. For example, in testimony before the Senate Special Committee on Aging, HHS Assistant Secretary for Health, Philip Lee, stated that universal coverage through qualifying plans and Medicare would add "at least a 10 percent to 20 percent increase in the demand for prescription drugs."³ However, the Administration has not pro-

³ F-D-C REPORTS—THE PINK SHEET (Chevy Chase, Md.) Nov. 22, 1993, at 8 (quoting Dr. Philip Lee, HHS Assistant Secretary for Health, Hearings before the Senate Special Committee on Aging, Nov. 16, 1993).

vided any substantiation of its claims in this regard.

The consensus among various groups that have examined this issue is that increased demand will occur from universal coverage but on a more moderate scale than projected by the Administration. These outside estimates tend to be in the range of five to ten percent of current prescription expenditures and generally cluster around the low end of this range. These estimates are also before the consideration of various revenue offsets in the Act such as mandatory government rebates to the Medicare program.

In 1989, the Congressional Budget Office (CBO) analyzed the issue of induced insurance demand for Medicare outpatient prescription drug coverage for the Medicare Catastrophic Coverage Act (MCCA).⁴ The analysis recognized that prescription drugs are jointly determined goods with physician services. Hence, insurance coverage for medical services will be an important determinant of drug consumption, along with the specific terms of any insurance coverage for prescription drugs.

In the case of the MCCA, the CBO estimated that induced demand from insurance coverage would be only two percent of outpatient prescription drug expenditures.⁵ This low value occurred in part because there was a high deductible of \$600 for outpatient prescription drug expenditures under the MCCA. Additionally, the estimate reflected the fact that roughly half of the Medicare population already had prescription drug coverage, under employment-based plans and Medicaid, and the remaining Medicare enrollees without drug insurance had very good physician coverage under Medicare Part B and supplementary Medigap policies.⁶ While some increase in expenditures for this latter group is expected, a large induced demand for prescription drugs through increased physician visits is unlikely.⁷

⁴ CONGRESSIONAL BUDGET OFFICE, UPDATED ESTIMATES OF MEDICARE'S CATASTROPHIC DRUG INSURANCE PROGRAM 44-52 (Oct. 1989).

⁵ *Id.* at 52.

⁶ Over 99% of Medicare enrollees elect the Part B program, which covers physician services subject to deductibles and co-payments. Additionally, all but 11% of total Medicare enrollees have some type of supplementary coverage (such as Medigap). While individually purchased Medigap policies do not typically cover prescription drugs, these policies do enhance the insurance for physicians' services. George S. Chulis et al., *Health Expenditures and the Elderly*, HEALTH AFF., Spring 1993, at 111.

⁷ This hypothesis is reinforced by data collected on drug expenditures from the 1987 National Medicare Expenditure Survey. In particular, enrollees with supplementary Medigap policies (typically without drug coverage) spend only 7.5% less for prescription drugs than enrollees which have supplementary employer-based policies (which typically have drug coverage). CONGRESSIONAL BUDGET OFFICE, *supra* note 4, at 50-51.

In a forthcoming report, the CBO utilizes the same basic methodology as in its earlier analysis of the MCCA in order to estimate the increase in prescription usage from universal coverage under the Act. However, the CBO took account of the lower deductible under the Administration's health care plan and other factors. The CBO estimated that prescription drug expenditures will increase in the range from five to seven percent.⁸

The CBO estimated values are consistent with independent estimates of this phenomenon by Donald Muse of the Policy Research Group and by Lewin-VHI, Inc. While each of these organizations models the increased demand in different ways, their overall increase is quite similar. In particular, Donald Muse estimates increased pharmaceutical utilization of between 4.7% and 6.9%, depending on whether there is a high or low shift to managed care under the Act.⁹ Lewin Associates estimates the average pharmaceutical firm will experience a 6.1% increase in volume from universal insurance coverage.¹⁰

Of course, the Health Security Act represents a new world where we have never been before, and the estimates of increased demand from universal coverage are subject to considerable uncertainty. But the specter of runaway demand for prescription drugs appears highly unlikely. In particular, under the Act most individuals will be subject to similar or more constrained prescription drug benefits than what they currently enjoy. Furthermore, all the new Medicare beneficiaries and those in the health alliances' high-cost sharing plans will pay significant co-insurance rates over the range in which most health expenditures fall. The co-payments are significantly less for those enrolled in the low-cost sharing plan, but these plans control prescription drug expenditures in more direct ways.

The Act, however, would have major distributional consequences in terms of who pays for prescription drugs. While approximately half of all prescription drugs are now paid for out-of-pocket, this would change dramatically under the Act. Out-of-pocket expenditures would drop to about twenty percent of pre-

⁸ CONGRESSIONAL BUDGET OFFICE, HEALTH CARE REFORM AND PHARMACEUTICAL RESEARCH AND DEVELOPMENT (forthcoming 1994).

⁹ Donald N. Muse, *Costs Estimates of Prescription Drug Benefits Contained in the Health Security Act* (Policy Research Group, Washington D.C.), Dec. 17, 1993, at 4.

¹⁰ Robert Rubin, Effect on the Pharmaceutical and Biotechnology Industries and on Investors in Health Care Technology and Services, Presentation, in *Health Care Reform by the Numbers: An Assessment of President Clinton's Health Security Act* (Dec. 9, 1993) (on file with author).

scription drug expenditures. Third-party insurance plans under contract to the regional and corporate alliances, along with the federal government, would account for nearly eighty percent of all expenditures.¹¹ From the federal government's perspective, the estimated expenditure for Medicare outpatient drugs is \$66 billion between 1995 and 2000.¹² This would be an expensive new entitlement, and the Medicare program will become a bigger purchaser of pharmaceuticals than most single-payor countries.

B. Medicare Rebates and Other Measures

There are a number of cost containment measures imposed on manufacturers supplying prescription drugs to Medicare recipients.

First, there are mandatory rebates to Medicare on all single-source and innovator multiple-source drugs. The standard rebate for each unit of a covered drug consumed by a Medicare beneficiary would be equal to the greater of (1) seventeen percent of the average manufacturer retail price or (2) the difference between the average manufacturer retail price and non-retail price. There is also an additional rebate designed to capture any increases in a manufacturer's price over time above the rate of inflation as measured by the consumer price index. There are no rebates required for generic drugs.

For drugs that are available from multiple suppliers, reimbursement under Medicare is limited to the unweighted median price of all products that could be dispensed to meet the patient's needs. A physician can specify in writing that a specific brand name product must be dispensed because it is medically necessary. Unless this is done, however, payment is limited to the median drug price. Hence, Medicare beneficiaries have a strong incentive under this provision to use generic drugs.

The Act would also allow the HHS Secretary to require advanced approval for outpatient drugs which the Secretary determines are not cost effective. Prior approval is a cost-containment measure that particular states have employed in implementing the Medicaid drug benefit program.¹³ Because physicians are generally reluctant to spend time getting permission from external par-

¹¹ *Id.* at 6.

¹² Alice M. Rivlin et al., *Financing, Estimation, and Economic Effects*, HEALTH AFF., Spring 1994, at 30, 33.

¹³ Henry Grabowski et al., *The Effect of Medicaid Formularies on the Availability of New Drugs*, 1 PHARMACOECONOMICS 32 (Supp. 1992).

ties for their prescriptions except in extreme cases, this designation can result in a significant obstacle to a drug's utilization under Medicare.

The most stringent of the cost-containment measures involves the reimbursement of new drugs by Medicare. The HHS Secretary could negotiate an extra rebate for any new drug marketed at a lower price in twenty-one reference countries or one whose price is determined to be "excessive." Where HHS and the manufacturer cannot agree on a negotiated rebate, a new drug can be excluded from Medicare coverage. Under the proposed legislation, a new drug is defined as any drug first marketed in the United States after June 30, 1993.

If a new drug is marketed in any of the twenty-one reference countries at a lower price, then the Secretary can negotiate a rebate as high as the difference between the average manufacturer's retail price and any price at which the drug is available to wholesalers in such countries. Referencing U.S. new drug prices to foreign ones in the Medicare Program could have the effect of importing outcomes of foreign regulatory schemes, with their diverse objectives, into this country. All twenty-one of the cited countries regulate drug prices in one way or another.¹⁴ Most of these countries have significantly lower standards of living than the United States. Only a few have research-intensive pharmaceutical and biotechnology industries of any consequence. Beyond this, this provision is likely to engender strategic behavior with undesirable and unintended consequences, discussed below.

If a new drug is marketed only in this country, or marketed abroad at a significant discount, then the HHS Secretary can negotiate an extra rebate based on a determination that the U.S. price is excessive. To determine if a new drug's price is excessive, the Secretary is to consider the prices of other drugs in the same therapeutic class, other cost and pricing information, special manufacturing requirements, prices abroad (where available), and other relevant factors. These are the factors that foreign countries typically employ in regulating the prices of pharmaceuticals.

In addition, the legislation also would establish an Advisory Council on Breakthrough Drugs. This council would be located

¹⁴ The 21 countries are those previously singled out for special drug export treatment under the Food, Drug and Cosmetic Act. These countries are: Australia, Austria, Belgium, Canada, Denmark, Germany, Finland, France, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

within HHS and would have a mandate to investigate the reasonableness of launch prices in the case of drugs that represent a breakthrough or significant advance over existing therapies. This council would utilize costs and other criteria to evaluate the reasonableness of prices to Medicare as well as reimbursers (the health and corporate alliances). The Secretary would review and publish the council's findings, along with minority opinions. The council initially would serve only an investigative and informational function, but the prospects of undergoing such a review could adversely affect the expectations of firms and investors financing very long-term, risky R&D prospects.

C. Health Alliances and Premium Caps

While there are no drug specific cost-containment measures in the Act applicable to the health alliances and health plans (except for the Advisory Council on Breakthrough Drugs), drug utilization would be influenced by the proposed system of managed competition and the caps on the growth of premiums for health care insurance purchased through the alliances.

The basic idea underlying the original managed competition concept is that all providers should have strong incentives to compete on cost grounds in supplying the basic benefit package. Health insurance purchasing cooperatives, dubbed health alliances in the Act, play an important role in this regard. But the health alliances proposed in the Act go far beyond those envisioned by the Jackson Hole group.¹⁵ In the latter case, health alliances were designed to help small employer groups and individuals obtain cost-efficient insurance through pooled purchasing arrangements.¹⁶ In the Act, health alliances are much larger in scope and are vested with considerable regulatory powers. They would have the authority to regulate provider fee schedules and negotiate budgets with fee-for-service plans.

¹⁵ Alain C. Enthoven & Sara J. Singer, *A Single-Payor System in Jackson Hole Clothing*, HEALTH AFF., Spring 1994, at 81.

¹⁶ A system of managed competition along these lines would likely accelerate trends already in place for pharmaceuticals. In particular, the growth of managed care organizations has resulted in increased price competition for pharmaceuticals over the past several years. Managed care organizations, especially staff-type Health Maintenance Organizations, tend to pursue aggressive cost-containment strategies in the case of prescription drugs. These include mandatory generic drugs utilization, drug formularies, and the negotiation of significant price discounts on formulary drugs. Furthermore, corporate PPOs and fee-for-service plans have been increasingly utilizing pharmacy benefit services which employ many of these same managed care type strategies toward pharmaceuticals.

Furthermore, the Health Security Act imposes a system of budgetary caps on the growth of insurance premiums for the basic set of health care benefits. In particular, the Act sets a general target for premium growth of no more than 1.5% over the rate of general inflation in 1996, and this is subsequently scaled down to growth no greater than the consumer price index by 1999. It is the responsibility of the National Health Board and the alliances to see that these targets are met. The Board would administer these targets by establishing an allowable weighted average premium for each alliance. The weighted premium's average growth would be limited to the general inflation target, adjusted for changes in the demographic characteristics and health status of alliance enrollees. If an alliance exceeds the targeted increases, the health plans in that alliance would be assessed pro-rated amounts to make up for the projected deficit.

As several other economists have pointed out, the caps on health insurance premiums under the Act are very ambitious and would constrain the growth in overall health care expenditures more tightly than what even single payor countries like Canada have been able to achieve.¹⁷ If these targets are to be met over the specified time frame, significant price controls and rationing would be the expected consequences. Furthermore, technological change has been a primary factor underlying the growth of aggregate health care expenditures. Hence, medical advances would likely bear a disproportionate burden of these expenditure caps.

A top-down cost-containment approach with severe budgetary targets would distort the incentives for pharmaceutical innovation. Specifically, new medicines aimed at improving quality of life would be facing reduced patient access, unless they could demonstrate that they also lowered health care costs. Drug innovation recently has been focused on chronic and disabling illnesses such as asthma, depression, hypertension, rheumatoid arthritis, multiple sclerosis, and senile dementia.¹⁸ Sometimes new drug therapies for chronic diseases improve a patient's quality of life and also lower overall health care treatment costs. But this is not always true for cost-beneficial drugs. Furthermore, it often takes several years to demonstrate the cost-effectiveness of a new medicine in practice. Medicines that increase health care costs today, with the prospects

¹⁷ See Enthoven & Singer, *supra* note 15.

¹⁸ Henry Grabowski, *The Health/Economic Benefits of Drug Therapy: Efficacy, Low Risk, Cost Effectiveness, Patient Information and Emancipation*, 9 SWISS PHARMA No. 3A, at 29 (1987).

of future benefits and cost savings, would also be adversely affected.¹⁹

Myopic top-down cost-containment systems can be expected to discourage innovative advances that cannot demonstrate immediate cost savings. Nothing in the Clinton Administration's health care plan addresses these disincentive effects or the lost opportunities for gains in patient welfare, as well as long-term cost efficiency.

D. Evaluating the Effects of the Act on Innovation

There have been some very preliminary assessments of the effects of the Act on the research-based pharmaceutical industry. These assessments may be characterized as short-term revenue analyses. In particular, they attempt to quantify the effects of certain provisions of the Act, such as universal coverage and government rebates on the net revenues of pharmaceutical firms. Both Donald Muse and Lewin-VHI, Inc. have conducted such analyses, and have concluded that research-intensive firms can be expected to suffer net revenue losses after the Act is implemented. In particular, they find that the revenue gains from universal coverage will be outweighed by revenue losses from the Medicare rebates, increased generic utilization, and increased price competition from managed care options.²⁰

The principal concern of this analysis is the effect of the Act on long-term incentives for pharmaceutical innovation. In this regard, the most important aspects of the Act are the cost-control measures that impinge directly on new drug returns. These measures are the negotiated rebates and the related authority to exclude new drugs under Medicare, the Advisory Council for Breakthrough Drugs, and the premium caps on the growth of health care expenditures. These measures are the hardest to quantify, and they have not been specifically analyzed in any of the short-term revenue analyses of the pharmaceutical industry.

The cost-control measures are potentially the most harmful to innovation incentives because they are tantamount to a system of incipient price controls over pharmaceuticals. Furthermore, the very stringent budgetary targets for Medicare and the Alliances increase the likelihood that price controls will be applied to new drugs in a vigorous manner.

HHS will be under strong pressure to restrict Medicare pre-

¹⁹ For example, drugs like the cholesterol-reducing medicines which lower the long-term probability of cardiovascular illness.

²⁰ Muse, *supra* note 9, at 4-5; Rubin, *supra* note 10, at 13.

scription drug expenditures, given the large overall savings mandated from Medicare.²¹ Hence, HHS would be expected to invoke the negotiated rebate process in the case of new drugs that significantly increase the Medicare drug budget, no matter how cost-beneficial they might be to patients. In effect, the most innovative and commercially successful new drugs are likely to be subjected to public utility-type cost constraints.

The CBO budgetary analysis of the Act suggests that immense cost pressures also will develop under the premium caps for the Alliances.²² Outpatient pharmaceuticals are a small part of total health care expenditures, only 4.8% in 1991.²³ Nevertheless, pharmaceuticals are an attractive government vehicle for price controls because of their low production costs and the fact that the negative consequences of price controls (declines in future innovation) are not likely to be apparent for many years. The Act also creates the infrastructure for a system of broader government controls on the launch prices of new drugs in the form of the Advisory Council on Breakthrough Drugs.

While it is uncertain how far and fast the government might proceed down the road toward full price controls over pharmaceuticals, research-intensive firms must make projections that extend far into the future. As discussed in Section III, the typical new drug introduction takes twelve years or more of testing and also entails very large investments of resources. Hence, firms must make an assessment of the economic and policy environment that will prevail over the next several decades to see whether undertaking these investments is worthwhile.

Firm expectations must take account of the likelihood that prices will be regulated to a greater extent in the future. Moreover, the prospects of expanding controls over time can have a strong negative effect on resource commitment to R&D, even if this is not a certainty under the provisions of the Act. In recognition of this fact, we look at price control scenarios in Section IV as a way of quantifying what is at stake for the research-based pharmaceutical industry.

²¹ Medicare savings of \$124 billion are projected in the years 1995 to 2000. Rivlin, *supra* note 12, at 34.

²² See CONGRESSIONAL BUDGET OFFICE, AN ANALYSIS OF THE ADMINISTRATION'S HEALTH PROPOSAL 74-77 (Feb. 1994).

²³ CONGRESSIONAL BUDGET OFFICE, TRENDS IN HEALTH SPENDING: AN UPDATE 64 (June 1993).

III. CHARACTERISTICS AND TRENDS IN DRUG INNOVATION

In order to evaluate the Health Security Act's proposed controls on new drugs, one needs a baseline or frame of reference. In this section, I review economic studies of drug innovation with special attention to the factors affecting the expected return to pharmaceutical R&D.

A. *R&D Costs of a New Drug Introduction*

The industrial R&D process in pharmaceuticals is essentially an uncertain economic investment decision. Despite dramatic gains in basic biomedical knowledge, drug discovery and development are still characterized by considerable trial and error search efforts. This trial and error approach is reflected by the fact that thousands of compounds are synthesized and tested in animals for every one that is tested in humans. Furthermore, only about one in five of the drug candidates tested in humans becomes a new drug introduction.²⁴

As a result of technological uncertainties and several regulatory hurdles, the investment process for new drugs is also lengthy. The average time that it takes for a new drug candidate to proceed from initial synthesis to final Food and Drug Administration (FDA) approval is nearly twelve years.²⁵ This includes three and one-half years of pre-clinical testing, six years of clinical testing, and two and one-half years for the new drug application review period.²⁶

Figure 2 shows the trend in total industry R&D expenditures, new chemical entities (NCEs), and Investigational New Drugs (INDs) applications between 1980 and 1992. INDs are new drug molecules approved by the FDA for clinical testing. NCEs are chemically distinct new drugs approved for marketing.

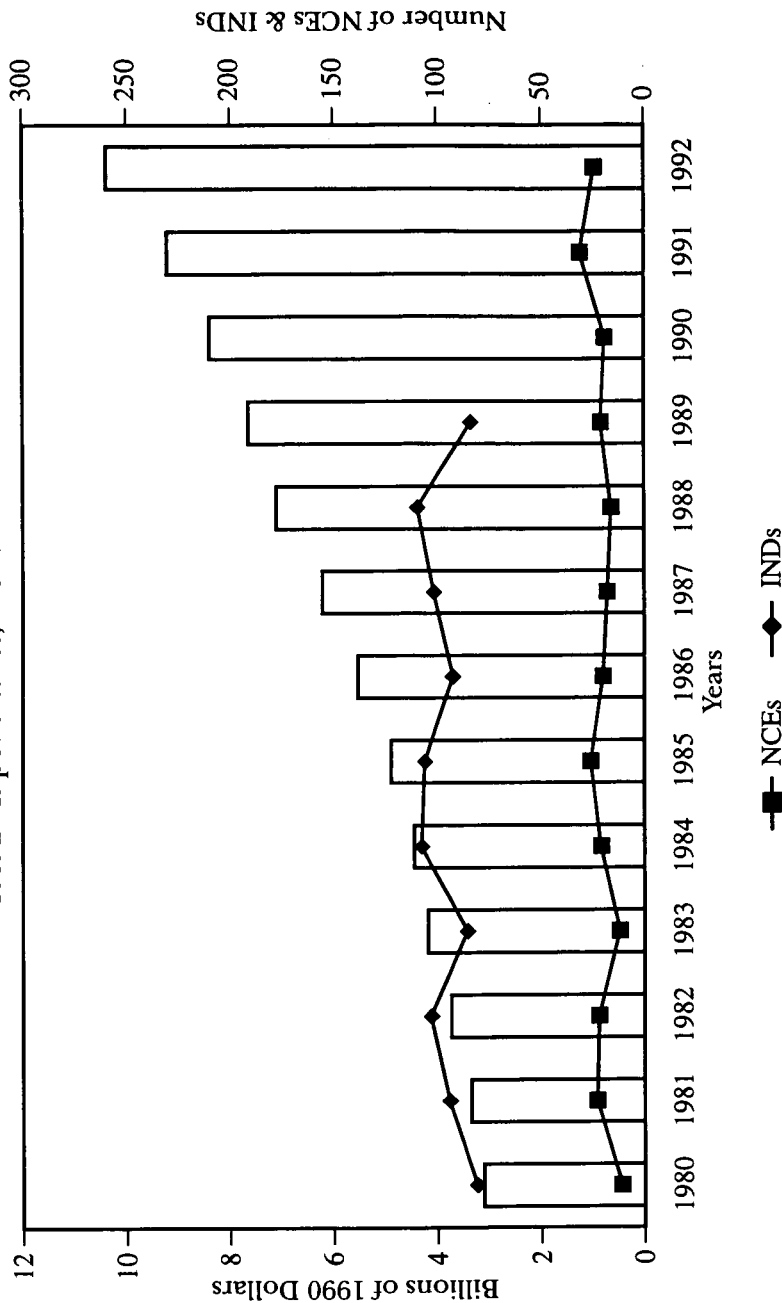
Figure 2 indicates that total R&D expenditures have been growing at a very rapid rate in real terms since the early 1980s. At the same time, the IND and NCE approvals have increased only modestly over time. This suggests that the average R&D costs for a new drug currently entering the market are substantial and rising. Among the factors set forth in the literature for causing R&D costs per NCE to rise over time is the increased emphasis on chronic

²⁴ Joseph A. DiMasi et al., *Cost of Innovation in the Pharmaceutical Industry*, 10 J. HEALTH ECON. 107, 124 (1991).

²⁵ *Id.* at 132.

²⁶ In fact, this ignores the time in the discovery process prior to synthesis in which basic research knowledge and leads are pursued. This part of the discovery process is essentially on-going and open-ended.

Figure 2
R & D Expenditures, NCEs and INDs



Source: Center for the Study of Drug Development; Pharmaceutical Manufacturers Association

disease categories, which require more pre-market testing, as well as expanded patient trials.²⁷

Joseph DiMasi, Ronald Hansen, Louis Lasagna and I have recently analyzed the investment cost of a representative new drug candidate, taking account of both the sizable attrition in new drug candidates and the time costs of this long investment process. This study was based on R&D cost data for a random sample of drugs first undergoing testing in humans between 1970 and 1982. The study found the average new drug cost \$231 million (pre-tax value and 1987 dollars), and takes account of time costs by capitalizing out-of-pocket R&D costs to the point of marketing at an average cost of capital of nine percent.²⁸

In a subsequent analysis of R&D costs, the Office of Technology Assessment (OTA) estimated that the pre-tax R&D costs of a representative new drug was \$359 million (1990 dollars).²⁹ Their analysis utilizes the out-of-pocket cost values from the DiMasi et al. study but employs a variable cost of capital. The cost of capital declines from fourteen percent to ten percent as one moves from the discovery phases of research through clinical development and FDA approval. This causes the time costs in the OTA study to be much higher than the DiMasi et al. study, accounting for most of the higher capitalized pre-tax R&D cost estimate of the OTA analysis.

B. Returns to Pharmaceutical R&D

John Vernon and I have been engaged in an ongoing study of the returns to NCEs introduced in the U.S. since 1970. A key issue that we address is whether the average NCE earns a return on R&D investment commensurate with the pharmaceutical industry risk-adjusted cost of capital. We also examine the distribution of returns. Our analysis is based on a comprehensive sample of U.S. NCE introductions, and is performed on a real after-tax basis.³⁰

We have recently completed a study of the returns on R&D

²⁷ Henry G. Grabowski, *The Changing Economics of Pharmaceutical Research and Development*, in *MEDICAL INNOVATION AT THE CROSSROADS: THE CHANGING ECONOMICS OF MEDICAL TECHNOLOGY* 35, 40 (Annetine C. Gelijns & Ethan A. Halm eds., 1991).

²⁸ DiMasi, *supra* note 24, at 125-26.

²⁹ OFFICE OF TECHNOLOGY ASSESSMENT, *PHARMACEUTICAL R&D: COSTS, RISKS AND REWARDS* 47-69 (1993).

³⁰ Our initial paper analyzed the returns on R&D for NCEs introduced during the 1970s. A basic finding was that the average NCE during that period had returns roughly equal to the industry's cost of capital. However, the distribution of returns was highly skewed. In particular, only the NCEs from the top three deciles had present values on post-launch cash flows in excess of the estimated R&D costs for a new

investment to 1980-84 NCEs.³¹ This analysis is the baseline for the simulations presented in Section IV on the effects of health care reform on returns to R&D. The representative 1980-84 NCE has the pattern of cash flows presented in Figure 3. R&D outlays are taken from the DiMasi study; cash flows after product launch are derived from sales life cycle curves and other information.³²

Cash flows are negative over the pre-clinical and clinical R&D period and become increasingly so in the years prior to marketing due to large launch and capital investment outlays. By year three after launch, cash flows become positive. They then escalate rapidly and reach a peak in year eleven. Most of the drugs in our 1980-84 sample have effective patent lifetimes of nine to thirteen years. This accounts for the peak in cash flow for the representative NCE in year eleven. The rapid decline after year eleven is due to generic competition and product obsolescence.

The baseline values shown in Figure 3 provide the basis for computing the internal rate of return (IRR) and net present value (NPV) for the mean 1980-84 NCE. In addition, our analysis uses a 10.5% real cost of capital for pharmaceutical firms over this period.³³

A basic finding is that the IRR for the mean NCE is 11.1%. This is only slightly above the industry's 10.5% cost of capital over this period. The capitalized value of R&D investment costs for the representative 1980-84 NCE is \$201.9 million after tax (1990 dollars). The discounted value of net cash returns resulting from this R&D investment is \$224.1 million. Hence, the net present value (NPV) for the mean 1980-84 NCE is \$22.1 million.

Although the average NCE's returns on R&D are moderately higher than the cost of capital, there are large variations in present values and returns across NCEs. As in our earlier work on 1970s NCE introductions, we found that the distribution of present values is highly skewed. Figure 4 shows the present value by deciles for the sixty-seven NCEs in our sample. The top decile of NCE has

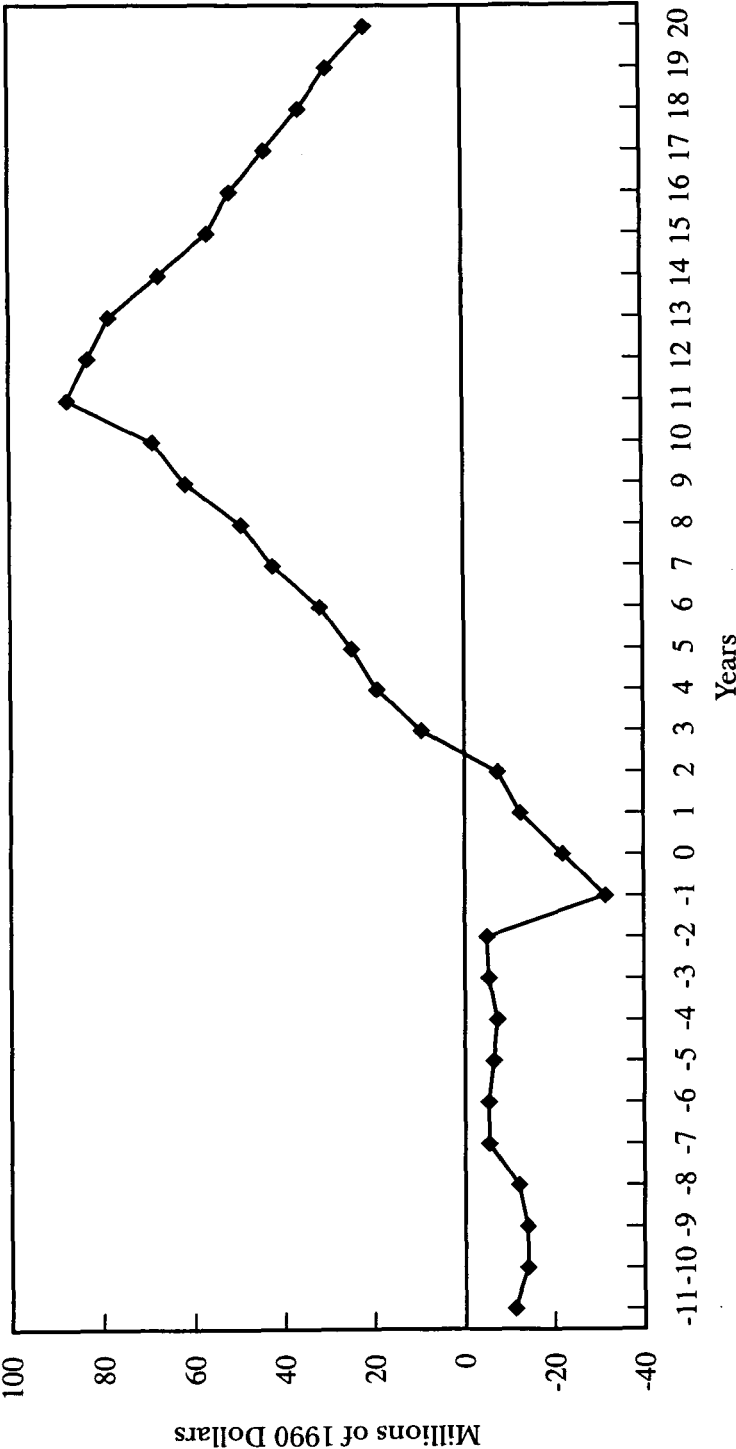
NCE. Henry Grabowski & John Vernon, *A New Look at the Returns and Risks to Pharmaceutical R&D*, 36 MGMT. SCI. 804 (1990).

³¹ Henry Grabowski & John Vernon, *Returns to R&D on New Drug Introductions in the 1980s*, J. HEALTH ECON. (forthcoming 1994).

³² *Id.*

³³ This is based on a study by Myers and Shyam-Sunder performed for the OTA. Specifically, they found that the real cost of capital on total investments of the pharmaceutical industry varied between 10% and 11% during the 1980s. Stuart C. Myers & Lakshmi Shyam-Sunder, *Cost of Capital Estimates for Investment in Pharmaceutical Research and Development*, in COMPETITIVE STRATEGIES IN THE PHARMACEUTICAL INDUSTRY (Robert Helms ed., forthcoming 1994) [hereinafter COMPETITIVE STRATEGIES].

Figure 3
Total Cash Flows for Mean 1980-84 NCE



Source: Grabowski and Vernon

an estimated present value of cash flows after launch that is more than five times the capitalized value of average R&D costs. In addition, only the top three deciles have present values that exceed average R&D costs.

This extreme skewness of returns to pharmaceutical R&D has an important implication for the proposed cost controls under the Health Security Act considered in Section IV. That is, if a type of price regulation develops under the new health care plan that focuses on restricting returns to the "big winners"—the top few deciles—then the overall returns to new drug innovation will be reduced significantly. This is one of the key issues that will be addressed later in this Article.

The OTA has also conducted an analysis of the mean returns to pharmaceutical R&D using a similar sample cohort of 1981-83 NCEs.³⁴ While the OTA utilizes some different assumptions, its estimated NPV is similar in value (\$36 million versus \$22 million). Both studies imply that the returns for the average NCE are within one percentage point of the industry's cost of capital.³⁵

The analysis of returns to pharmaceutical R&D, therefore, indicates that the returns to NCEs introduced in the 1980s have been within a very close range of the industry cost of capital. This finding is often surprising to policy-makers and other observers familiar with accounting measures of return, such as those published in the *Fortune 500* analysis or *Business Week*. Indeed, in recent debates, legislators critical of the industry have pointed to the high accounting returns for pharmaceutical R&D as an indicator of serious performance problems in this industry.³⁶ However, several economic studies have demonstrated that accounting returns are not good measures of the underlying internal rate of return for a firm or industry. These measures are subject to particularly significant bias in industries such as pharmaceuticals with high rates of intangible capital investment. Various empirical studies have corrected for this bias by depreciating intangible investment flows like R&D and advertising, and have found that adjusted returns on the total investment of pharmaceutical firms converge toward the industry's cost of capital.³⁷

Because my focus in this study is on the effects of the Clinton

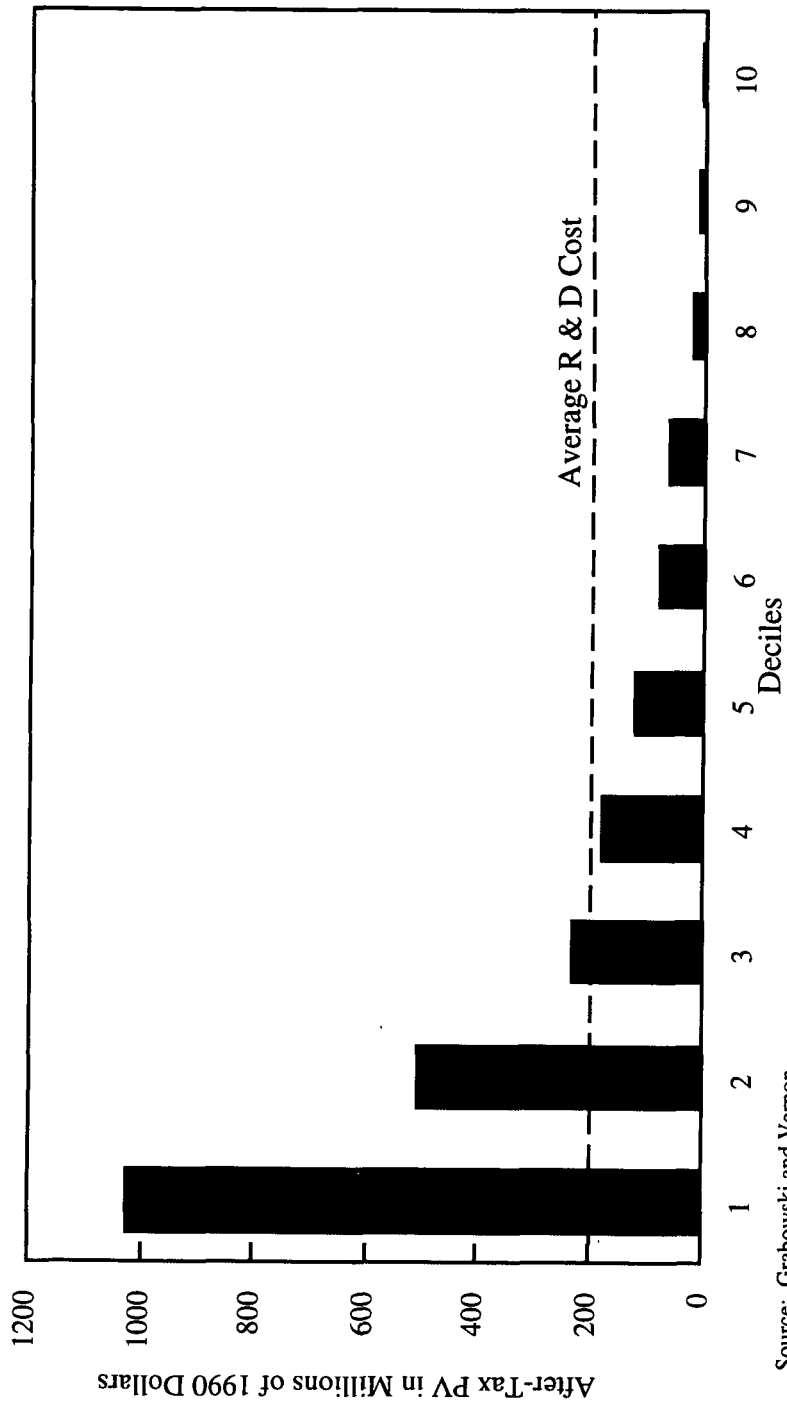
³⁴ See OFFICE OF TECHNOLOGY ASSESSMENT, *supra* note 29, at 73-94.

³⁵ Grabowski & Vernon, in *COMPETITIVE STRATEGIES*, *supra* note 33, at Section II.

³⁶ STAFF OF SENATE SPECIAL COMMITTEE ON AGING, 102D CONG, 1ST SESS., *THE DRUG MANUFACTURING INDUSTRY, A PRESCRIPTION FOR PROFIT* (1991).

³⁷ Pamela Megna & Dennis Muller, *Profit Rates and Intangible Capital*, 73 REV. ECON. & STAT. 632 (1991); Kenneth W. Clarkson, *Intangible Capital and Profitability Measures*:

Figure 4
Present Values by Decile: 1980-84 NCEs



Source: Grabowski and Vernon

Administration's proposal on pharmaceutical innovation, the returns on NCE introductions is the appropriate measure of profitability. Furthermore, when accounting rates are adjusted for various biases and distortions, they provide a reasonably consistent picture with that which emerges from the NCE returns analysis discussed above.

C. Recent Changes in Market Competition

During the last several years, there has been a trend toward increased price competition for brand name pharmaceuticals. This reflects changes on both the demand and supply side of the market. On the demand side of the market, there has been the increased presence of managed care organizations and pharmacy benefit managed plans. On the supply side of the market, there has been the increased availability of generic drugs since the passage of the Waxman-Hatch Act in 1984, as well as other significant changes discussed below.³⁸

Managed care organizations, especially staff-type HMOs, tend to pursue aggressive cost-containment strategies for prescription drugs. These strategies include mandatory generic utilization, drug formularies, and drug utilization reviews.³⁹ Drug formularies are approved lists of prescribable drugs for participating physicians. Drug formularies allow HMOs to negotiate significant price discounts in exchange for the utilization of a particular drug among a class of closely substitutable ones. Pharmacy benefit management plans also make use of drug formularies, drug discounts, and generic substitution in managing prescription drug services for employer indemnity plans.

This increasing growth and influence of managed care on the demand side has interacted with several supply-side forces to produce more price competition for prescription drugs. This has been manifested in a number of ways. One important effect has been increased generic utilization. Since the passage of the Waxman-Hatch Act in 1984, the market share of generics has increased from less than ten percent of all new prescriptions in the early 1980s, to close to forty percent in 1992.⁴⁰ Moreover, more than

Effect of Research and Promotion on Rates of Return, in COMPETITIVE STRATEGIES, supra note 31.

³⁸ Henry G. Grabowski & John M. Vernon, *Brand Loyalty, Entry and Price Competition in Pharmaceuticals After the 1984 Drug Act*, 35 J.L. & ECON. 331 (1992).

³⁹ SYLVIA MORRISON, CRS REPORT FOR CONGRESS, *PRESCRIPTION DRUG PRICES: THE EFFECT OF GENERICS, FORMULARIES, AND OTHER MARKET CHANGES* (August 17, 1993).

⁴⁰ *Id.* at 1 & n.2.

100 drug patents are scheduled to expire between 1992 and the end of the decade, with market sales of over \$25 billion.⁴¹ As a consequence, one analyst projects that generic drugs potentially could account for more than sixty-five percent of all new prescriptions dispensed by the year 2000.⁴²

The expected increases in generic utilization by managed care and indemnity plans will mean an accelerated rate of sales declines for new drugs after patent expiration. The rate of decline in cash flows for the mean 1980-84 NCE shown in Figure 3 is based on sales decay rates for drugs experiencing patent losses in the last part of the 1980s. Drugs coming off patent in the latter part of this decade and the first part of the next, can be expected to experience much faster sales declines.⁴³ This trend could also be accelerated by the move to universal care under the Clinton Administration Plan as discussed in the next section.

The effects of increased price competition, however, are not confined to the period of generic entry after patent competition. These effects are also manifest in the launch price of follow-on drugs in major therapeutic classes. In particular, follow-on competition drugs are now typically introduced at significant discount to the market leader and also frequently offer aggressive discounts to managed care organizations to gain access to their formularies. This contrasts to historical patterns where competition by follow-on drugs tended to center around product differentiation.

The new competition is illustrated by the experiences in one of the major new categories of drugs of the 1980s: the ACE inhibitor cardiovascular medicines. The pioneering drug in the ACE inhibitor class was Capoten, introduced in 1981. The second drug introduction was Vasotec in January 1986. Vasotec was introduced at a lower price per daily dose than Capoten, and subsequently has become the market leader. Through December 1992, there have

⁴¹ Hemant K. Shaw, *Catalysts for Change: The Impact of Generic Drugs on the Pharmaceutical Industry*, SPECTRUM (Decision Resources, Inc., Burlington, Mass.), Dec. 28, 1992, at 38-8.

⁴² *Id.*

⁴³ Brand name firms may be able to prevent much of the expected decline in *unit* shares by producing their own generic line or licensing other firms to produce or market them under their original approved new drug application (NDA). Brand name firms are increasingly adopting this strategy. However, the generics emanating from brand name manufacturers will have to compete on a price basis, and this competition is intensifying for the reasons discussed above. Our analysis of generic competition in the late 1980s found that generic prices decline on average to about one-third of the brand name's price within two years of initial market entry. See Grabowski & Vernon, *supra* note 38, at 336.

been six additional entrants into the ACE inhibitor class. These new entrants have provided significant price competition to Vasotec and Capoten, and also have gained substantial market share from these drugs.⁴⁴

Another major class of drugs first introduced in the 1980s is the non-tricyclic anti-depressants (i.e., the serotonin uptake inhibitors). The pioneer drug product in this class was Prozac, launched in 1988. Within six years of its market introduction, there have been three additional entrants also engendering substantial price competition within this therapeutic class.⁴⁵

A third competitively active therapeutic class during the 1980s has been cholesterol-reducing agents. The breakthrough product introduction was Mevacor in 1987. Bristol-Myers priced the second drug in this class, Pravachol, below Mevacor, and Merck followed with its second cholesterol-reducing drug, Zocor, also priced below Mevacor. More recently, Sandoz has announced that its new entrant into this class in 1994 will be priced at a discount of fifty percent below Mevacor.⁴⁶

From the perspective of the research-intensive pharmaceutical industry, one must also balance the prospects of increased demand from universal coverage with expected revenue offsets from various cost control measures in the bill. These measures include rebates to the Medicare program, strong incentives toward increased generic usage, and a number of other government controls on pharmaceuticals.

There is, therefore, evidence that, even without enactment of Clinton's health care proposal, downward market pressures are already developing on the prices and sales of new drugs. As a consequence, one might expect to observe product life cycles which peak sooner and at lower levels than that experienced by the 1980-

⁴⁴ For example, Ciba-Geigy's Lotensin was introduced in 1991 at a price that was 50% lower than Capoten, and 28% lower than that for Vasotec. Three other introductions in 1991 also had sizeable price discounts compared to the market leader. Capoten and Vasotec, which had 87% of the ACE inhibitor market in January 1990, had only a 60% share by January 1993. Elyse Tanouye, *Drug Prices Get Dose of Market Pressure*, WALL ST. J., March 11, 1993, at B1.

⁴⁵ Zoloft (the second entrant) and Paxil (the third entrant) sell at average wholesale prices of approximately 10% and 16%, respectively, below Prozac. In addition, health networks and institutions that buy in volume can negotiate big discounts for all of the drugs in this class. According to a recent article, Kaiser has been able to negotiate discounts of 40% or more below average wholesale prices. Milt Freudenheim, *The Drug Makers are Listening to Prozac*, N.Y. TIMES, Jan. 9, 1994, at F7.

⁴⁶ Tanouye, *supra* note 44, at B1; Elyse Tanouye, *Price Wars, Patent Expirations Promise Cheap Drugs*, WALL ST. J., Mar. 24, 1994, at B1.

84 cohort, as shown in Figure 3. This is consistent with life cycle data gathered for 1985-89 NCEs. While it is still quite early to evaluate the returns for these NCEs, this cohort appears to have cash flows peaking much sooner than the 1980-84 cohort, as a result of the competitive forces presented above.⁴⁷

D. Innovation by the Biotechnology Sector

Among the factors leading to the rapid increase of pharmaceutical industry R&D expenditures during the 1980s were the rise of new technologies of drug discovery and development. The most prominent of these technologies were those connected with biotechnology. Indeed, a separate industry subgroup was created by the entry of several newly established "biotech" firms, founded to exploit fundamental advances in biomedical research that typically originated in university settings.

The dedicated biotechnology sector accomplishments over the past decade has been impressive. By 1992, there were more than 200 biotechnology firms whose primary business involved the development of new pharmaceuticals, with cumulative R&D expenditures of over \$2 billion.⁴⁸ Through 1992, the FDA has approved sixteen biopharmaceuticals for the U.S. market, most of which originated in the biotechnology segment.⁴⁹ About one in three new drug candidates from all sources are now based on biotechnology,⁵⁰ and a 1991 PMA survey indicates that there are over 100 biotechnology medicines currently in clinical development, as well as twenty-one additional ones with submitted applications at the FDA.⁵¹

In terms of their research agendas, the dedicated biotechnology firms share many common elements with traditional research-oriented pharmaceutical firms. Nevertheless, biotechnology firms currently have important structural and organizational differences from traditional pharmaceutical firms. First, most of the biotech firms are still basically research firms, focused on particular disease

⁴⁷ Grabowski & Vernon, in *COMPETITIVE STRATEGIES*, *supra* note 33, at Section II.

⁴⁸ Mark D. Dibner, *Biotechnology's Contribution to Pharmaceuticals*, *DRUG NEWS & PERSP.*, May 1993, at 553.

⁴⁹ These include: erythropoietin (used to treat anemia in end-stage commercial diseases and AIDS), granulocyte (colony stimulating factor for neutropenia), insulin (for diabetes), TPA (to dissolve blood clots in acute myocardial infarction), and human growth hormone (for children with growth deficiencies). *PHARMACEUTICAL MANUFACTURERS ASSOCIATION, BIOTECHNOLOGY MEDICINES IN DEVELOPMENT* (1991).

⁵⁰ Brigitta Bienz-Tadmor et al., *Biopharmaceuticals and Conventional Drugs: Clinical Success Rates*, 10 *BIOTECHNOLOGY* 521 (1992).

⁵¹ See *PHARMACEUTICAL MANUFACTURER ASSOCIATION*, *supra* note 49, at 1.

and technologies areas. Only a few firms are vertically integrated with regulatory expertise and an independent sales force.⁵² Another major difference between biotech firms and established pharmaceutical firms involves the financing of R&D. Established drug firms have relied primarily on internal funds to finance their R&D.⁵³ By contrast, biotech firms rely on external financing in the form of venture capitalists, R&D partnerships, and stock offerings.

The fact that biotechnology firms are essentially R&D organizations, heavily dependent on external financing, makes them particularly vulnerable to the thrust of the Administration's proposed health care reforms for new drugs. In particular, the focus of the cost-containment controls on new drugs, particularly breakthrough therapies, could have especially damaging effects on the prospects of the dedicated biotech sector. This is discussed further in the next section.

E. Innovation by U.S. and Foreign Firms

The pharmaceutical industry is a globally competitive industry. Multi-national firms from the United States, Switzerland, the United Kingdom, and other countries typically have R&D facilities, manufacturing plants, and marketing both domestically and abroad. If U.S. health care reform adversely impacts on innovation incentives, it will have a negative effect not only on American-owned firms, but also on the multi-national drug firms of other countries. Nevertheless, American-owned firms will be most affected by the proposed government regulations on innovative new drugs. This is because U.S. firms currently discover and develop a very large share of the important "consensus" new drugs, and the United States is the largest and most important market for these products.

In an earlier analysis of worldwide new drug introductions, I found that U.S. firms accounted for 43.4% of the consensus new drugs between 1970 and 1985.⁵⁴ A more recent survey of 265 glob-

⁵² This is illustrated by the fact that most of the 16 biopharmaceuticals approved to date originated in the dedicated biotechnology sector. However, a majority of these products were developed and gained regulatory approval in collaboration with established pharmaceutical firms, and many are marketed in whole or in part by large drug firms.

⁵³ Henry G. Grabowski & John Vernon, *The Determinants of Research and Development Expenditures in the Pharmaceutical Industry*, in *DRUGS AND HEALTH: ECONOMIC ISSUES AND POLICY OBJECTIVES 2* (Robert Helms ed., 1981).

⁵⁴ Henry G. Grabowski, *Innovation and International Competitiveness in Pharmaceuticals*, in *EVOLVING TECHNOLOGY AND MARKET STRUCTURE: STUDIES IN SCHUMPETERIAN ECONOMICS 167* (Arnold Heertje & Mark Perlman eds., 1990).

ally prescribed drugs first introduced between 1970 and mid-1992 indicated a similar share of 42.8% for American-owned firms.⁵⁵ The U.S. share is roughly equal to all of the major Western European countries combined. Furthermore, U.S. leadership extended across all major therapeutic categories.

In recent years, scholars have attempted to explain the sources of the strong leadership position of U.S. industry in drug innovation. Lacy Thomas, in a series of international comparative analyses, has examined this issue in some detail. He has concluded that the absence of price regulation in the United States, the strong support of basic biomedical research by the U.S. government and its academic institutions, and the high medical and quality standards for new drugs in this country have been important factors in nourishing the strong U.S. leadership position in drug innovation.⁵⁶

The Health Security Act represents a sharp departure from past U.S. policies with the introduction of broad price control provisions for new pharmaceuticals. These controls subject the R&D investments of the private pharmaceutical industry to great uncertainties and can be expected to lead to many undesirable consequences. These are analyzed in the next section.

IV. IMPLICATIONS OF THE ACT FOR PHARMACEUTICAL INNOVATION

As discussed, the most important provisions of the Act for pharmaceutical innovation are the cost control measures that impinge directly on new drug returns. These are the negotiated rebates and the related authority to exclude new drugs under Medicare, the Advisory Council for Breakthrough Drugs, and the premium caps on the growth of health care expenditures. These measures constitute an incipient system of price controls over new drugs. This section considers some of the adverse consequences that would follow from their enactment.

A. *Referencing U.S. New Drug Prices to Foreign Ones Under Medicare*

The negotiated rebates on new drugs would be referenced to the outcomes of regulatory processes in other countries. In particular, for products introduced in any one of the twenty-one refer-

⁵⁵ See Redwood, *supra* note 2, at 72-80.

⁵⁶ Lacy G. Thomas, *Price Regulation, Industry Structure and Innovation: An International Comparison of Pharmaceutical Industries*, 1 PHARMACOECONOMICS 9 (Supp. I 1992); L.G. Thomas, *Trends of Innovation in the World Pharmaceutical Industry*, RIVISTA INTERNAZIONALE DI SCIENZE SOCIALI, Sept. 1992, at 333 [hereinafter Thomas, *Trends*].

ence countries at a lower price, the HHS Secretary can negotiate a rebate as high as the difference between the average manufacturer's retail price in the United States and any price at which the drug is available to wholesalers in these countries. This essentially allows the Secretary to piggyback on the regulatory outcomes in these countries. But it also allows manufacturers to manage strategically their introductions outside the United States (for new drugs not yet introduced in any of the referenced countries) in order to try to maximize their global returns.

This provision opens up a Pandora's box of unintended and undesirable consequences. Because the United States has been the largest and most profitable market, firms would want to introduce their products into other countries before the U.S. only where they could get a price equal to or better than their optimal U.S. launch price. This could involve significant delays of important products into the U.S. market while they attempt to manage strategically their introductions and reimbursement process abroad.

While the United States has traditionally not been the first country of introduction, recent legislation has passed attempting to speed up U.S. regulatory approvals significantly through the introduction of user fees.⁵⁷ The foreign reference pricing provisions of the Act could contravene the objectives of the user price legislation to get important new drugs introduced sooner into this country.

Beyond the problem of increased delays, this provision would expose U.S. new drug prices to the vagaries and opportunistic behavior of foreign regulatory authorities. Lacy Thomas, in comparative international research, has shown that countries like France and Japan exhibit a strong nationalistic approach in drug pricing, with domestic firms enjoying decidedly favorable treatment in terms of launch prices.⁵⁸ Firms from these countries could exploit these protectionist policies in terms of their new drug introductions into the United States under the reference pricing provisions of the Act. Moreover, most European governments are willing to trade off favorable new drug prices to companies that will locate R&D or manufacturing facilities in their countries. Consequently,

⁵⁷ Congress authorized user fees on pharmaceuticals in October 1992. H.R. 6181, 102d Cong., 2d Sess. (1992). This Act mandates a \$100,000 NCE application fee in the 1993 fiscal year, rising to \$233,000 in five years. 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 to utilize the fees and on its progress in achieving time approval goals.

⁵⁸ Thomas, *Trends*, *supra* note 56, at 341-43.

U.S. multinational firms may find it to their advantage to move jobs abroad in order to gain higher foreign prices, which then can be leveraged into higher U.S. prices under the Act.

The HHS Secretary is also not without a strategic set of countermoves in this game of international reference pricing. In particular, the Act does not appear to impose a time frame in which the Secretary must initiate or complete rebate negotiations for new drugs. The Act specifies only that exclusion from reimbursement would take effect on the earlier of (1) six months after the effective date of FDA marketing approval for the drug, or (2) the date the manufacturer terminates negotiations.⁵⁹ Hence, the HHS Secretary might delay negotiating the extra rebate on new drugs until the price has declined in foreign markets due to regulatory constraints, exchange rate fluctuations, or other factors. The prospects of such delays would add considerably to the large technological and commercial risks that already exist in the case of R&D on new drugs and would further discourage R&D on very risky projects with the promise of premium returns.

The Act is also ambiguous on whether the negotiated rebates for new drugs are limited to a one-time affair, or whether the HHS Secretary could subject these drugs to repeated negotiations over the product's life cycle. For example, even drugs introduced at the same price abroad often have large differentials after several years due to regulatory constraints on price increases, exchange rate fluctuations, and other factors. The Act does not appear to prevent the HHS Secretary from reopening rebate negotiations on a new drug, and subjecting them to increased rebates.⁶⁰ If the Act were interpreted to permit such multi-stage negotiations, this would cause further disincentives because the HHS Secretary could invoke this negotiated rebate whenever it found it advantageous to do so for budgetary or other reasons.

The reference pricing provisions are designed to force U.S.

⁵⁹ If the Secretary delayed negotiations for an extended period, the Act also apparently leaves open the possibility that manufacturers could be subject to retroactive recoupments of a substantial magnitude.

⁶⁰ The Act stipulates that the general agreement requiring each manufacturer to pay rebates to HHS for Medicare beneficiaries shall be effective for a period of at least one year and shall be automatically renewed by the HHS Secretary for a period of not less than one year, unless terminated for violations or other good cause, or by the manufacturer with proper notice. However, the extra rebate on new drugs is negotiated outside this general agreement, and the law does not appear to prevent the Secretary from responding to economic developments for specific new drugs with a demand for an increased rebate, under threat of that drug being excluded from Medicare.

new drug prices down to those in regulated foreign countries. But they can be expected to lead to delays and distortions in the international diffusion of new pharmaceuticals which will be harmful to the drug innovation process in all countries.

B. Public Utility-Type Cost Controls on New Drugs

This section analyzes some scenarios that can be viewed as long-term implications of President Clinton's proposed health care reform. As discussed above, the Act establishes a regulatory framework for drug price controls and, in particular, one which is focused on commercially important new drugs. In negotiating the extra rebates on new drugs under Medicare, the HHS Secretary can employ a cost-based standard similar to what is employed by regulatory agencies for electricity and other public utilities. Initially, these price controls are restricted to the Medicare program and would apply mainly to new drugs introduced first in this country or drugs selling abroad at significant discounts to the U.S. price. Nevertheless, as discussed in Section II, firms with early-stage research projects, which would not be coming to the market until the year 2000 or later, would have to contemplate the strong likelihood that drug price caps would spread from Medicare to the entire market. The infrastructure for doing so would be established through the Advisory Council on Breakthrough Drugs. Moreover, as the aggregate controls on premium growth take hold in the early years of the Act, the National Health Board and the Alliances would come under increasing pressure to use every measure possible to lower health care costs.

In order to model the effect of a general system of price controls focusing on commercially important new drugs, I draw on the analysis of the returns on NCEs by John Vernon and myself that was discussed previously.⁶¹ In particular, this analysis involves the cohort of new drug introductions for the 1980-84 period. I utilize the returns for this cohort to construct the base case situation and then analyze how the prospects of particular price control schemes would influence expected returns to pharmaceuticals.

In the initial scenario, I assume that government officials focus their attention only on the top decile of products. The best way to describe this scenario is to refer to Figure 4, which shows the present value by decile for the sixty-seven NCEs in our own 1980-84 sample. As discussed above, it is reasonable that officials would

⁶¹ See Grabowski & Vernon, in *COMPETITIVE STRATEGIES*, *supra* note 33, at Section II & III.

concentrate their attention on the products with the largest expected sales. First, the distribution of sales and returns for new drugs is highly skewed, as shown in Figure 4. Second, the Clinton Administration has very ambitious cost-saving targets for Medicare and the health alliances. Accordingly, I assume that the government utilizes a cost-based utility standard, but only for these top decile drugs. In particular, it is assumed that their prices are constrained so that the IRR for the top decile drugs are just equal to the cost of capital in our model (i.e., 10.5%).

In the first scenario, I also assume that the components of the Health Security Act have a neutral effect on the other ninety percent of the NCEs not subject to cost-based regulation. If anything, this assumption causes an understatement of the adverse impacts of the Act. As noted, prior analyses of the Act indicate that the increased revenues from universal coverage are expected to be outweighed by revenue reductions from the other cost control mechanisms (mandatory rebates to Medicare of at least seventeen percent, prior approval, generic reimbursement limits, as well as increased competition and generic usage from the health care alliances).

The second row of Table 2 shows the effect of a "breakeven" pricing assumption for the top ten percent of new drugs. The effect for the average NCEs is a negative change in the expected NPV from \$22.2 million to -\$60.2 million. This is more than thirty percent of the total present value of the average NCE ($-82.4/224.1$). With such large expected losses for the representative new drug, firms would be expected to respond by curtailing expenditures on future R&D projects until expected returns again become positive.

Table 2 also presents the effect of broader restraints that eliminate the excess returns to the second and third deciles, respectively. The NPV falls from -\$60.2 million, when only the top decile is restrained, to -\$91 million and -\$94 million, when the restraint extends to the next two deciles. Hence, there would be further losses as additional drugs are constrained to break-even status, but at a sharply diminishing rate. This latter result reflects the extreme skewness in the returns distribution (Figure 4).

In interpreting these results, it must be remembered that the search for blockbuster drugs is what motivates pharmaceutical R&D. However, government price regulators typically have a myopic bias. They are unlikely to allow for the fact that the probability of commercial success for any given R&D project is very low and that the returns to blockbuster drugs must compensate for

TABLE 2
Government Price Constraints on Top Decile Drugs—
Implications for the Mean NCE Introduction

Case	PV Cash Flow (mil '90 \$)	R&D Costs (mil '90 \$)	NPV (mil '90 \$)	Δ NPV (mil '90 \$)
Baseline	224.1	201.9	22.2	—
Top Decile Constrained to Breakeven	141.7	201.9	-60.2	- 82.4
Top 2 Deciles Constrained to Breakeven	110.8	201.9	-91.0	-113.2
Top 3 Deciles Constrained to Breakeven	107.8	201.9	-94.0	-116.2

low or negative returns on most other new drug introductions. This will be especially true when returns are distributed so unevenly across firms in any given period, making intra-firm pooling of successes and failures very difficult.

The prospects of price regulation under Medicare and the likelihood that it would spread to other sectors of the market can be expected to have an especially chilling effect on the most long-term risky R&D projects. If one regards R&D investment as somewhat like a lottery—with low probabilities of achieving high returns—price regulation clearly changes the attractiveness of any “R&D lottery.” Winning the lottery would provide the likelihood of only a breakeven return. As a consequence, firms would be expected to devote more of their R&D and marketing activities to certain incremental or “niche” type advances that entail less technological and regulatory risks. To the extent that prospective social gains are positively correlated with risk bearing in pharmaceutical R&D, these are precisely the wrong signals to send to the U.S. market.

Price controls on new drugs would have the most severe effects on the emerging biotech firms. These firms have concentrated their R&D activity on long-term discovery research and are highly dependent on venture capital and external investment sources. Specifically, they are typically too small to pool R&D successes and failures in any meaningful way. Second, their external sources of R&D funding are likely to respond to the price regulation provisions and enhanced commercial uncertainties by sharply raising the risk premium and reducing the availability of R&D in-

vestment funds. Currently, all but the very largest biotech firms operate with cash surpluses for R&D (denoted in the trade as "burn rates") of only a few years. Many biotech firms would not survive a system of controls targeted to the most important commercial products.

As discussed earlier, the type of new drugs that would be most negatively impacted by a myopic top-down system of price controls are those that increase current budgeted health care expenditures. This would include maintenance therapies directed to improvements in quality of life. Another negatively impacted class of drugs involve therapies where the patient benefits are long-term in character. Even drugs that can demonstrate that they are cost-reducing to the health care system in current periods may not be encouraged in this environment if they raise the pharmaceutical budgets of government entities. This is because expenditure decisions in government bureaucracies are often made on an individual component basis. Savings to other health care expenditure budgets receive lesser weight and can go unrewarded. The administration of the Medicaid drug program by the states offers a number of illustrative examples.⁶² This is discussed further below.

Finally, it should be emphasized that public utility style price regulation will be much more difficult to implement in the case of important new drugs compared to traditional utilities. To practice cost-based regulation, one must forecast the expected sales of a new drug. These are subject to much more inherent uncertainty than the demand for electricity or water. The HHS Secretary and the Advisory Council could presumably use sales in other countries, demand for other drugs in the same therapeutic class, and other factors in making sales forecasts. But this process would be subject to large margins of error. This would also add to the risks of new drug development and make R&D investment more problematic.

⁶² Moore and Newman recently found that restrictive Medicaid formularies resulted in prescription drug savings, but substitution of other medical services caused expenditures to rise elsewhere in the Medicaid system. William J. Moore & Robert J. Newman, *U.S. Medicaid Drug Formularies: Do They Work?*, 1 PHARMACOECONOMICS 28 (Supp. I 1992).

Similar results were observed in a study by Soumerai and Avorn, which found drug payment limits for Medicaid recipients caused admissions to hospitals and nursing homes to increase. S. Soumerai & J. Avorn, *Effects of Medicaid Drug-Payment Limits on Admission to Hospitals and Nursing Homes*, NEW ENG. J. MED., Oct. 1991, at 1072. My analysis of state Medicaid programs also found that enrollees experienced delays in the availability of important new drugs in several states due to formulary restrictions. See Grabowski, *supra* note 13.

C. Encouraging Generic Competition

An alternative cost containment approach would be for the government to improve market information and encourage the utilization of lower-priced generics when they become available after patent expiration. This is another cost containment approach present in the Act. There are several reasons why this is a more preferable direction to build on compared to the price regulation of important drugs. First, the market is likely to evolve strongly in this direction in any case, and the government would be reinforcing, rather than retarding market forces. Second, as noted earlier, a large number of the current top-selling drugs will experience patent expiration over the next several years, thereby providing opportunities for large cost savings. Third, and most relevant to the current analysis, the encouragement of generics can be expected to have less adverse consequences for innovation incentives compared to a price regulation approach.

To illustrate this latter point, John Vernon and I also have examined the effects of two very severe generic competition scenarios. In our base case for the 1980-84 cohort, we assumed sales losses after patent expiration that were derived from the actual experiences of major products coming off patent in the period immediately after the 1984 Act was passed.⁶³ In the present analysis, we assume that severe government and market pressures will develop to use lower-priced generics by the time patents expire on new drug candidates currently in R&D.

In particular, in the first scenario, we assume that firms expect sales to fall seventy percent in the year after patent expiration and remain at that level for four years. Thereafter, sales follow a ten percent decline for the remainder of market life. In the second scenario, we assumed that sales are expected to fall ninety percent in the first year after patent expiration and ten percent thereafter. Figure 5 shows the cash flow profile for our base case compared with the most severe generic competition case.

The results are shown in Table 3. In the seventy percent case, the present values for the mean NCE falls by approximately 6.0% (13.4/224.1), and the IRR falls from 11.1% to 10.7%. In the ninety percent sales loss scenario, the present value falls by 13.3%, and the IRR decreases to 10.3%.

The observed change in NPV for the mean NCE under the

⁶³ The average percentage declines in sales in the first four years following patent expiration in the baseline case were 30%, 21%, 12%, and 12%. Grabowski & Vernon, *supra* note 38.

TABLE 3
Alternative Scenarios on Generic Price Erosion
Implications for Mean NCE Introduction

Case	Mean NPV (mil '90 \$)	Δ NPV (mil '90 \$)	Mean IRR (%)	Cost of Capital (%)
Baseline	22.2	—	11.1	10.5
Severe Erosion after Patent Expiration				
70% case	8.8	-13.4	10.7	10.5
90% case	-7.4	-29.9	10.3	10.5

most severe generic erosion scenario, therefore, is much less than the change which occurs when the top decile drugs are constrained to a zero NPV (-\$29.9 million versus -\$82.4 million). This reflects the fact that the severe erosion cases take effect only after an effective patent life of approximately ten to twelve years, and sales losses which occur later in the product life cycle are heavily discounted in an NPV analysis.

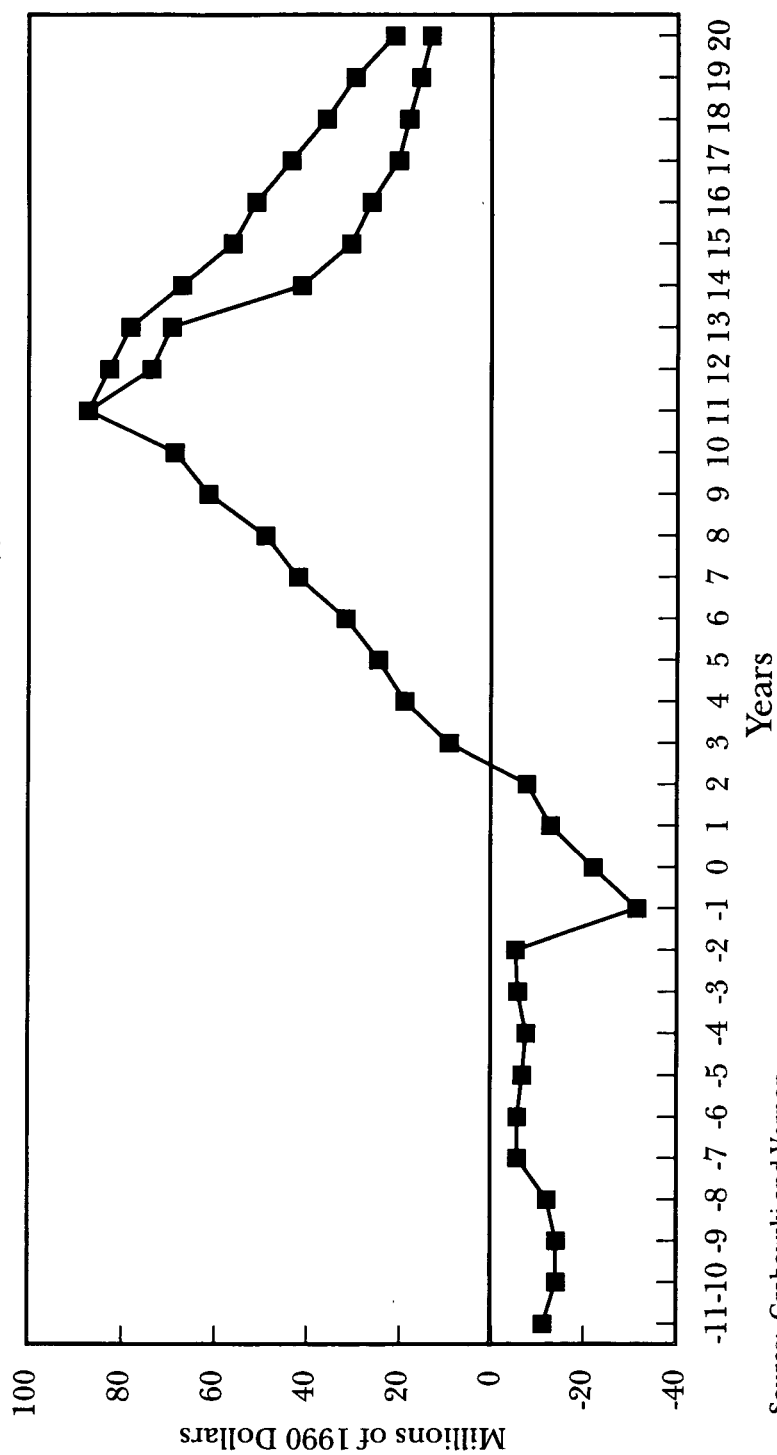
More generally the increased generic competition scenarios are consistent with the primary public policy strategy for encouraging technological advances in this country—namely, an unregulated patent exclusivity period followed by a period of vigorous competition after patent expiration. By contrast, there has been a general movement over the last two decades away from the economic regulatory approaches like those shown in Table 2, for a number of reasons, including the adverse consequences for industrial innovation.

D. Regulatory Versus Competitive Cost-Control Strategies

Even prior to health reform becoming a national issue, important changes were taking place in the health care marketplace that have had a marked influence on the pharmaceutical industry. As discussed in Section III, the most significant of these changes has been the growth of managed care plans. To an increasing degree over time, these organizations have employed strategies such as drug formularies, generic prescribing, and drug utilization reviews to achieve substantial savings in their pharmaceutical expenditures. The effect of managed care and related demand-side factors has been reflected in various industry developments. These include a dramatic growth in generic utilization, lower launch prices for follow-on products in competitively active therapeutic classes,

Figure 5

Total Cash Flows: Base Case vs 90% Erosion Case



Source: Grabowski and Vernon

and slower rates of overall inflation in pharmaceutical prices during the 1990s.⁶⁴

Health reform should build on and reinforce these market competition forces. While the Administration has claimed that its health reform plan utilizes market-based incentives to achieve cost savings, they actually employ regulatory strategies such as the premium caps to accomplish this objective. There is a basic distrust in market mechanisms manifested throughout the Act.

The proposed Medicare drug benefit is illustrative of the Administration's basic approach. The benefit would create an expensive new entitlement for all of the elderly, one that is seventy-five percent subsidized by government expenditures. In doing so, it would replace private insurance coverage that approximately forty percent of the elderly currently enjoy through retirement plans. Then, in order to control Medicare expenditure on prescription drugs, the Administration proposes extensive price controls over new drugs in the form of the negotiated rebates and other provisions.

The prescription drug benefit, in fact, affords an opportunity for the federal government to introduce some market-based incentives to Medicare instead of keeping this program sheltered from recent market developments. In particular, the Administration could make enrollment in an accredited managed indemnity plan or HMO a precondition to obtaining prescription drug benefits under Medicare. This would inject some needed cost-consciousness into the Medicare Program.

A decentralized market-based approach has a number of advantages to a regulatory one in managing health care expenditures. Government regulatory bureaucracies tend to make price the central focus of their attention and to utilize controls on individual medical care services rather than a system-wide approach to health care outlays. As discussed above, the expected consequences of the Administration's proposed regulations in the case of pharmaceuticals are significant negative effects for new drug innovation, as well as a less than optimal approach to health care savings and cost-effectiveness.

⁶⁴ The producer price index (PPI) for pharmaceuticals increased 3.1% in 1993, down from an average increase of 9.1% from 1984 to 1989. It should also be noted that recent research indicates that the procedures used by the Bureau of Labor Statistics to construct the PPI for pharmaceuticals are subject to significant upward bias due to sample selection and other factors. Ernst R. Berndt et al., *Auditing the Producer Price Index: Micro Evidence from Prescription Pharmaceutical Preparations*, 11 J. Bus. & ECON. STAT. 251, 261-62 (1993).

Encouraging consumers to enroll in cost-effective plans will have more positive implications for both drug innovation and cost-efficiency than a top-down regulatory approach. While managed care plans have become tough negotiators with pharmaceutical firms over drug prices and quality, they employ a system-wide approach to the assessment of costs and benefits and are also willing to pay for innovative products that are cost-beneficial to their patients. The trade-offs between health care benefits and costs are much better done on a decentralized market basis than a centralized regulatory one.

V. SUMMARY AND CONCLUSIONS

Increasing insurance coverage for prescription drugs is a desirable objective. While prescription drugs provide the most cost-effective approach to treating many diseases, they are currently the least insured element of basic health care in the United States. If the country is to move toward universal insurance coverage, pharmaceuticals should be in the basic benefit package. This would be the case under the Health Security Act. However, the accompanying system of incipient price controls on new drugs in the Act is unwarranted. It will lead to many unintended and undesirable outcomes.

The features of the Act that will have the most harmful effect for pharmaceutical innovation are the price control provisions over new drugs within Medicare and the associated Advisory Council on Breakthrough Drugs within HHS. Under these provisions, the HHS Secretary can demand a price on new drugs to Medicare that is equal to the best price that exists in twenty-one reference countries, all of which regulate new drugs in one fashion or another. These provisions also allow the Secretary to utilize a public utility-type cost analysis in determining whether prices are excessive.

Some members of the Administration have stated publicly that the extra rebates and exclusionary powers over new drugs would be utilized only rarely and in extreme situations. However, the primary sources of financing for the Act are targeted reductions in overall Medicare expenditures. The HHS Secretary will be under enormous budgetary pressure to meet these targets. Any new medicines that are projected to increase Medicare's drug budget, no matter how cost beneficial to patients, are likely to become candidates for the extra rebates.

The budgetary pressures in the Act are not unique to the

Medicare program. The extraordinary tight caps over the growth of premiums in the health alliances make it likely that lower regulated prices in the Medicare program would spread to the health care alliances. The incipient system of price controls could evolve quickly into a centralized system of public utility prices like that which exists in many single payor countries. The proposed Advisory Council on Breakthrough Drugs would provide the staff with an infrastructure for a centralized system of price controls, even though they would be limited initially to an evaluative and advisory role on drug pricing for new breakthrough drugs.

There is clearly uncertainty about how far and fast the government might move down the path toward a full system of price controls over new drugs. But the Act provides some giant steps in this direction. A firm undertaking long-term risky R&D programs on new drugs must make an investment decision on the basis of expectations. The Act would be sending the message that new drug candidates that become the breakthrough and blockbuster drugs of tomorrow are likely to be subjected to public utility-type cost controls in this country. The Act makes this highly probable for reimbursements from Medicare and creates a significant likelihood that it will also be true as well for non-Medicare expenditures.

The incentives for drug research would be impacted enormously by price controls over the largest selling new drugs. My work on the pharmaceutical industry with John Vernon shows that the distribution of returns in pharmaceuticals is highly skewed. A large percentage of new drugs tested in humans never reach the marketplace. Only about a third of new drug introductions earn premium returns, while the majority do not cover average R&D costs. The analysis performed in Section IV shows the effects of subjecting only the returns on the top decile of new drug products to a public utility-type cost standard. There is a precipitous drop in overall expected returns from new drug introductions. Under these circumstances, the high rate of technological progress that has been characteristic of this industry would not be sustainable.

The greatest negative impact of the Act can be expected on long-term discovery research. This research is the riskiest and furthest away from commercial introduction. The negative effects will not be confined solely to U.S. pharmaceutical firms, but will also affect the innovative research of foreign firms. U.S. industry will be most negatively impacted, however, because it has been the principal source of major innovative advances, and it also has the highest market shares in this country.

The government, like private sector reimbursers, should be a prudent purchaser of pharmaceuticals. But this does not require price controls and global premium caps. Health care reform should build on and encourage market competition, rather than retard it through the institution of a new system of bureaucratic government controls. Some of the provisions of the Act regarding pharmaceuticals appear rooted in such a market approach (e.g., the encouragement of generic competition). However, the regulatory controls on pharmaceuticals proposed in the Act would overwhelm these tendencies.

At present, firms in the pharmaceutical industry are adapting to very fundamental changes on the demand side of the market. Employers have been the focal point of efforts encouraging very significant organizational changes. The evolving managed care plans of the private sector offer a better way of ensuring that pharmaceutical purchases are efficient and cost effective. These plans have become tough bargainers with pharmaceutical firms over drug prices and quality, but they are still willing to pay for innovative products that are cost beneficial to medical patients. These organizations can provide cost efficiency to government-run programs, as well as private purchasers, without destroying incentives for drug innovation.

From a public policy perspective, little can be gained from the proposed cost controls over new drugs and a great deal lost. Even if the government were to eliminate all profits from new drugs coming into the market in the future, the prospective savings in terms of overall health care costs would be very small (less than one percent of health care costs). However, these actions would have precipitous effects on the incentives for research on innovative new medicines. Over the long term, patient welfare would be lower and total health care costs higher from such an unfortunate outcome.