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ABSTRACT

Previous empirical studies that have examined the links between pharmaceutical price controls, profits, cash flows, and investment in research and development (R&D) have been largely based on retrospective statistical analyses of firm- and/or industry-level data. These studies, which have contributed numerous insights and findings to the literature, relied upon ad hoc reduced-form model specifications. In the current paper we take a very different approach: a prospective micro-simulation approach. Using Monte Carlo techniques we model how future price controls in the U.S. will impact early-stage product development decisions in the pharmaceutical industry. This is done within the context of a net present value (NPV) framework that appropriately reflects the uncertainty associated with R&D project technical success, development costs, and future revenues. Using partial-information estimators calibrated with the most contemporary clinical and economic data available, we demonstrate how pharmaceutical price controls will significantly diminish the incentives to undertake early-stage R&D investment. For example, we estimate that cutting prices by 40 to 50 percent in the U.S. will lead to between 30 to 60 percent fewer R&D projects being undertaken (in early-stage development). Given the recent legislative efforts to control prescription drug prices in the U.S., and the likelihood that price controls will prevail as a result, it is important to better understand the firm response to such a regulatory change.

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I. INTRODUCTION

The debate over prescription drug prices in the United States is both contentious and longstanding. Politicians and consumer groups have been calling for government price controls for well over a decade. Industry representatives, however, argue that current pricing structures are necessary to cover the high fixed cost of research and development (R&D) and to induce future investment in R&D. In the midst of these debates it appears that the regulatory landscape is about to change: the recent passage of the Medicare Modernization Act (MMA) in 2003 and the anticipated ratification of a reimportation bill are evidence of an overarching policy agenda that seeks to provide greater access to today's medicines. It seems likely, therefore, that pharmaceutical price controls are just 'around the corner.' Indeed, the U.S. pharmaceutical market is currently the *only* market in the world where drug prices remain largely unregulated. In every other major market, governments regulate drug prices either directly or indirectly (Danzon, 2000).

While there is little doubt that expanding access to currently marketed medicines through price controls (or possibly reimportation) would benefit consumers in the short run, the *net* social welfare effect of such a policy is unknown. This is because the long-run costs of price controls, in terms reduced pharmaceutical innovation, may be quite substantial (Grabowski, 1994; Scherer, 2001; Vernon, 2004). The research in this paper will focus on this latter cost, and specifically the impact price controls in the U.S. will have on firm-level R&D investment behavior. To date, there have been very few studies that have examined this important tradeoff from a rigorous empirical perspective, and no studies have examined this tradeoff from a microeconomic, firm-level perspective, using standard financial modeling techniques, such as net present value analyses (NPV).

Instead, previous studies have employed retrospective statistical analyses of firm- and industry-level data, using ad hoc reduced-form empirical specifications.

Our approach in this paper will therefore be more closely aligned with the actual structure of the firm R&D investment decision. Specifically, we will use Monte Carlo simulation analyses and partial information (i.e., Stein) estimators to model the impact of various U.S. price control policies on the level of investment in pharmaceutical R&D. This will be done within the context of a hypothetical firm's early-stage R&D investment decision-making process. We find that R&D investment is quite sensitive to U.S. price expectations, and policies regulating drug prices in the U.S. could lead to a significant decline in industry R&D expenditures.

Our paper will proceed as follows. Section II will review the literature on the linkages between pharmaceutical price regulation, profits, cash flows, and investment in R&D. This section will also identify how our approach represents a more formal, micro-theoretic approach to quantifying the effects of price controls on R&D investment. Section III will provide a background on the pharmaceutical R&D process and present our conceptual model. Data used in calibrating the financial simulation model are presented and discussed in Section IV. In Section V we present and discuss our simulation results. Section VI considers policy implications and concludes.

II. LITERATURE REVIEW

Economic theory is unambiguous in its prediction that pharmaceutical price controls in the United States will diminish the incentives to invest in new drug R&D[1]. However,

[1] Own-price elasticity estimates for pharmaceuticals have been consistently inelastic. Thus, even though the quantity of prescription medications demanded will increase (under price controls), total revenues will

very few studies have examined this prediction (explicitly or implicitly) from an empirical perspective. Notable exceptions include Grabowski (1994), Scherer (2001), Vernon (2003, 2004) and Giaccotto, Santerre, and Vernon (2005). An overview of these studies is provided in the current section, along with a description of how our study will approach this empirical question from a very different perspective: one that is more firmly grounded in microeconomic theory and the financial decision-making processes of the firm.

The literature on the relationship between pharmaceutical price regulation and firm R&D investment has employed a variety of methodological techniques and approaches. These have included retrospective statistical analyses of firm- and industry-level data (Vernon, 2004; Giaccotto, Santerre, and Vernon, 2005), prospective simulation analyses in the spirit of Nelson and Winter's (1982) evolutionary economic models (Vernon, 2003), and other, more general quantitative analyses that have documented the close links between gross pharmaceutical profitability, cash flows, and R&D investment. In the case of the later, the argument was informally made that the effect of price controls will be to reduce current and expected future profits (and also cash flows), which in turn will reduce R&D expenditures (Grabowski 1994 and Scherer 2001). We will begin by reviewing these earlier studies, upon which the more recent studies were based.

In his analysis of how the Clinton Administration's proposed 1993 Health Security Act would impact pharmaceutical R&D investment, Grabowski (1994) assumed that U.S. regulators would employ a cost-based standard similar to that followed by regulatory agencies for electricity and other public utilities. More specifically,

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decline. The most recent GAO study examining the likely expenditures under the new MMA utilized an elasticity estimate of –0.30, which was based on a study by Coulson & Stuart (1995).

Grabowski assumed that the proposed Act, which called for a Council on Breakthrough New Drugs, would target only the top-selling products and regulate prices in a manner that resulted in their after-tax present value net revenues equaling the average after-tax cost of developing a new drug. This analysis demonstrated how such a regulatory approach would result in pharmaceutical R&D investment, on average, having a negative expected net present value (NPV). This is because, as Grabowski noted, only 3 out of every 10 pharmaceutical products generate after-tax present value returns in excess of average, after-tax R&D costs (Grabowski and Vernon, 2000). As will be discussed in detail in Section III, our approach will be based on a formal financial simulation model adapted from Grabowski's work: one that closely examines the firm R&D investment decision and distinguishes between expected returns to R&D on average, and expected returns on a project-by-project basis given some degree of information on how a particular project differs from the average project.

In a more recent and more empirically based study, Scherer (2001) documented the remarkably close link between gross pharmaceutical profitability and R&D investment at the industry level. This link, which Scherer found held tightly both when measured in absolute levels and in deviations from an exponential trend, was argued to exist for two principle reasons: 1) in the presence of capital market imperfections (when internal funds represent a cheaper source of R&D finance relative to external debt or equity), profits exert a positive influence on firm R&D spending through a cash-flow, or financing, effect, and 2) future profit expectations, which are tempered inter alia with current market conditions, and thus contemporaneous pharmaceutical profits, can result in a demand-pull influence on R&D investment. Indeed, in subsequent research, Vernon

(2004) observed a high correlation between contemporary pharmaceutical profit margins and firm market capitalizations, which are a well-known measure of future profit expectations (Grunfeld, 1958; Grunfeld and Griliches, 1960). Another reason why pharmaceutical profitability and R&D might be linked, as Scherer noted, is that R&D leads to new products, which in turn lead to future profits. However, as Scherer emphasized, this linkage occurs with considerable lags, and is thus unlikely to explain the relationship observed in his data, which was a contemporary relationship between current profits and current R&D. Finally, Scherer, like Grabowski, concluded that any regulatory policy—such as price controls—adversely affecting pharmaceutical profitability would result in a decline in industry R&D investment. In contrast to these studies, more recent research has examined the mapping between price regulation and pharmaceutical R&D investment explicitly and in a more structural fashion. These studies are briefly reviewed next.

Building upon the earlier work by Grabowski and Vernon (1981, 1990, 2000), Vernon (2004) utilized firm-level financial data for 14 major pharmaceutical firms from 1994 to 1997 to estimate models of the determinants of firm R&D investment. Within the context of these empirical models, he took advantage of a unique stylized fact: relative to the rest of the world, the U.S. pharmaceutical market is relatively unregulated with respect to price. Using this fact in conjunction with data on the distribution of firm pharmaceutical sales across U.S. and non-U.S. markets, and firm-level pharmaceutical profitability in each year, he estimated average pharmaceutical price-cost margins in these two broadly classified markets, and argued much of this difference could be attributed to price regulation. Using these profit margin estimates within the context of a

system of quasi-structural equations, Vernon modeled how R&D investment would change (decline) if prices in the U.S. were regulated in a manner that resulted in pre-tax pharmaceutical profit margins in the U.S. falling, on average, to the level observed in non-U.S. markets. The result from this hypothetical policy analysis, while accompanied by several caveats, was that R&D would decline, ceteris paribus, by approximately 25 to 33 percent.

Whereas Vernon modeled the mappings from profitability and lagged cash flows into R&D investment, Giaccotto, Santerre and Vernon (2005) modeled the more direct relationship between pharmaceutical *prices* and R&D investment. This study employed time series econometric techniques to explain R&D growth rates using industry-level data from 1952 to 2001. The researchers found that real pharmaceutical prices in the U.S. (defined as the ratio of the pharmaceutical price index to the consumer price index) are a major determinant of industry-level R&D investment, and obtained an R&D elasticity estimate (with respect to real pharmaceutical prices) of 0.583. This suggests that for every 10 percent increase (decrease) in real pharmaceutical prices in the U.S. R&D investment increases (decreases) 5.83 percent. Using this short-run elasticity estimate, the authors modeled the forgone R&D (capitalized to 2001) that would have accompanied a U.S. price control policy that limited the rate of growth in pharmaceutical prices to the rate of inflation from 1980 to 2001. This policy scenario, while both retrospective and hypothetical in nature, was nevertheless based on an actual legislative approach employed under the Veteran's Health Care Act of 1992, which limited drug prices increases for federal agency purchases to the rate of growth of the urban consumer price index. Under such a price control policy in the U.S., the authors estimated that

capitalized industry R&D expenditures would have been approximately 30 percent lower than the observed level for this time period.

In yet another approach, Vernon (2003) employed Monte Carlo simulation techniques to model the long-run impact of various types of U.S. price controls on pharmaceutical innovation. Specifically, he ran simulation experiments over a 50-year time horizon based upon public-utility type, cost-based price controls that targeted only the top-selling pharmaceutical products: those products generating present value net revenues in excess of average, capitalized R&D costs. Several other, less extreme forms of price control experiments targeting top-selling products were also run. While the simulation experiments were based upon a hypothetical pharmaceutical industry, the industry was, however, constructed to reflect many of the relevant aspects of innovation and competition found in today's global pharmaceutical industry. The industry model, which was developed in the spirit of Nelson and Winter's evolutionary economic models, was driven by firm routines. It was also calibrated using the most contemporary technical, financial and cost data available at the time (DiMasi, 1995; DiMasi, Hansen and Grabowski, 1991, 2003; Grabowski and Vernon, 2000).

The mechanism through which price controls impacted R&D investment, and thus future drug discoveries and the number of new products brought to market was through a reduction in the internal funds used to finance firm R&D investment. Given the wide range of price control policies simulated, the results were similarly broad, and depending on the types of price controls employed, annual innovative output (the number of new products brought to market by the industry in a given year) fell relative to baseline (with no price controls) by between 21 and 73 percent. More relevant, however, cumulative

innovative output (the total number of new products brought to market over the 50-year time horizon modeled) fell relative to baseline by between 6 and 37 percent. There is, however, a major draw back to this evolutionary modeling approach: R&D investment is based upon firm routines and cash flows exclusively. Thus, R&D investment in Vernon's model was reactive and not forward looking. As such, only realized profitability, which increased the level of a firm's internal funds, determined R&D investment.

While recent research has come a long way in quantifying the potential effect that a U.S. price control policy in the U.S. will have on firm R&D investment, no study has been grounded within the context of a formal investment-decision-making process. Grabowski's study examined this process at the very highest level, using average returns and costs. However, firms do not make investment decisions in this manner. Instead, firms make investment decisions in a sequential and project-by-project fashion. Therefore, our approach in this paper is to model this process using simulation techniques that account for the ex ante uncertainty around R&D project costs, developmental success rates, and the financial returns to successfully-launched products. The next section of this paper outlines our conceptual model in detail.

III. BACKGROUND AND CONCEPTUAL MODEL

The Pharmaceutical R&D process is one of discovering, developing, and bringing to market new ethical drug products. For a compound to make it to market, it must successfully pass through several stages of research and development: discovery research, pre-clinical testing in animals, and clinical testing in humans (of which there are three phases: I, II, and III). Finally, subsequent to these R&D stages, the new drug must

receive FDA approval for marketing in the U.S. This scientific process is heavily regulated and involves significant technical risk: only one in several thousand investigational compounds ever makes it through the full development process to gain FDA approval (P*h*RMA Industry Profile, 2004). The vast majority of R&D projects fail for reasons related to safety, efficacy, or commercial viability. For compounds that do gain FDA approval, and are thus brought to market, the entire process from discovery to launch takes on average approximately 15 years (DiMasi, Hansen, and Grabowski, 2003). The pharmaceutical R&D process is illustrated below in Figure 1.

[INSERT FIGURE 1 ABOUT HERE]

The economic cost of developing an FDA-approved drug is significantly influenced by both the technical risk of the R&D and the long investment time horizon. This is because of expenditures on R&D projects that ultimately fail and the opportunity cost associated with the firm's R&D capital. A common practice in the literature is to capitalize R&D expenditures up to the year of FDA approval. This capitalized value, which incorporates expenditures on both successful and failed R&D projects, represents the true economic cost of bringing a new drug to market. Mathematically, the expected average cost per drug developed by a given firm at the time of FDA approval (year n) can be represented as follows:

$$\overline{C}_n = \frac{\left[\bar{c}_0 p_0 (1+r)^n + \bar{c}_1 p_0 p_1 (1+r)^{n-1} + \ldots + \bar{c}_{n-1} \prod_{t=0}^{n-1} p_t (1+r) + \bar{c}_n \prod_{t=0}^{n} p_t\right]}{\prod_{t=0}^{n} p_t} \qquad (1)$$

The variables in equation (1) are defined as follows:

$\overline{C}_n$ = the average capitalized cost per drug approved at time of approval (year n);
$\bar{c}_t$ = the average annual cost per R&D project in year t;
p_t = the annual probability a project will advance in development (note: $p_0 = 1$);
r = the firm's cost of capital.

One recent estimate places this cost on a pre-tax basis at $802 million (DiMasi, Hansen and Grabowski, 2003), although both higher and lower estimates exist. On an after-tax basis, assuming the firm has sufficient revenues to capture the tax benefits of R&D or is in a position to sell these tax benefits, the estimated cost of developing an average drug is $480 million (Grabowski, Vernon and DiMasi, 2002).

In exchange for investing in these research projects, the firm ultimately hopes to bring to market products that it can sell. Although individually there is a great deal of uncertainty about which projects will succeed and what the product net revenues will be, one can estimate the corresponding average present value of net revenues from a pharmaceutical product as follows.

$$\overline{R}_n = \left[\sum_{t=1}^{T} \bar{r}_t (1+r)^{-t} \right] \qquad (2)$$

where,

$\overline{R}_n$ = the average present value of revenues per drug approved (year n);
$\bar{r}_t$ = the average annual revenue in year t;

Grabowski, Vernon and DiMasi 2002 estimate the present value of the average net revenues to by $525 million, after tax. Thus, at the time of a product launch, the average economic value of pharmaceutical research and development activities is approximately $45 million[2].

[2] Although one might be tempted to call this Net Present Value, that would be incorrect. The term Net Present Value is generally a forward looking construct used in decision making to assess the present value

$$EV = \overline{R}_n - \overline{C}_n \quad (3)$$

This value is what provides the incentives for investment in the pharmaceutical industry, and under current conditions it appears that on average there is an incentive for continued investment.

In our analysis, we want to look at this economic value at the time of the first critical decision point in the life of a pharmaceutical product's development, the time of the Phase I Go / No Go decision. This is the point at which a company decides a compound it has been examining in the laboratories is ready for testing in humans. All of the in vitro and animal testing is complete, the mechanism of action is reasonably well understood, and there is a general belief that the compound has a favorable benefit-risk ratio for a specific indication. It is also at this point that the first financial modeling of the compound's commercial potential is conducted. We denote the time of this decision as t = 0, and develop a simple, net present value decision-analytic model of how a rational, profit-maximizing firm decides on whether or not to extend an R&D project into Phase I clinical development. This key developmental decision, referred to as the Phase I Go/No-Go decision, is described next.

The Phase 1 Go/No-Go Decision

As previously indicated, the structural aspects of our model will be couched within the context of the firm's financial decision of whether or not to take an R&D project into clinical development. This decision, referred to as the Phase I Go/No-Go decision, is one of the most critical developmental decisions in the pharmaceutical R&D

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of all future cash flows. In this case, the costs have already been incurred (i.e are sunk) and hence should not be included in the decision making at time n.

process. Moreover, as will be discussed in fuller detail in Section III, it is at this stage in the R&D process that good data first become available on the average costs, times, and technical success rates of particular R&D investment projects: a requirement for the simulation model we develop. Therefore, in our analyses of how pharmaceutical price constraints in the U.S. will impact R&D investment expenditures, we will focus on this critical investment decision-making node.

When considering whether or not to take a specific R&D project into Phase I clinical development, the determining criterion is the project's expected net present value, NPV_0.

$$NPV_0^i = E(R_0^i - C_0^i \mid I_0) \tag{4}$$

where C_0^i is the present value of development costs at launch date *n* for project *i*, and is expressed explicitly as follows:

$$C_0^i = [c_0^i + c_1^i(1+r)^{-1} + ... + c_{n-1}^i(1+r)^{-(n-1)} + c_n^i(1+r)^n]$$

and c_t^i is the development costs for project *i* in year *t*.

R_n^i is the present value of all future net revenues for project *i* at launch date *n*, and is given by the following:

$$R_n^i = \left[\sum_{t=1}^{T} r_t^i (1+r)^{-t}\right]$$

where r_t^i is the revenues for project *i* in year *t*.

Clearly, at this early stage in development there is considerable uncertainty as to whether a project will advance through all subsequent development stages (technical risk) and what the developmental costs will be in each year. Moreover, if successful in reaching the market, there is also a high degree of uncertainty surrounding the financial

success (or failure) the product will experience. The uncertainty around future sales revenues is driven by factors related to same-therapeutic class competitors, new and possibly unforeseen technological developments, general market conditions, and political dynamics such as new regulations or policies affecting the profitability and or prices of pharmaceuticals. Indeed, historical returns to pharmaceutical R&D have been highly skewed, with recent research suggesting that only 3 out of 10 products generate after-tax returns in excess of the average after-tax cost of R&D (Grabowski, Vernon, and DiMasi 2002).

In developing our conceptual model it is important to carefully consider the information set available to the firm as it makes this decision. Differences in the information set can yield huge differences in the valuation of equation (4). Before directly addressing the question of what this information set is, we examine several extreme situations.

Perfect Foresight

If we assume that the firm has perfect foresight, and knows not only whether or not the project will be successful, but also exactly what the future costs and revenues will be. Under these assumptions, we can write the net present value of the project as follows:

$$NPV_0^i = [R_0^i - C_0^i] \tag{5}$$

where C_n^i and R_0^i are defined above**.** Under these assumptions, firms never invest in projects that fail, and the net present value of successful R&D projects is very high – we've assumed away all technical risk. Clearly, under these conditions, a pharmaceutical firm would only invest in those projects with positive NPV (i.e. successful ones).

Unfortunately, this is not a very realistic model of behavior in the pharmaceutical industry. Fewer than 1 out of every 5 projects started in clinical development actually reach the market as a product. Factoring in the uncertainty around technical success is essential to understanding the behavior of the industry. In fact, the pharmaceutical industry has come under intense criticism for focusing on only minor innovations (me-too products) because of their greater probability of success, at the expense of conducting more revolutionary research that carries a higher risk of failure but also yields greater health improvements.

Full Information

If we acknowledge that the firm is not able to predict project success, but instead assume that they have full information with respect to developmental costs and revenues, then the only source of uncertainty is the technical success of the project, and we can re-write the net present value for an investment project as

$$FNPV_0^i = [P * R_0^i - C_0^i] \tag{6}$$

where C_0^i is the now the expected cost of development for project *i* taking into account that the project may fail in development (and hence only some of the developmental costs will be incurred). Therefore, we represent the expected present value of bring project/drug *i* to market as:

$$C_0^i = \left[c_0^i + c_1^i (1+r)^{-1} p_1 + \ldots + c_{n-1}^i (1+r)^{-(n-1)} \prod_{t=1}^{n-1} p_t + c_n^i (1+r)^n \prod_{t=1}^{n} p_t \right]$$

where the probability of successfully completing year t of development is given by p_t.

At the same time, the revenues will only be received if the project is successful at all stages, thus the expected revenues must be multiplied by the overall probability of success (P) where,

$$P = \prod_{i=0}^{n} p_i$$

and the other terms are defined as before. In this case the firm is assumed to know the true probability of success for each developmental stage.

No Private Information

In some cases, firms have little or no private project-specific information. In this case, the firm could still form an estimate of the value of the project based on the knowledge that it came from this underlying distribution. It can form the NPV based on the average values of the parameters, that is

$$ANPV_0 = [\overline{R}_n - \overline{C}_n](1+r)^{-n} \qquad (7)$$

where $\overline{C}_n$ is given in equation (1) as the average, expected cost of project development, and $\overline{R}_n$ is the average, present value of future revenues, given in equation (2). We have essentially simply discounted the economic value of the project, as defined in equation (3).

Conditional Expectations

In practice, firms do not know the true costs of development and future revenues, and instead must form estimates of these critical parameters. Specifically, we assume that firms form expectations conditional on the information set available to them.

$$E(NPV_0^i \mid I_0) = [P * E(R_0^i \mid I_0) - E(C_0^i \mid I_0)] \qquad (8)$$

If we assume that the firm treats the probability of success at each stage of development as fixed (across projects), equation (8) is linear in the unknown costs and revenues. This means that without loss of generality, we can replace each with their appropriate conditional expectation. That is,

$$E(C_n^i \mid I_0) = \left[\begin{array}{l} E(c_0^i \mid I_0) + E(c_1^i \mid I_o)(1+r)^{-1} p_1 + \ldots \\ \ldots + E(c_{n-1}^i \mid I_0)(1+r)^{n-1} \prod_{t=1}^{n-1} p_t + E(c_n^i \mid I_0)(1+r)^n \prod_{t=1}^{n} p_t \end{array} \right]$$

and

$$E(R_n^i \mid I_0) = \left[\sum_{t=1}^{T} E(r_t^i \mid I_0)(1+r)^{-t} \right]$$

Our analytical technique focuses on this conditional expectations model of firm behavior. In particular, we assume that a firm will move a project into Phase I clinical development, if and only if $E(NPV_0^i \mid I_0) \geq 0$ for project *i*. That is, ex ante, the firm expects to make a profit by investing in the project. Specifically, we will examine how these expectations are impacted by changes in the political environment, as summarized by changes in the expectations of future prices and revenues.

Distribution of Potential Projects

To determine the impact of changes in the political environment on the investment decisions of firm in the pharmaceutical industry, we must examine the distribution of $E(NPV^i_0 \mid I_0)$ using simulation techniques. Specifically, we view an individual project as a draw from a known distribution $\mathbf{F(C^i,R^i)}$, where $\mathbf{C^i}$ is a vector of

the actual developmental costs, and $\mathbf{R^i}$ is a vector of potential future revenues[3]. Although these vectors are observed by us, the researchers, firms do not have access to the same information. Instead, firms must form expectations about these costs and revenues based on their private information (I_0) – as described above. For purposes of our simulation, we assume that these expectations can be approximated by a linear combination of the average return on an R&D project and the full information valuation.[4]

$$ENPV^i \equiv ANPV^i_0 \quad + \quad \alpha\,(FNPV^i_0 \quad - \quad ANPV^i_0) \approx E(NPV^i_0 \mid I_0) \qquad (9)$$

Where the parameter α is an information parameter that represents how much of the project specific information the firm is able to observe.

Since the basis for this distribution is the set of projects firms actually chose to develop during the 1990's, we maintain that given the information set firms possessed for all of these projects, $E(NPV_0 \mid I_0) > 0$. This puts a constraint on α, the amount of information the firms actually have at the time of making this critical decision.

IV. DATA

The critical data needed to calibrate our financial Go/No-go investment model are the mean and standard deviation of developmental costs and revenues. For development costs we also require a measure of the covariation in costs across development phases.

[3] Using data from successful projects, we construct estimates of the parameters of this distribution of potential projects and use simulation to generate potential projects. For the current analysis, we assume there is only one distribution from which projects are drawn. Future work will examine whether there are different distributions based on whether the product is a "novel" compound or a "me-too."

[4] We draw an analogy to a similar forecasting question. How would one rationally form a forecast for the number of points Allen Iverson (point guard for the Philadelphia 76ers) score in tonight's game? First, one would look at Allen's long term scoring average. Then one would adjust this average upwards or downwards depending upon how he had been playing lately, on who the opponent was, whether there were any key injuries on either team. On average, such a forecast would be right. However, using this methodology, one would never accurately predict the extreme games; thus the variance in the forecasts would be much lower than the variance in the actual outcomes.

DiMasi et al (2003) provides information on the mean, median, standard deviation, and correlation across phases of R&D developmental costs. These estimates are presented in Table 1.

[INSERT TABLE I ABOUT HERE]

These cost data represent the average after-tax out-of-pocket expenses for projects in each phase (rather than annual costs). Thus, it is necessary, and appropriate, to discount these back to the time of the Phase I Go/No-go decision, as done in equation (2). For purposes of the simulation, we assume that these costs are distributed log-normally. In addition to these cost estimates, DiMasi and colleagues also report statistics on the median developmental time per stage, and the probability of success for each stage. We assume that these values are fixed across projects and common knowledge to all firms.

On the revenue-side of our model, we rely on the data from Grabowski and Vernon (2000) and Grabowski, Vernon and DiMasi (2002). These studies provide data on the distribution of the after-tax net present value of a product's worldwide sales revenues, and are reported on a decile-by-decile basis. Importantly, these data were collected from products brought to market during the same time period as that the products in the DiMasi et al. cost study were brought to market (Grabowski, Vernon, and DiMasi, 2002). These data, which are presented in Figure 2, represent after-tax revenues, net of promotional activities and rebates, and are discounted to the launch date.

[INSERT FIGURE 2 ABOUT HERE]

Therefore, in our analyses, we only need to discount these values back to the time of the Go / No-Go decision. Again, for purposes of our simulation analyses, we model the revenues as having a log-normal distribution. As a result, the 10th decile drug products in the simulations are slightly positive in present value, rather than the slightly negative as was shown in figure 2. Based on these parameters, we developed a Monte Carlo simulation model to generate values of $(\mathbf{c_1,c_2,c_3,R_n})^{\mathbf{i}}$ for a set of potential projects firms could invest in.

V. EMPIRICAL MODEL

The theoretical model of project valuation assumes that decisions are made on an annual basis. In pharmaceutical product development, the process is divided into three specific stages of development: phases I, II, and III. At the end of each stage, there is a project review to determine whether the data are sufficient to continue development. For our empirical work we focus on these stages as shown diagrammatically below in Figure 3.

[INSERT FIGURE 3 ABOUT HERE]

This means that we need to re-write our equations in terms on these developmental stages, rather than years.

$$ENPV_P = p_1 p_2 p_3 \frac{\hat{R}_n}{(1+r)^{t4}} - \left[\frac{\hat{c}_1}{(1+r)^{t1'}} + p_1 \frac{\hat{c}_2}{(1+r)^{t2'}} + p_1 p_2 \frac{\hat{c}_3}{(1+r)^{t3'}} \right] \quad (10)$$

where the only tricky part is the discounting. We need to define time with respect to the phase I Go/No-Go decision, where t_1, t_2, and t_3 represent the median expenditure times during each phase of development.

Equation (10) can be calculated either with sample means (i.e. no information), full information or firm specific private information (i.e. conditional expectations) yielding ANPV, FNPV or E(NPV | I_0) depending on which data are used for the costs abd revenues. Likewise we are able to construct our estimated ENPV.

Tuning the Model

In section III we laid out the rational for combining the full-information estimate with the no-information estimate to form tuned estimates of the distribution of firm expectations. The constant α in equation (9) is the primary method of doing this tuning. Specifically, we selected for α that value which led to 98% of the baseline projects having a positive ENPV – see figure 4.[5] This corresponds to α = 10%. Using this value for the information parameter results in the distribution of ENPV shown in figure 5.[6]

[5] The rationale for choosing such a high confidence level is the following: we know that the observed projects from which our data are drawn are ones that real firms invested real money into developing. Thus, we would rationally expect them to have believed that these projects had positive NPV. At the same time we know that there are many, unobserved, projects that these firms chose not to invest in. Thus our sample is a selected group from the population of all possible projects and represents those that in the current environment firms are willing to invest in. If there were additional positive NPV projects, we would have expected these firms to invest in them as well. Thus, our expectation is that the marginal project should have just passed the financial threshold, i.e. E(NPV) = 0. We approximate this marginal project as being at the 98th percentile of our observed distribution.

[6] It is critical to note, however, that if one thought these were random projects drawn from a broader distribution of potential projects (some with positive and some with negative NPV), then one might have expected to find more of a censored distribution. That is, there would be a lot of projects that would have just barely made it – especially if we think that we are observing the upper tail of the distribution and that there are many more unprofitable projects than profitable ones. However, in our defense, the distribution is nicely skewed and reflects both the type I and type II errors involved in firms estimating the ex-post financial return on a given project.

[INSERT FIGURES 4, 5 ABOUT HERE]

V. PRICE CONTROL SIMULATION EXPERIMENTS

To examine the impact of various political actions that could influence the price of drugs in the US, we need to estimate the impact of these policies on the net revenues of the firm. We assume that most of the distribution and promotional costs are largely fixed, and that the impact of price changes on net revenues will be driven primarily by its impacts on total revenues. Furthermore, we assume that whatever the environmental policy is, either direct price controls or large-scale importation from Canada or other countries, the expected impact on branded products is uniform across the projects and is not targeted only at the "block-buster" products. We also assume that these environmental changes can be summarized in terms of the average price change – compared to what would have been expected based on the current US market environment. Under these conditions, the expected change in net revenues can be calculated in a straightforward manner as follows:

$$\%\Delta\text{Revenues} = (1 - \eta) \times (\text{U.S. Market Share}) \times (\%\Delta\text{Prices}) \qquad (11)$$

For our simulation analysis, we use as the base case an elasticity of demand of -0.3, and then examine a wide range of values in the sensitivity analysis. This value is consistent with recent estimates of the elasticity of demand for pharmaceuticals in the United States (Coulson and Stuart, 1995).

For purposes of the simulation experiments, it is also important to know the impact that the environmental changes have on the standard deviation of the revenues. Under the assumption that the price effects are uniform across all products, the impact on the standard deviation is of the same proportion:

$$\%\Delta SD = (1 - \eta) \times (\text{US Market Share}) \times (\%\Delta \text{prices}) \qquad (12)$$

The results of price changes of various magnitudes are shown in Figure 6.

[INSERT FIGURE 6 ABOUT HERE]

As shown, relatively modest price changes, such as 5 or 10%, are estimated to have relatively little impact on the incentives for product development[7]. Our empirical estimates suggest that product development would decrease only about 5 percent. Steeper cuts, like those suggested by some proponents of importation from Canada (e.g. 40 to 45% price reductions) would result in significant decreases in R&D investment. Our model suggests that investment in new products would decrease as much as 50 to 60%.

VI. POLICY IMPLICATIONS AND CONCLUSIONS

Our paper examines the impact that policy changes that succeed in cutting pharmaceutical prices in the United States would have on the incentives for private firms to invest in pharmaceutical research and development. The current system of drug

[7] This is, of course, a result of not having a truly censored distribution but having a more normal shaped distribution.

development relies on private firms to make significant investments in developing products to bring to the market. Successful firms are rewarded for their innovation with patent protection and the ability to price products, in the United States, at prevailing market prices. Many are concerned that these protections encourage pharmaceutical firms to exploit consumers and price their products unfairly. Presumably, the exploitation is facilitated by the inefficiencies generated through the existing insurance system, that encourages those with insurance to choose expensive therapies, which then pushes up prices for everyone.

Our simulations find that if successful, cutting pharmaceutical prices significantly (40 to 45%) would have a significant impact on the incentives for private firms to invest in research and development. Specifically, our results suggest that the number of compounds moving from the laboratory into human trials would decrease by 50 to 60 percent. Because of the uncertainties involved, fewer compounds moving into clinical trials directly translates into fewer new products – the effects of which wouldn't be fully felt for several decades because of the long development cycle. Moreover, because of the spillover effects of R&D, less activity today reduces the possibilities for new opportunities in the future. Thus, these effects would likely compound themselves over time.

Limitations and Caveats

There are a number of limitations and caveats to the current analysis. Although we believe that the parameters of the model accurately portray the current state of pharmaceutical research and development, this process continues to evolve – particularly

as a result of information generated through the Human Genome project. Most observers believe that the impact of our growing knowledge of the effects of genes and proteins will be the potential to develop highly targeted drugs for specific genotypes. The impact of this on the financial incentives for R&D could be dramatic; as the costs of development appear to be increasing and the potential market for each product seem to be shrinking. Thus, one might expect the prices of these newer, individualized medicines, to be extraordinarily high if they are to provide positive NPV projects at the initial Go / No-Go decision point. Policies that put pressure on pharmaceutical prices could be expected to stifle such innovation.

A second limitation of the model is that it assumes that there is little impact on the costs of development. If public policies were crafted in such a way as to increase government support for research and development as prices (and hence expected revenues) are reduced, either in the form of greater investment in basic science or more targeted support for clinical development, these incentives could offset some of the effects of the price regulation.

Third, throughout the analysis we assumed that there were no changes in the level of promotional activity. Implicitly, we are assuming that promotional activities are pursued to the extent that they are rational to do so, i.e. to the point that additional promotion does not provide a positive ROI. Furthermore, we assumed that when faced with modest price cuts, these promotional activities were fixed. This enabled us to translate the effects of prices on total revenues into the effect on net revenues. If, however, there were concurrent changes that reduced the need for promotional activities, such as broader Medicare coverage and fewer formulary restrictions, then these liberating

policies might stimulate demand and maintain revenue expectations. However, at least part of the incentives for making political change in today's environment is precisely fears that demand will be stimulated. Thus, policy makers, by and large, are concerned primarily about total expenditures for drugs (not prices per se) and what is one persons' expenditure is another person's revenue. Thus, it does not appear that if policy makers were able to enact price controls of one form or another, they would be inclined to offset the impact of those budget controls by enacting policies that would stimulate demand.

A fourth weakness in the model is that we are unable to observe the information sets that firms use at the critical decision time to bring a project into clinical testing. We had to approximate this by the use of the information parameter, α Our sensitivity analysis, however, shows that our fundamental conclusions – large price cuts lead to large reductions in R&D investment is insensitive to this assumption.

A final criticism that we have heard of this approach is that we do not allow for firms to engage in a variety of strategic behavior that might thwart the intent of policy makers. Such behavior might include restricting the supply of drugs to Canada, tying wholesalers' hands with contracts prohibiting them from re-exporting and other such mechanisms. While such behavior is perhaps likely, we mitigate the need to examine the direct consequences of such policy changes by instead using the expected impact on prices as the driving policy parameter. If one believes that policies such as Canadian re-importation will only have a limited impact on US prices because of strategic behavior on the part of the industry, then assume the impact on prices will be small and our model suggest that the impact on R&D activity will be corresponding small.

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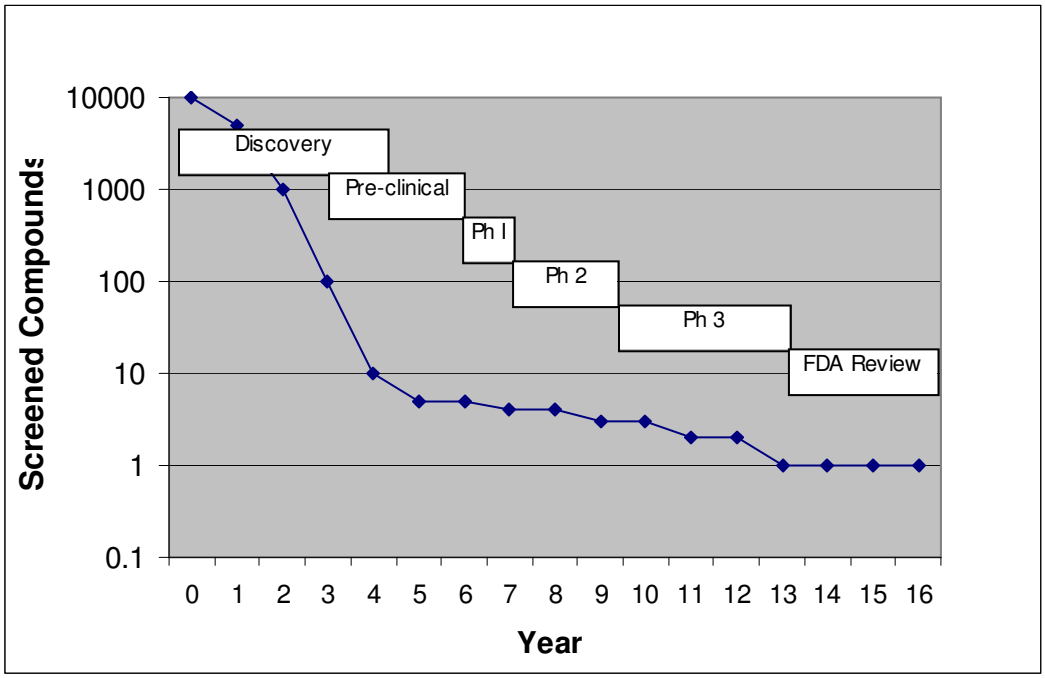
Figure 1: The Pharmaceutical R&D Process



Source: PhRMA based on date from Center for the Study of Drug Development, Tufts University, 1995.

Table 1: Distribution of After-tax Developmental Costs

	Mean Cost in $MM (SD)	**Mean Time to Next Phase (in Months)**	**Probability of Success**
Phase I	15.2 (12.8)	12.3	71.0%
Phase II	23.5 (22.1)	26.0	44.2%
Phase III	86.3 (60.6)	33.8	68.5%

Figure 2: Distribution of Product Net Revenues

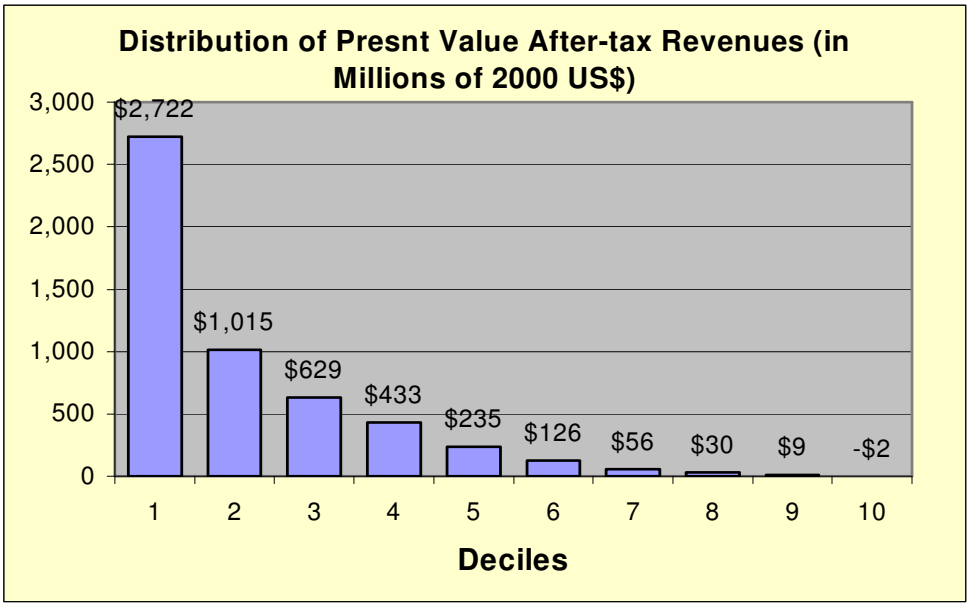


Figure 3: A Simple Model of Compound Valuation

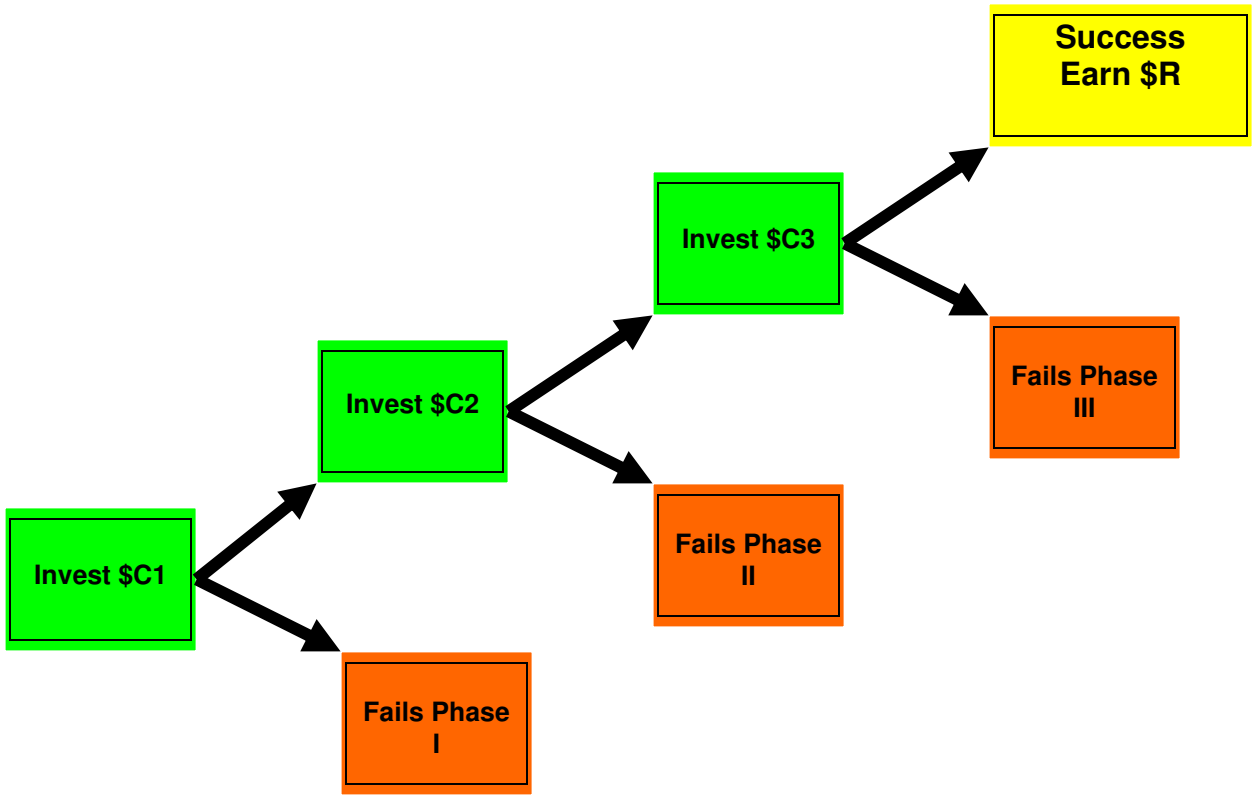


Figure 4: Proportion of ENPV>0 as a Function of Information Parameter (α)

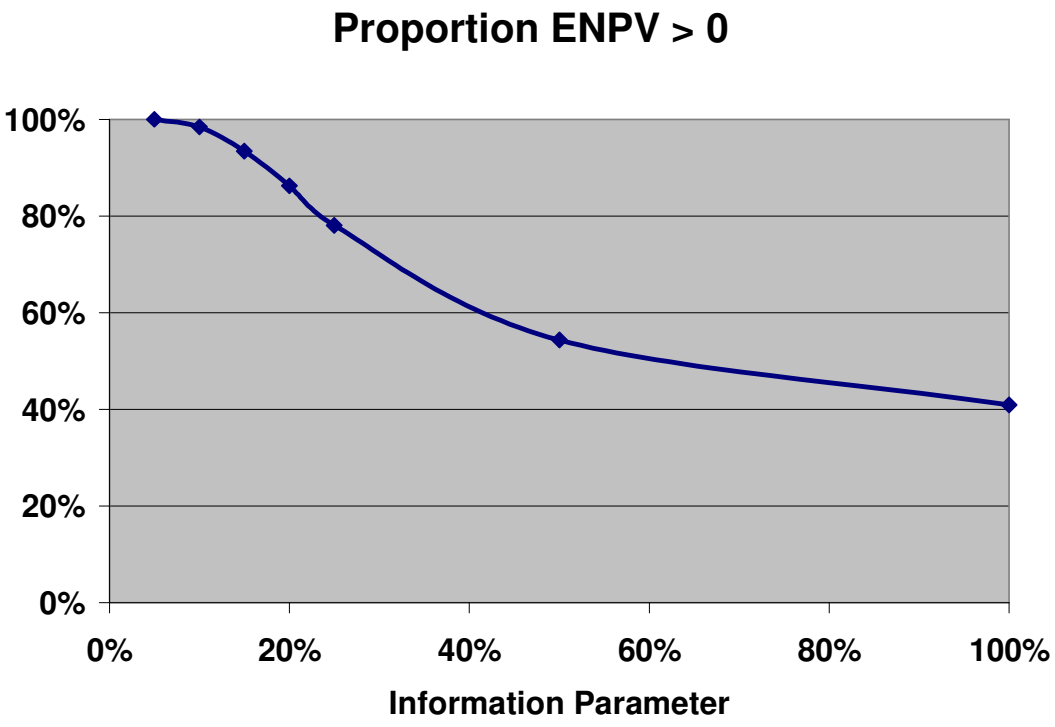


Figure 5: Distribution of ENPV

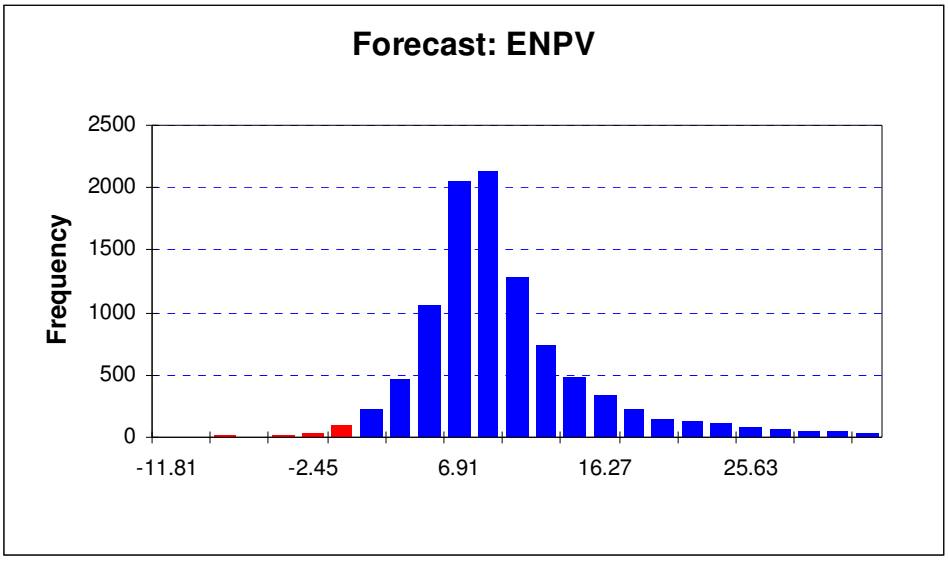


Figure 6: Impact of Price Reductions

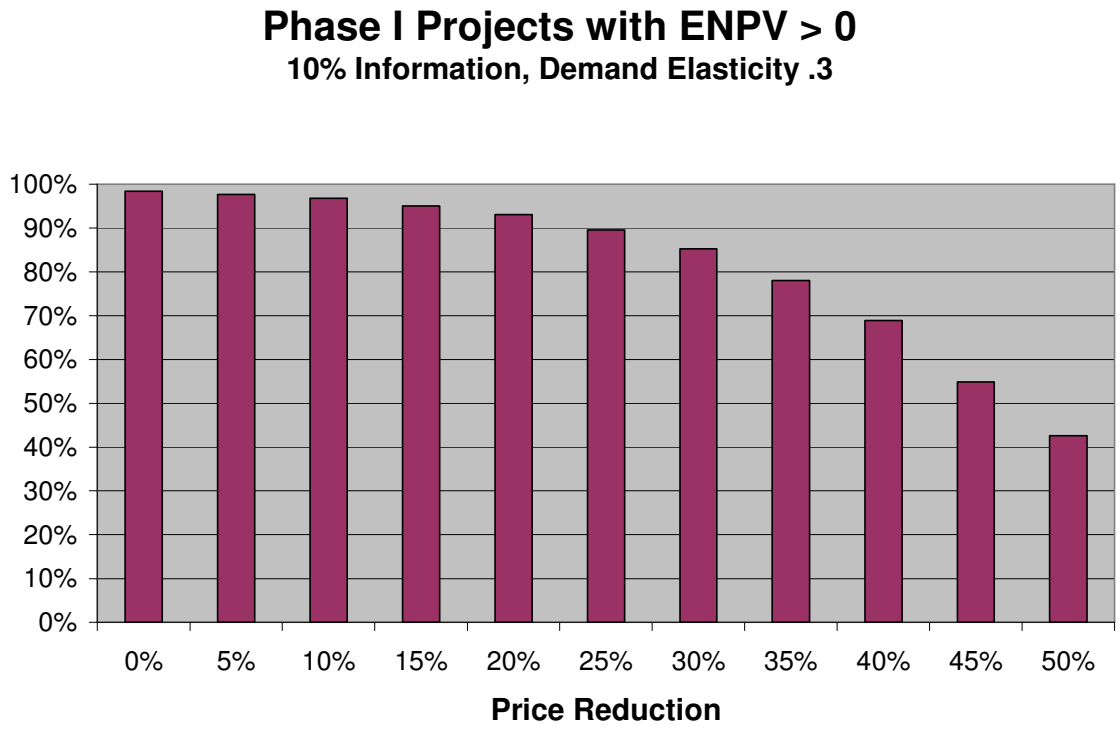


Figure 7: Sensitivity Analysis on Price Elasticity

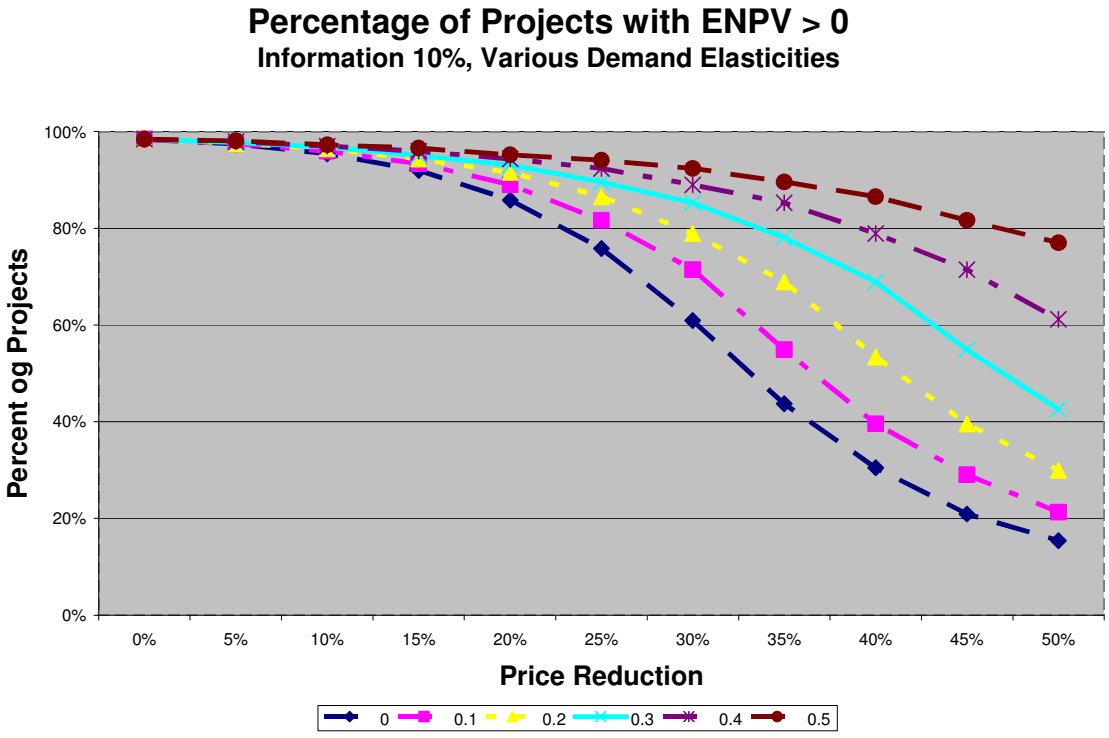


Figure 8: Sensitivity analysis of Tuning Parameter