A Model of R&D Valuation and the Design of Research Incentives

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Abstract

We develop a real options model of R&D valuation that takes into account the uncertainty in the quality (or efficacy) of the research output, the time and cost to completion, and the market demand for the R&D output. The model is then applied to study the problem of pharmaceutical under-investment in R&D for vaccines to treat diseases affecting the developing regions of the world. To address this issue, world organizations and private foundations are willing to sponsor vaccine R&D, but there is no consensus on how to administer the sponsorship effectively. Different research incentive contracts are examined using our valuation model. Their effectiveness is measured in the following five dimensions: expected cost to the sponsor, probability of development success, consumer surplus generated, expected number of successful vaccinations and expected cost per person successfully vaccinated. We find that, in general, purchase commitment plans (pull subsidies) are more effective than cost subsidy plans (push subsidies). Moreover, we find that a hybrid subsidy plan constructed from a purchase commitment combined with a sponsor research cost-sharing subsidy is the most effective.

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I. Introduction

There are three diseases which kill more than five million people a year in the developing regions of the world. They are malaria, tuberculosis and African strains of AIDS (Davey (2002)). Multinational pharmaceutical companies have not devoted sufficient resources to develop vaccines for these diseases.[2] The reason is simple: those who need the vaccines most cannot pay for them. As a result, pharmaceutical companies cannot justify undertaking expensive drug research for these small markets. Aware of this problem, international organizations and private foundations have expressed willingness to provide funding to support vaccine research. For example, the Bill and Melinda Gates Foundation has made an initial grant of $750 million USD to fund the Vaccine Fund that would serve as the new funding mechanism for the Global Alliance for Vaccines and Immunization (GAVI).[3] In turn, GAVI, which plans to raise $2 billion USD in funds, has pledged to award $800 million USD in the next 5 years to help expand global vaccine coverage. There are various ways in which sponsor organizations can provide for these funds. An important question then becomes "*how should funds be distributed to ensure cost effectiveness and high levels of R&D activities?"* The literature on pharmaceutical R&D has provided qualitative discussions and anecdotal evidences on the effectiveness of different sponsorship methods.[4] In particular, sponsorship arrangements that involve subsidizing the cost of R&D investments (push programs) and the income of the R&D output (pull programs) have received most of the attention.

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[2] See Davey (2002) and Kremer (2002a,b,c) for a comprehensive review on the problems of insufficient pharmaceutical research on diseases specific to the developing countries of the world.

[3] The Global Alliance for Vaccines and Immunization is formed by WHO, UNICEF and the World Bank in addition to various other nongovernmental organizations (NGOs), private foundations and government organizations.

[4] See Kremer (2002b,c,d), Hughes, Moore, and Snyder (2002), Batson and Ainsworth (2001) and Rey (2001) for more details on creating pharmaceutical R&D incentives.

However, currently, there is no analytical framework available for analyzing the advantages and disadvantages of the different research sponsorship programs.[5] To fill this gap, in this paper we develop an R&D valuation model that allows us to study in a more quantitative manner, the effectiveness of different research sponsorship programs.

R&D investments lend naturally to valuation using the real options approach. Pindyck (1993) provides a model for valuing projects with uncertain cost to completion. The innovation is the realization that the firm can learn about the difficulty of the research project as it invests. Learning, in this setting, occurs through undertaking the R&D and incurring research expenses. Consequently, the research effort provides double benefits. On one hand, it produces intermediate R&D outputs; on the other hand, it helps the firm determine the difficulty of completing the research project (the expected remaining time and cost to completion) allowing the firm to optimally abandon the effort if necessary. The learning and the option to abandon make the valuation problem different from standard valuation analysis. Schwartz and Moon (2000) extend the analysis to include uncertainty in project revenue and the possibility of catastrophic events that disrupt the research effort. Miltersen and Schwartz (2004) further introduce strategic competition in a duopolistic market to the valuation framework.

One crucial feature of the R&D process, the quality (or efficacy) of the research output, has, however, been ignored thus far in the literature. Traditionally, the literature abstracts from the quality variable to model, instead, an exogenous revenue process for the R&D output. While the revenue from the R&D is certainly related to the quality of the R&D output, it is also predicated on the firm's pricing strategy that depends on the competitive structure of the product marketplace and the revenue subsidy or tax incentive offered. Therefore, an exogenous revenue specification

[5] Glennerster and Kremer (2001) provide a discounted cash flow analysis for purchase commitments only. However the DCF analysis does not focus on the valuation of the R&D to the firm, but rather on the cash flows associated with the vaccine delivery.

prevents the analysis of firm responses to different research incentives. We address this issue by modeling the quality variable explicitly. The revenue arising from the sales of the R&D output is then a function of the firm's pricing strategy given the market demand and the subsidy program in place.

We apply our valuation framework to analyze several incentive programs, reviewed in Kremer (2002a,b) and Batson and Ainsworth (2001), for encouraging pharmaceutical R&D in diseases affecting the developing countries. Using realistic parameters, we find that the small market problem is so severe that the granting of extremely favorable patent protection could not stimulate vaccine R&D.

Push subsidy programs that subsidize research investment cost, can induce research activities with relatively low expected cost to the sponsor. Sponsor cost-sharing subsidy contracts, in which the sponsor pays a fixed fraction of the research and development costs, represent the most cost effective contracts, studied in this paper, for increasing research output. However, because the pharmaceutical firm retains the right to the developed vaccine under a push subsidy, the quantity supplied is lower than what is socially optimal, which results in low consumer surplus generated and high expected cost per individual successfully vaccinated.

Pull subsidy programs that commit to a price/quantity schedule for the developed vaccine, are comparably more expensive methods for stimulating research. However, the pharmaceutical company can be contracted to supply the socially efficient quantities. This feature greatly increases the benefit delivered per dollar cost to the sponsor. Moreover, a hybrid subsidy combining both a purchase commitment subsidy and a cost-sharing subsidy delivers better results than either subsidy program can independently.

Measured in the dimensions of sponsor cost, vaccine development probability, consumer surplus, and cost per individual successfully vaccinated, we find hybrid subsidy contracts slightly outperform pure purchase commitment contracts which in turn, significantly outperform sponsor cost-sharing contracts.

Note that in the push or cost subsidy plan the firm retains the rights to the product and sets the monopoly price when the product is commercialized, whereas in the pull plan the sponsor can negotiate a price-quantity contract, hence can require that the socially optimal quantity be sold. If the sponsor of a cost subsidy program would require the firm to deliver the socially optimal quantity it would also have to specify the price it would pay for the product; this is precisely what we consider in the hybrid programs. The main conclusion of our analysis is that cost subsidies alone are not an effective method to promote R&D for vaccines; some sort of price-quantity commitment is also required to induce the firm to produce the socially optimal amount.

The remainder of the paper is organized as follow. Section II introduces the R&D valuation framework and the technique required for solving the valuation problem. Section III discusses the problem of pharmaceutical under-investment in research on diseases that primarily affects the developing countries and illustrates this problem explicitly with our valuation model. Section IV analyzes different types of R&D incentive programs that have been proposed in the literature. Finally, section V concludes the paper.

II. A Model for Valuing R&D Projects

In this section we develop a model for valuing general research and development projects. We offer first a description of the R&D process that we have in mind. This is then made precise when we formalize the model in the subsequent sections.

Overview of the Firm's R&D Valuation Problem

We consider a firm with either a single R&D project or a portfolio of on-going R&D projects and R&D opportunities. If the firm in consideration owns a portfolio of R&D projects, we assume that the externalities created by one project on the rest of the R&D portfolio is sufficiently small to allow for the valuation of each R&D project independently. Prior to engaging in the project, the firm assesses the expected quality of the final output of the R&D as well as the revenue associated with marketing the product. In addition, it assesses the expenses that will be incurred from the R&D and the production of the product. The firm then decides whether to undertake the new R&D project or not.

The firm's investment decision rule, however, is complicated by its option to abandon the project at any stage of the development. As the firm commits its resources to research and develop the product, it also learns about its ability to successfully complete the R&D and to produce a quality and profitable product. Specifically, at different stages of the development, the firm revises its expectation on the time required (and therefore the cost required) to complete the R&D, the quality of the final research output, and the revenue from bringing the product to market. Based on the updated expectations, when continuing the R&D is unlikely to lead to profit, the firm abandons the project and cut its losses.

The firm's R&D valuation problem is, therefore, a "real options" problem. The optimal abandonment policy (optimal threshold for cost and/or quality beyond which the project with not proceed) in our model, which is not possible to solve for in closed-form, is approximated very efficiently through the application of the least square procedure developed by Longstaff and Schwartz (2001). Once the optimal policy function is solved for, the valuation of the R&D project is straightforward.

We now introduce the model formally. We present the timeline of the model in Figure 1 to help the reader visualize the firm's R&D process. For simplicity of exposition, we assume that the project is divided into 3 distinct phases.[6] Phase *I* and Phase *II* represent preliminary and advanced stages of research and development respectively, while Phase *III* is the scaling up for mass production and sales and marketing phase. The generalization to any larger number of phases is straightforward. In addition, the firm is assumed to make the abandonment decision only at the beginning of each phase with the information acquired from the completion of the previous phase.[7] This assumption is a realistic description of the vaccine development process. However, it is not crucial for solving the model or for generating the predictions of the model and can again be easily extended to accommodate more frequent abandonment policies.

Rate of Investment

For Phase *I* and *II* of the R&D, the firm is assumed to commit a constant rate of investment of I_1 and I_2, respectively, to the research effort. In some cases, the firm may wish to change its rate of R&D investment as it learns more about the prospect of the project; however, for simplicity, we assume that I_1 and I_2 are exogenously determined and fixed through each R&D phase.[8] Under our current assumption, I_1 and I_2 are parameterized from the observed research investment intensities common for the type of project in question. For example, if we wish to value a pharmaceutical

[6] In the vaccine development industry, developments are usually divided into 5 stages: 1. Basic preclinical research, 2.a. Identification of a candidate vaccine using non-human primates (for compound efficacy), 2.b. using human subjects (for compound safety) 3. Candidate vaccine testing on targeted human subjects, 4. Scaling up of manufacturing capacity and 5. Commercialization in target population. Stage 1 and the earlier phase of stage 2 are considered preclinical stage where bio-chemical compounds are researched and engineered. While the later part of stage 2 and stage 3 is the clinical trial stage, which is usually the most expensive and lengthiest stage in the development. Stages 4 and 5 are where the successful vaccine is brought to the market. See Batson and Ainsworth (2001). Struck (1996) uses a 7 stage definition, where the clinical trial is broken into 3 separate phases.

[7] Restricting to discrete abandonment makes both the exposition simpler and more realistic. Vaccine projects are usually not reviewed for abandonment until a milestone in the development is reached. That is, the scientists conducting the research are not empowered to abandon the research effort. The decision to abandon or continue rest on the management body (usually the external granting agency or the firm's investment committee), which does not observe the progress of the research continuously but rather at long discrete intervals, usually corresponding to the stages of the development.

[8] We expand on this point further in the subsequent sections.

vaccine project (which we do later in this section), we would estimate the rate of R&D expenditure for Phase *I* and Phase *II* by examining the industry average expenditures devoted to the bio-chemical compound development and the subsequent stages of clinical trials respectively.

Expected Time and Costs to Completion

We now introduce the variables associated with the cost and the time for completing each phase of the R&D. Let

τ_1 = the total (random) time needed for completing Phase *I* R&D,

τ_2 = the total (random) time needed for completing Phase *II* R&D,

$\tau = \tau_1 + \tau_2$ = the total (random) time needed for completing the entire R&D project.

Further we define

$K_1(t)$ = time t conditional expected remaining cost for completing Phase I R&D,

$K_2(t)$ = time t conditional expected remaining cost for completing Phase II R&D,

$K(t) = K_1(t) + K_2(t)$ = time t conditional expected remaining cost for completing the entire R&D project.

Since the rates of investment are constant, the R&D cost and the R&D time to completion are one-to-one mappings of each other; we can choose to characterize either K_1 and K_2 or τ_1 and τ_2. We choose to model the stochastic processes of the conditional expectations K_1 and K_2, which is more natural in our context.

We follow, in spirit, the modeling of cost uncertainty in irreversible investment projects described in Pindyck (1993). The dynamics of the conditional expected remaining costs to completion are:

$$dK_1(t) = -I_1 dt + \sigma_1 dW_1(t), \text{ for } 0 < t < \tau_1, \qquad (1)$$

$$dK_2(t) = \sigma_2 dW_2(t), \text{ for } 0 < t < \tau_1, \quad (2)$$

and

$$dK_2(t) = -I_2 dt + \sigma_2 dW_2(t), \text{ for } \tau_1 < t < \tau, \quad (3)$$

where dW_1 and dW_2 are Brownian motions and are assumed to be uncorrelated with the market portfolio returns, such that the true and the risk-adjusted process are the same. In addition, the instantaneous correlation between dW_1 and dW_2 over $0 < t < \tau_1$ is ρdt.

The interpretation of equation (1) and (3) is straightforward. The expected remaining cost to completion decreases as the firm continues to invest in the R&D. However, the firm also learns more about its ability to complete the project on time and on budget. Prior to the beginning of Phase *I*, the firm expects that the total cost to complete the Phase *I* research to be $K_1(0)$. Negative shocks to the R&D delay the Phase *I* completion and increase the total development cost for the phase, while positive shocks shorten development time and reduces the development cost.

Equation (2), on the other hand, captures the idea that revisions in the firm's expectation on the cost for completing Phase *I* research also brings about revisions in the Phase *II* expected cost to completion. Unexpected delays in Phase *I* suggest that the firm's resources in place may not be as suited for the development of the product as is previously anticipated. This indicates that subsequent delays in Phase *II* are likely, thus raising the conditional expected Phase *II* cost $K_2(t)$. Therefore K_1 and K_2 are modeled as joint diffusions over $0 < t < \tau_1$ with an instantaneous correlation of ρdt.

We note that the firm makes decision to abandon or continue the project only at the beginning of each phase. Therefore, we only need to characterize the conditional expected remaining costs at these discrete points in time—namely at times 0, τ_1, and τ. However, since

$K_1(0)$ and $K_2(0)$ are exogenously specified and $K_1(\tau_1) = 0$ and $K_2(\tau) = 0$ trivially, we need only to characterize $K_2(\tau_1)$. Appendix A provides the closed formed solution for the first hitting time (the first time the process reaches zero) density corresponding to the stochastic processes (1)-(3).

Given that the problem is solved by simulation the approach allows for more general specifications of the stochastic processes (1)-(3). In particular, the variances of the stochastic processes could depend on the level of the expected cost to completion. This would eliminate the possibility that $K_2(\tau_1) < 0$.[9]

Quality of Research Output

We now introduce the variables that characterize the quality (or efficacy) of the final research output. We define:

$Q(\tau)$ = the quality of the final product at the completion of the entire R&D project.[10]

We then define:

$Q(t) = E_t\left[Q(\tau)\right]$ = time t conditional expected quality of the final product.

Again, it is only necessary to characterize $Q(t)$ at times 0, τ_1, and τ. This time we do not model the stochastic process of $Q(t)$; instead, we conveniently model $Q(t)$ as draws from a Beta distribution that has support over [0,1]. This maps naturally into the standard intuition of product quality (and certainly seems more appropriate than unbounded distributions—for situations in our analyses). A developed product that falls miserably short of the specifications of the development objective, would have a quality index near 0. While a product that meets most of the specifications, would have a quality index near 1. For a pharmaceutical vaccine development

[9] With the parameters used in the simulations none of the simulated paths give values of $K_2(\tau_1) < 0$.

[10] We assume that this quality variable, being a technical factor, is also uncorrelated with the market portfolio and therefore the true distribution and the risk-adjusted distributions are the same. However, as we explain later, we could allow for demand shocks which are correlated with the market portfolio. This would introduce risk premiums into the model.

project, $Q(\tau)$ could be interpreted as the efficacy of the developed vaccine. A vaccine that is effective for 90% of the subjects being immunized, would have $Q(\tau) = 0.9$.

As mentioned before, unexpected delays in the R&D implies that the firm's resources in place and its particular approach toward development may not be as suited as is initially anticipated—thus leading to an increase in the subsequent expected research expenditure. The delay could also lead to a similar revision in the expected quality of the final product. Therefore the mean of the distribution for $Q(\tau_1)$ and $Q(\tau)$ could depend negatively on the shock delays occurring in Phase *I* and Phase *II* R&D respectively. Furthermore, the variance of the distribution could also depend on the amount of learning that can occur during the R&D. If the firm does not learn much about its R&D prospect in the current phase, it cannot revise its expectation on the quality of the final output.

The probability distribution of product quality can then be represented by the Beta density function:

$$\varphi(Q) = c(a,b)Q^{a-1}(1-Q)^{b-1}, \quad 0 < Q < 1, \quad 0 < a, \quad 0 < b \tag{4}$$

where $c = \dfrac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}$, and $\Gamma(\cdot)$ is the gamma function. The mean and variance of the beta distribution are:

$$\mu_Q = \frac{a}{a+b} \tag{5}$$

and:

$$\sigma_Q^2 = \frac{ab}{(a+b)^2(a+b+1)}. \tag{6}$$

However, the Beta distribution, due to the boundedness of it support, cannot admit any arbitrary pair of mean and variance. Expressing the parameters *a* and *b* in terms of the distribution's mean and variance we have:

$$a = \frac{\mu_Q\left(\mu_Q\left(1-\mu_Q\right)-\sigma_Q^2\right)}{\sigma_Q^2} \tag{7}$$

and:

$$b = \frac{\left(1-\mu_Q\right)\left(\mu_Q\left(1-\mu_Q\right)-\sigma_Q^2\right)}{\sigma_Q^2}, \tag{8}$$

which give rise to the restriction:

$$\mu_Q\left(1-\mu_Q\right)-\sigma_Q^2 > 0. \tag{9}$$

Therefore the dependence of the mean and variance on the other parameters of the model needs to be specified carefully to avoid non-admissible Beta distribution parameters.

To allow for the probability distribution of product quality to depend on the realized cost (or time) of a given phase, we parameterize its mean and variance to be functions of the time to completion. The specific parameterization for the mean and the variance of the expected quality variable we adopt are given in Appendix B.

Revenue from Sales of Product

When the R&D is completed, the firm must assess whether to bring the product to market. The revenue from the sales of the product will depend on the market demand for the product given its quality and the firm's pricing strategy. The firm, which is assumed to have monopoly market power in this newly developed product through patent protection, would set the monopoly price associated with the market demand. In addition, there is a plant construction cost K_3 (assumed non-stochastic) and construction time τ_3 associated with scaling up for the mass production of the

vaccine.[11] The firm is assumed to own the patent for the product for a duration *T* after the initial patent application; after which the patent expires and the firm is assumed to earn zero profit.[12] Other characterizations of the patent process can also be incorporated in our framework.

Since our model can accommodate any reasonable market inverse-demand function, we do not restrict ourselves to a particular form here. A specific demand function, however, will be assumed in the later section to illustrate our valuation framework. For the moment we assume only that the inverse-demand function, $P(Q,q)$, is a function of the quantity supplied per unit time, *q*, and the quality of the product, *Q*. In addition, we assume a unit production cost function $c(Q,q)$. The firm's maximizing behavior leads to the following (monopoly) condition:

$$\frac{\partial((P-c)\cdot q)}{\partial q}=0. \qquad (10)$$

With the monopoly condition and the market inverse-demand function, we can solve for the monopoly price P_M and quantity q_M. The profit rate is then $(P_M - c)\cdot q_M$.

It would be straightforward to add a demand shock to this framework. A multiplicative demand shock following a geometrical Brownian motion would make the inverse-demand function stochastic.[13] Since demand shocks may be correlated with the market portfolio, this state variable may have a risk premium associated with it and the true and risk neutral distributions would not be equal. To simplify our presentation we do not include demand shocks in our model.[14]

[11] This feature of vaccine manufacturing is different from drug manufacturing, where the capacity building is done during the clinical trial.
[12] In general pharmaceutical companies apply for patents on its bio-chemical compounds prior to clinical testing.
[13] See for example Miltersen and Schwartz (2004).
[14] The fluctuations in market demand for HIV/AIDS, malaria or TB vaccines in developing countries are probably not very correlated with the equity market returns. Shocks to third world demand then would not play a big role in the valuation process. However, when dealing with other types of diseases such as arthritis, obesity or cardiovascular problems, demand may be correlated with economic conditions.

Catastrophic Events

Finally, we introduce the possibility of a catastrophic event occurring during the lifecycle of the product that discontinues the R&D effort or forces the product to be withdrawn from the market. Catastrophic events may include: firm financial distress that causes the project to be abandoned, departure of the lead scientists in the R&D effort, introduction of a superior product by a competitor, or safety hazards created by the product which causes the product to be withdrawn from the product market (Batson and Ainsworth (2001), Struchiner et. al. (1994), Malaria Vaccine Initiative (MVI) Market Consultation Report (2001), and MVI Memo (2004)).

We model these events as Poisson processes with possibly different intensities or hazard rates, λ_1, λ_2, and λ_m, in the different phases. As shown by Brennan and Schwartz (1985), if these processes are independent from each other and uncorrelated with the market (no risk premium associated to them) they simply enter into the analysis through increasing the discount rates. Consequently, the effects of these Poisson events only show up in the discounting of the cash flows through increasing the discount rate by the hazard rate.

Discount Rates

For simplicity, we assume that the risk free rate, *r*, is constant. As is usual in the real option literature, we discount risk-adjusted cash flows at *r* instead of true cash flows at the risk-adjusted discount rate. We have assumed that the R&D expenditure and the product quality processes described before are uncorrelated with the market portfolio and therefore have no risk premiums attached to them and therefore do not require risk adjustment. As mentioned earlier a stochastic demand function with an associated risk premium can be incorporated without much difficulty.

Valuation and Abandonment at Time $\tau = \tau_1 + \tau_2$

With the model now fully specified, we can solve the firm's optimal abandonment policy and the R&D valuation problem. We start solving the model from the firm's last decision node that occurs at the end of Phase *II* (time τ). At the end of Phase *II*, the firm evaluates the time τ discounted expected profit, $v(\tau)$, from bringing the product to market. The required inputs for evaluating $v(\tau)$ are the patent life of the product and the firm's forecasted monopoly rate of profit, associated with the forecasted market inverse-demand function $P(Q,q)$, the unit cost function $c(Q,q)$, and the required time τ_3 and the investment intensity I_3 for scaling up production. Since the market demand function, the unit cost of production and the time and investment cost associated with building production capacity are assumed exogenous in our model, $v(\tau)$ depends entirely on the quality parameter $Q(\tau)$ and can be computed by:

$$v(\tau) = e^{-r\tau_3}\int_{\tau_2+\tau_3}^{T}(P_M - c)\cdot q_M \cdot e^{-(r+\lambda_m)t}dt - \frac{1}{r}I_3\left(1-e^{-r\tau_3}\right), \qquad (11)$$

where, again, the subscript *M* indicates the monopoly solution to the firm's profit maximizing problem characterized by (10).

Here, the firm's optimal abandonment policy is simple. If $v(\tau)$ is positive, the product is brought to market; otherwise the product is abandoned. The time τ present value of the R&D project given the option to abandon then is:

$$V(\tau) = \mathbf{1}\{v(\tau) > 0\}\cdot v(\tau), \qquad (12)$$

where $\mathbf{1}\{v(\tau) > 0\}$ is the firm's policy function (an indicator function) which takes on the value 1 when $v(\tau) > 0$, and 0 otherwise.

Valuation and Abandonment at Time τ_1

Moving backward one decision node, at the end of Phase *I* (time τ_1), the firm decides whether to commence Phase *II* R&D. Based on the progress made in Phase *I*, the firm now has a new expectation $Q(\tau_1)$ on the final quality of the product and hence an expectation of the profit from the sales of the product. The firm also has a new expectation $K_2(\tau_1)$ on the additional R&D expense from Phase *II* development. The firm would continue with the R&D if the time τ_1 discounted expected profit $v(\tau_1)$ (profits from sales minus the Phase *II* R&D cost), for continuing is positive. We compute $v(\tau_1)$ by:

$$v(\tau_1) = E\left[V(\tau) \cdot e^{-(r+\lambda_2)\tau_2} - \int_0^{\tau_2} I_2 e^{-(r+\lambda_2)t} dt \,\middle|\, Q(\tau_1), K_2(\tau_1) \right]. \qquad (13)$$

The firm's policy function is to abandon the project at the end of Phase *I* R&D if $v(\tau_1) \le 0$ and to continue with Phase *II* R&D if $v(\tau_1) > 0$. The present value of the project at time τ_1 is then:

$$V(\tau_1) = \mathbf{1}\{v(\tau_1) > 0\} \cdot v(\tau_1), \qquad (14)$$

where $\mathbf{1}\{v(\tau_1) > 0\}$ is the firm's policy function which takes on the value 1 when $v(\tau_1) > 0$, and 0 otherwise.

However, unlike $v(\tau)$, the conditional expectation $v(\tau_1)$, which is a function of the state variables $Q(\tau_1)$ and $K_2(\tau_1)$, cannot be computed in closed-form. Using the Longstaff and Schwartz (2001) least-square numerical technique we can estimate an approximate function for $v(\tau_1)$ very simply and rapidly. With the approximated $v(\tau_1)$, we can then solve the time τ_1 R&D present value function defined in equation (13). The additional benefit of applying a numerical solution is the flexibility it allows in the modeling of the market demand function, the unit cost function, the distribution of the conditional expected quality variable, and the stochastic process of

the conditional expected cost variables. All of the above functions and processes can be modified from what is assumed in this paper to model other R&D processes, and the numerical technique developed here applies regardless. We describe the numerical solution technique in greater detail in Appendix C.

Valuation and Abandonment at Time 0

At time 0, prior to beginning Phase *I* R&D, the firm bases it decision to commence R&D on its priors on the quality, $Q(0)$, of the eventual product and the expected research costs $K_1(0)$ and $K_2(0)$. The time 0 discount expected profit, $v(0)$, can be computed as:

$$v(0) = E\left[V(\tau_1) \cdot e^{-(r+\lambda_1)\tau_1} - \int_0^{\tau_1} I_1 e^{-(r+\lambda_1)t} dt \middle| Q(0), K_1(0), K_2(0) \right]. \qquad (14)$$

The firm gains $v(0)$ in present value if it undertakes the project. However, since the firm rationally foregoes the R&D when $v(0) < 0$, the value of the project to the firm is:

$$V(0) = \mathbf{1}\{v(0) > 0\} \cdot v(0). \qquad (15)$$

Unlike the time τ_1 conditional expectation $v(\tau_1)$, which is a random function of the state variables $Q(\tau_1)$ and $K_2(\tau_1)$, the time 0 conditional expectation $v(0)$ is a constant and can be computed simply by evaluating the expectation.

Illustrative Example

In this section we illustrate the implementation of our model by valuing a realistic HIV/AIDS vaccine R&D project using data reported in various industry studies. The parameters of the model are calibrated to fit the vaccine R&D process in our fairly simplistic setting. The model is certainly capable of accommodating more sophisticated assumptions, however we refrain from extensions for the clarity of exposition.

We interpret the Phase *I* vaccine R&D as the bio-chemical compound discovery stage, where the pharmaceutical company develops bio-chemical compounds that immunize against a particular infection. Phase *II* R&D would be the clinical trials stage, where the vaccine is tested on human subjects to determine its toxicity, immunogenicity and efficacy and to ultimately obtain FDA approval.[15] We assume that the pharmaceutical company applied for a patent at the end of Phase *I* R&D and that the patent life is 20 years.[16]

For this example, the firm starts with a prior that its developed vaccine will be 20% effective ($Q(0)=0.20$), that is the firm expects to be able to deliver a very low efficacy vaccine given its know-how and technologies in place.[17] Calibrating to data, we assume an expected Phase *I* development time of 2.5 years[18] with an annual research investment I_1 = 2.5 million dollars[19], and an expected Phase *II* development time of 6 years[20] with an annual research investment I_2 = 15

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[15] Phase *II* R&D correspond to the usual clinical trial phases I-III, where Phase I (duration 8-12 months) involves 10-30 subjects and tests the vaccine's safety on healthy adults, Phase II (duration 18-24 months) involves 50-500 adults and examines dosage and immunization schedule and Phase III (duration > 36 months) involves 5000-15000 adults and examines efficacy. Information from IAVI website.

[16] Under the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), the vaccine developer retains the exclusive right to the vaccine for 20 years after the introduction of the vaccine, which occurs prior to the clinical trial. The actual length of the time during which the vaccine is mass marketed under the patent protection depends on the length of the clinical trial. The WHO (Davey (2002)) reports that the typical vaccine patent life usually lasts another 10-20 years after it is initially brought to market. Batson and Ainsworth also report the same numbers.

[17] The ex ante expectation on the vaccine efficacy in conjunction with the variance of the Beta distribution for $Q(\tau_1)$ and $Q(\tau)$ are calibrated to produce an unconditional vaccine success probability of 22% and a transition probability (from Phase *I* R&D to Phase *II* R&D) of 56% for a highly subsidized R&D. These probabilities are inferred from numbers reported in Struck (1996), which are derived from 591 general vaccine projects. Since there are very few HIV/AIDS vaccine projects that have advanced to large scale human testing, and no vaccine that has been demonstrated to be effective, there are insufficient data to estimate the success and transition probabilities for HIV/AIDS vaccines specifically.

[18] Using Struck (1996) that includes 591 separate case studies on various vaccines, the corresponding average Phase *I* development time is 2.4 years. Using numbers reported in Batson and Whitehead (1998) that examines only HIV/AIDS vaccines, the corresponding time would be roughly 2.5 years. An internal memo dated March 2004 from the Malaria Vaccine Initiative provides estimates which correspond to a minimal Phase I development time of 3 years for vaccines specific to malaria.

[19] Struck (1996) estimates an average Phase *I* total cost of 5-7 million USD for most vaccines. Batson and Whitehead (1998) estimate an average cost of 10 million USD for HIV/AIDS specific vaccines. The Malaria Vaccine Initiative estimate a corresponding minimum Phase *I* development cost of 2.0-3.1 million USD for malaria vaccines.

[20] Struck (1996)'s estimates correspond to an average Phase *II* development time of 6.3 years while Batson and Whitehead (1998)'s estimates correspond to a development time of 5 years. The International AIDS Vaccine Initiative

million dollars[21]. These parameters imply ex ante Phase *I* and *II* expected research costs of $K_1(0)$ = 6.25 million dollars and $K_2(0)$ = 90 million dollars.

Observe that the investment intensity is an exogenous variable; this modeling choice implies that the investment intensity is not an important choice variable in the firm's R&D problem. This is in fact realistic for vaccine and drug development. The investment intensity for medical R&D is often limited by how clinical trials can be conducted. Specifically, clinical trials usually involves three stages, with the first two stages, aimed at testing vaccine safety and immunogenicity, involving a few hundred people and costing between 3-7 million dollars, and the third stage, aimed at testing efficacy, involving tens of thousand of people, costing up to 30 million dollars and lasting a minimum of 3 years. Applying greater R&D expenditure during the clinical phase would not materially improve the speed of the clinical trial or the efficacy of the developed vaccine. The costs and the time required for completing the clinical trial are primarily dictated by the required size of the test population to establish vaccine efficacy as well as the nature of the infectious disease, such as its dormancy period and induced human immune system response (IAVI Website, MVI Website and GAVI Website).

The volatilities of the expected cost to completion process for Phase *I* and *II* are calibrated to be 0.5 and 5 million dollars respectively.[22] We plot the simulated density for the Phase *I*

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reports on their website numbers which correspond to a minimum Phase *II* development time of 5.2 to 6 years. The Malaria Vaccine Initiative reports a minimum Phase *II* development time of 10 years.

[21] Struck (1996) estimate an average Phase *II* cost of 89-125 million USD for most vaccines. Batson and Whitehead (1998) estimate an average Phase *II* cost of 50 million USD for HIV/AIDS vaccines. The Malaria Initiative estimate an average Phase *II* cost of million USD for malaria vaccines. If the vaccine is to be targeted for other population, additional clinical trial cost would be incurred.

[22] The volatility in the investment cost for vaccines has not been reported in the vaccine literature. Most papers and sources in the industry are only able to report that the R&D process is highly uncertain. Part of the reason is that very few vaccine R&Ds have advanced into the advanced phases of clinical research, where a large population testing program is undertaken; the few data points from widely different vaccines make it difficult to address specifically the cost volatility for any specific vaccine R&D. For our example, we assume numbers which would be consistent with the fact that pharmaceutical firms know a lot more about the bio-chemical compound development process/cost but much less about advanced stages of clinical research. In addition, our numbers are such that they are consistent with

development time τ_1 and for Phase *II* development time τ_2 in Figures 2 and 3. We note that the distributions for τ_1 and τ_2 show some right skewness, which is sensible since development time is bounded below at zero and unbounded above.

The parameters, characterizing the evolution of the mean and variance of the Beta distribution for the expected quality variables, $Q(\tau_1)$ and $Q(\tau)$, are selected to provide reasonable distributions for a vaccine R&D project. We note that calibrating to data would be particularly difficult here due to the scarcity of data on reported efficacy of candidate HIV/AIDS vaccines along the decision nodes in the development process. For parameters which we do not have data to calibrate to and do not have strong priors on, we assume fairly neutral values.[23] The ex ante probability of discovering a high efficacy vaccine is low. This is consistent with the state of the HIV/AIDS vaccine research.

We plot the time τ_1 Beta distribution for the efficacy parameter in Figure 4. We plot the median, the 90 percentile, and the 10 percentile path for the time τ Beta distribution in Figure 5. Observe that the conditional mean of the efficacy distribution diverges as time evolves, which captures the learning of the vaccine efficacy over time. In addition, the conditional variance increases, which captures that the additional learning in Phase *II* R&D is greater than what can be

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the noise observed in the average cost numbers reported in Struck (1996), Batson and Whitehead (1998), a recent Malaria Vaccine Initiate memo, and in recent World Bank, WHO and IAVI publications.

[23] For example we assume $\eta_{\mu,1} = 0$ and $\eta_{\mu,2} = 0$ (which control the sensitivity of the changes in the mean of the efficacy variable to delays in the R&D time τ_1 and τ_2) $\eta_{\sigma,1} = 0$ and $\eta_{\sigma,2} = 0$ (which control the sensitivity of the changes in the variance of the efficacy variable to delays in the R&D time). However, we do have some data on abandonment rate, which we attempt to match by calibrating parameters associated with the mean and variance of the efficacy *Q* distribution. The particular parameters for our example are $Q(0)=0.2$, $s_1=0.1$ and $s_2=0.3$ (which control the level of the average variance of the quality variable as a proportion of the maximum allowable variance); these parameters are chosen such that a 95% subsidized vaccine project would have a probability for success (reaching production) equal to ~22% and a probability for advancing to Phase II equal to ~56%, which correspond to the probabilities reported in Struck (1996) for an average vaccine project. The quality variance in Phase *II* is set higher than in Phase *I* to capture the idea that most of the learning about the efficacy of the vaccine occurs in the clinical stage of the R&D. See Struck (1996) and Davey (2002).

learned in Phase *I* R&D, which is consistent with the nature of vaccine R&D process. To further illustrate the evolution of the efficacy variable, we plot the corresponding unconditional sample density for $Q(\tau_1)$ and $Q(\tau)$ in Figure 6 and 7. We observe that the unconditional density of $Q(\tau)$ has a significantly greater variance than $Q(\tau_1)$, which is intuitive since more learning on the vaccine efficacy has occurred up to time τ than to time τ_1.

We assume the following market inverse demand function:

$$P = \alpha \cdot \max(Q - Q_{\min}, 0)^{\pi} \cdot q^{-1/\gamma}, \qquad (16)$$

with α =138.7, $Q_{\min}$ = 0.25, π = 0.507 and the demand elasticity γ =1.2. The parameter α is artificial (set at 10 x the actual alpha estimated from data) and is selected to make this example HIV/AIDS R&D positive NPV. The parameters π and γ are calibrated from estimated demand data for different efficacy HIV/AIDS vaccines for the Sub-Saharan African countries.[24] The parameter $Q_{\min}$ suggests that the consumers are unwilling to pay for a vaccine with very low efficacy in light of the alternative methods for protecting against contracting the virus.[25] We note that the price response to efficacy improvement can vary significantly between populations. Calibrating to the estimated North American and Western Europe demand for a B-strain vaccine, we find a $\pi > 1$, indicating a marginal willingness to pay that is increasing in the efficacy of the vaccine.

We illustrate the elasticity of the inverse demand function with respect to the efficacy variable and the price variable jointly in Figure 8. We observe that at high quantities, the market's willingness to pay for improved vaccine efficacy is lower than at low quantities. At 10 million

[24] See Appendix D.

[25] The minimum efficacy that the market find acceptable, differs for different vaccines and population. For HIV/AIDS vaccines, which in general have low efficacy, health organization officials report that Eastern European and Asian countries would reject these vaccines (Esparza et. al 2002). For malaria vaccines, 50% efficacy is esteemed to be the minimum acceptable level with > 70% efficacy considered desirable (Ballou 2002).

units supplied, the marginal consumer is only willing to pay an additional $3.5 per unit for the vaccine for a 10% improvement in efficacy (from 30% to 40%). However, at 3 million units supplied, the marginal consumer is willing to pay an additional $8 per unit for the same 10% improvement in efficacy. Assuming that persons belonging to the same population have similar utilities for health, the marginal consumer in the first case is presumably less able to pay for a vaccine than the marginal consumer in the latter case. Therefore, our inverse-demand function suggests that people with less absolute wealth allocated for medical expenditures are also less able (or willing) to pay for higher quality medical treatments. This is consistent with the health care expenditure behavior reported in Kremer (2002a,b).

Finally, to completely specify the firm's problem, we assume a constant unit cost of vaccine production, c = \$1 and a fixed cost for scaling up production of \$50 million.[26] This assumption is consistent with the observation that the variable cost of production for medical vaccines is usually very low while the fixed cost is very high.

We now compute the profits from the sales of firm's vaccine (conditional on a successful development). From monopoly condition specified in equation (10), the firm's pricing strategy is:

$$P_M = c\frac{\gamma}{\gamma - 1} = 6, \ (\gamma = 1.2, c = 1), \ \text{for } Q > 0.25. \qquad (17)$$

The price of the vaccine, if it is marketed, would be \$6 per unit, regardless of the efficacy; the efficacy of the vaccine affects only the quantity demanded:

$$q_M = \left[\frac{\alpha \cdot (Q - Q_{\min})^{0.507}}{P_M}\right]^{\gamma} = \left[23.12 \cdot (Q - 0.25)^{0.507}\right]^{1.2}, \ \text{for } Q > 0.25. \qquad (18)$$

[26] The unit cost for producing vaccine culture is usually very low. For polio vaccines, the cost is reported at \$0.85. However, according to Batson and Ainsworth (2001), the fixed cost for scaling up for mass production averages \$50 million for an average vaccine, which is high compared to the fixed cost for pharmaceutical drug production.

We then solve for the present value, $V(\tau_1)$, of the R&D project at time τ_1. The set of basis functions that we employ in this example include polynomials up to the third degree of the two state variables $K_2(\tau_1)$ and $Q(\tau_1)$. We plot the surface diagram for $V(\tau_1)$ in the Figure 9. The abandonment region for the parameters $(Q(\tau_1), K_2(\tau_1))$ is the region where $V(\tau_1)$ takes on the value 0.

We examine the impact of the abandonment decision on the probability of successful vaccine development as well as the distribution of the quality parameter. From the probability density functions presented in Figure 6 and Figure 10.1 roughly 35% of all R&D projects would be abandoned at the end of Phase *I*. From the PDF's presented in Figure 10.2 we find for the projects that are continued into Phase *II*, an additional 58% of the projects entering Phase *II* are expected to be abandoned, leading to an unconditional success rate of only 27%.

In our particular example, the firm expects to produce and sell 18.37 million vaccines worldwide per year. The average efficacy of the projects continued into Phase *II* is 26.3% and the expected final efficacy of a successful vaccine is 52.51%. The present value of the R&D project is 59.66 million dollars.

It is interesting to note that given our inverse demand function, a vaccine with an expected efficacy near 25%, at time τ_1, would not be profitable; observe in Figure 10.1, the minimum $Q(\tau_1)$ that is not abandoned appears to be just near 10%. Why then does the firm continue with the project when the expected final efficacy would be lower than the minimum acceptable efficacy? This is because the Phase *II* variance of the efficacy variable is high, which gives the R&D high option value. Note that the marketed vaccine has an efficacy substantially higher than what the firm, at time 0, expects to be able to achieve (which in 20%) and substantially higher than the minimum efficacy required by the market (which is 25%). This should not be surprising if we

realize that the firm has the option to discontinue the project at time τ_1 and again at τ prior to scaling up for mass production.

III. The Market for Vaccines

Malaria, tuberculosis, and African strains of AIDS are reported to kill more than five million people each year. However, pharmaceutical companies have devoted few resources to research vaccines for these diseases. The World Health Organization (WHO) reports in 1996 that 50 percent of the global health R&D is undertaken by private pharmaceutical firms.[27] However, less than five percent of the total private heath R&D is geared toward diseases that specifically affect the under-developed and thus poorer regions of the world. Pecoul, Chirac, Trouiller and Pinel (1999) report that less than 0.4% of the licensed drugs in the last quarter century are for tropical diseases which affect primarily the African, Latin American and South East Asian countries.

The lack of private pharmaceutical R&D for diseases affecting under-developed countries arises from the difficulty of marketing drugs profitably in these poorer regions of the world, where the per capita income is often less than $1/100^{th}$ of the U.S. per capita income and where the per capita annual heath care expenditure is $18 compared to more than $4000 for the U.S. Kremer (2002c) reports that, under the current patent regulation, a $250 million expected annual market is needed to justify pharmaceutical firms to undertake research to develop cures. These revenues are simply not attainable from drugs targeted at diseases specific to poor countries.

We illustrate this problem explicitly in the valuation framework we developed in Section II. Using model parameters identical to the example given in Section II, we consider the value of a pharmaceutical R&D project with the following inverse-demand function estimated from demand data provided in Esparza et. al. (2002) for HIV/AIDS vaccines in Sub-Saharan Africa region:

[27] The government-sponsored research is usually basic research that are not expected to produce consumer market health care products.

$$P = 13.87 \cdot \max(Q - 0.25, 0)^{0.507} \cdot q^{-1/1.2} \qquad (19)$$

Note that this inverse demand function is identical to the one used in section II except that the constant scalar α has been reduced from the inflated 138.7 to the realistic 13.87. This is consistent with the observation that people living in the developing regions of the world are simply unable or unwilling to pay for vaccines at a price that would make the vaccine R&D profitable to the pharmaceutical company. Applying the valuation method developed in Section II to this inverse demand function we find that undertaking the vaccine research would result in significant losses for the pharmaceutical company.

World organizations are interested in solving the pharmaceutical under-investment problem described above. The World Bank announced in 2000 plans to establish a $1 billion fund to subsidize the purchases of vaccines for developing countries. The U.S. budget plan for 2000 included a ten year $1 billion tax credit incentive program for pharmaceutical companies supplying vaccines to developing countries. The Bill & Melinda Gates Foundation has seeded the Global Alliance for Vaccines and Immunization (GAVI) with $750 million to increase global vaccine coverage and fund new research. However, the effectiveness of these subsidy programs has been questioned. Kremer (2002a,b) documents spectacular failures of numerous sponsored R&D projects. Moral hazard and adverse selection problems are prevalent, sometimes rendering subsidy programs completely ineffective. How to effectively administer the subsidy and monitor the progress of the R&D effort are important questions to be answered. However, the difficulty in creating the right subsidy program may lie at an even more fundamental level. There is in fact an absence of a convenient framework to contrast the effectiveness of the different types of subsidy programs and to determine the required level of subsidy to produce the desired level of R&D activity. We address the latter issue explicitly in the next section by studying different popular

incentive programs within our valuation framework. While recognizing their importance, we largely refrain from analyzing issues of moral hazard, adverse selection and contracting, and only comments briefly on their impact when the analysis permits.

IV. Research Incentive Design

In this section we compare different R&D incentive designs. Specifically, we focus on two main categories of incentive programs that have been proposed in the policymaking arena to encourage pharmaceutical vaccine research. The two types of incentives programs, the *push* and the *pull* incentive programs, are analyzed below to determine their costs to the sponsors and their contribution to social welfare.

The *push* incentive program spurs vaccine development by reducing the cost of the R&D to the developer. The cost subsidy may take on the form of full or partial discretionary research grants or awards, where funds are awarded to the developer to reimburse expenses, or as cost-sharing subsidy, where the sponsor pays for a fixed fraction of the firm's total R&D expenditure. The *pull* incentive program spurs research by increasing the revenue generated by the developed vaccine. The revenue subsidy can occur as price (and quantity) commitments from the sponsor, where the sponsor and the developer agree to a price schedule for the vaccine prior to development, or as special patent extensions, where the developer is granted patent protection beyond the usual length of time for pharmaceutical vaccines.

We limit our analysis of the push program to the cost-sharing subsidy plan, where the sponsor shares in the cost of the R&D. For the pull program, we consider separately the patent extension plan and the purchase commitment plan. We also consider, in addition, hybrid plans which combine revenue subsidy with cost-sharing subsidy. Throughout the analysis, we seek to answer five critical questions. 1. What is the expected total cost of the incentive program to the

sponsor? 2. What is the probability that a viable vaccine will be developed? 3. What is the expected consumer surplus generated? 4. What is the expected number of successful (efficacious) vaccinations, and 5. What is the expected cost per individual successfully vaccinated (CPISV)? In particular, in answering the last question, we develop a new summarizing measure *CPISV* which addresses simultaneously the cost and benefit of a given subsidy program:

$$CPISV = \frac{PV(\text{sponsor cost})}{E\left[Q(\tau)\cdot q\cdot T_1\right]}, \qquad (20)$$

where again, $Q(\tau)$ is the efficacy of the developed vaccine, q is the units of vaccination supplied per year, and T_1 (=[τ_1 +T]-[$\tau + \tau_3$]) is the number of years that the subsidy contract is in effect. The *CPISV* measure allows us to compare across subsidy plans that have different expected sponsor costs since it quantifies cost per unit of benefit delivered. More importantly, it defines vaccine benefit differently from consumer surplus. Note that consumer surplus measures benefit (or welfare) by the consumer's dollar valuation of his consumption; this measure ignores the large positive externality created by a successful vaccinations. In contrast, *CPISV* measures vaccine benefit as the expected number of successful vaccination, which assumes tacitly that each life saved is equally valuable and that each successful vaccination provides identical external benefit to the society in terms of stemming the infectious disease.

In the analysis we abstract from agency problems arising from asymmetric information between the vaccine developer and the sponsor. For example, we assume that subsidies are actually invested in the vaccine project and not diverted to other use. We also abstract from contracting issues, such as enforceability and renegotiation, related to purchase commitment plans.

Also note that we do not specify a utility function for the subsidy sponsor. Instead we simply focus on vaccine R&D attributes that we believe would be important to the sponsor.[28]

We begin by introducing the exogenous environment. We continue with the example presented in section III, which is used to illustrate under-investment in pharmaceutical R&D for diseases specific to poorer countries. In our specific example, engaging in the proposed vaccine research would imply an expected loss in present value to the firm. A sponsored subsidy program would therefore be needed to induce the vaccine R&D.

To help us contrast the different subsidy programs clearly, we assume throughout that the firm retains the right to the developed vaccine. The firm is also allowed to abandon the R&D project when it determines that further development would not be profitable even with the subsidy. We do not consider subsidy programs that transfer the ownership of the vaccine and the vaccine development process to the sponsor, because in general, public agencies lack the expertise to own, manage, and distribute pharmaceutical resources effectively.[29] Our aim is to solve the pharmaceutical market failure in the poor countries by offering the proper level of incentives.

In the sections that follow, we first describe the specifics of each subsidy contract considered in our analysis. We then characterize the pharmaceutical research outputs induced by these subsidy contracts.

Push subsidy programs

a. Cost-sharing subsidy plan

This plan assumes that the sponsor pays for a fraction X of the firm's per period investment cost. That is, the firm incurs only $(1-X)\ I_1$ and $(1-X)\ I_2$ in research cost per period in Phase *I* and *II*

[28] Had we specified a utility function, we would be able to determine first best contracts under the utility specification and compare the first best contract with the push and pull contracts that we study in this paper.

[29] This is a view echoed in Batson and Ainsworth (2001), who argue that transferring the science to the private companies is necessary in creating products that can be manufactured and sold on a large scale.

respectively and (1-X) I_3 in fixed cost for scaling up production, instead of I_1, I_2 and I_3. Again, the firm is free to abandon the research effort when and if it sees fit. The cost-sharing subsidy plan encourages innovation in vaccine development by reducing the cost of research and scaling up for production.

Pull subsidy programs

Kremer (2002b) concludes that pull subsidy programs would be more effective because it largely eliminates the agency issues between the sponsor and the vaccine developer. We illustrate in the analysis below that pull subsidy programs have many other advantageous attributes over push subsidy programs. However, not all pull subsidy programs can be effective, and different contract designs can achieve different sponsor objectives.

b. Patent extension program

The patent extension program is the most widely used pull subsidy for encouraging innovations in general. Some economists and policy activists have argued that strengthening patent protections or extending patent lives for pharmaceutical products in under-developed countries would improve firms' incentive to conduct research on diseases specific to the developing countries (Kremer 2002b). There is little doubt that better patent protection and longer patent life would improve the firm's expected revenue from the developed vaccine. However, does this mechanism deliver enough incentives? We analyze the patent extension program in this section. Specifically, we assume that the sponsor can grant the pharmaceutical company extra patent protection beyond what is allowed under the current international patent agreement. The increase in patent protection allows the firm to enjoy monopoly power for an additional period of time, leading to increased revenue from the R&D project.

c. Purchase commitment plan

We assume that the sponsor commits to a quantity-price purchase schedule with the vaccine developer. Under this price subsidy plan, the cost side of the vaccine R&D to the pharmaceutical firm remains unaffected, while the revenue side is altered by the purchase commitment.

Since the quality of the firm's developed vaccine is observable at time τ, under the purchase commitment plan, the contract establishes the socially optimal units of vaccine to purchase from the pharmaceutical firm; the quantity that the pharmaceutical company is contracted to deliver is then only dependent on $Q(\tau)$. Lastly, we assume that the vaccine is supplied to the target countries at the pharmaceutical firm's unit cost of production c[30]. The sponsor must design and commit to a price contract to induce the pharmaceutical firm to engage in research. In the sections that follow, we study how different price contracts can lead to different firm behaviors and outcomes. We limit our analysis to a few types of price contracts. Extending the contract space beyond what is presented here would be easy to do, but would not contribute to our understanding of the salient features of the purchase commitment plan.

The distinguishing feature of the purchase commitment plan is that the sponsor is able to dictate the supply of the developed vaccine. With the discretionary award or cost-sharing subsidy plan, the firm chooses to supply the monopoly quantity associated with the measured market inverse-demand function:

$$q_M = \left[\frac{\alpha \cdot (Q - Q_{\min})^{\pi}}{P_M} \right]^{\gamma}, \text{ for } Q > Q_{\min} = 0.25,\ \gamma = 1.2,\ \pi = 0.507,\ \alpha = 13.87. \quad (21)$$

Under a purchase commitment subsidy, however, the firm gives up its right to extract monopoly rent in exchange for a purchase commitment at an agreed price. The firm is contracted

[30] For concreteness, here we assume that the sponsor sells the vaccine at the marginal cost *c*. The analysis easily extends to any other sale price (or price schedule) including a price of 0.

to supply the socially efficient quantity q_c, which is characterized by the quantity such that the market-clearing price is equal to the marginal unit cost of production ($P = c$):

$$q_c = \left[\frac{\alpha \cdot (Q - Q_{\min})^{\pi}}{c} \right]^{\gamma}, \text{ for } Q > Q_{\min} = 0.25, \ \gamma = 1.2, \ \pi = 0.507, \ \alpha = 13.87 \quad (22)$$

c.1. Purchase commitment with a constant price schedule

We first analyze the simplest price contract—the constant price contract. Here the sponsor is assumed to offer a fixed price P for any vaccine with an efficacy above the minimum efficacy demanded by the market (25%). The revenue per year received by the developer is therefore equal to $P \cdot q_c$, where q_c is defined in (22). Since, the sponsor is assumed to supply the vaccine to developing countries at the marginal cost of production for the vaccine, it incurs a loss of (P - c) per unit of vaccine supplied. However, in the event that the vaccine research is unsuccessful, the sponsor would incur no expenses.

As we noted above, the constant price contract does not reward the developer directly for the efficacy of the vaccine. However, the firm is rewarded indirectly with a larger vaccine order, since the competitive quantity q_c defined in (22) does depend on the efficacy. As a result, the profit for the firm increases with the efficacy of the developed vaccine.

c.2. Purchase commitment with a variable price schedule

We further consider a more complicated purchase commitment contract, where the price offered to the firm depends on the efficacy of the vaccine supplied. One possible variable purchase contract is specified below:

$$P = c + w \cdot \max\left(Q - Q_{\min}, 0\right)^{\delta}, \quad (23)$$

where w is a constant parameter specified ex ante by the sponsor to target some specified expected total cost, δ is a parameter that describes the price sensitivity to the efficacy of the vaccine, and the constant c is added to ensure that a viable vaccine receives a price greater than the marginal cost of production. For the analysis presented below, we use a sensitivity parameter of 0.25 (this turns out to not matter much). We note that the price schedule specified is chosen *ad hoc*; the analysis, of course, can be performed in conjunction with other specifications.

d. Hybrid contracts: purchase commitment with cost-sharing subsidy

We can combine purchase commitment contracts with cost-sharing subsidy to create hybrid contracts. As we will show later, these hybrid contracts combine the positive attributes of both types of subsidies.

Analysis of the Subsidy programs

We use the valuation model developed to help us characterize the research output induced under different sponsorship contracts. The more interesting statistics are summarized in Table 1. In Table 1, the push, pull and hybrid contracts are specified such that they have the expected cost to the sponsor of $40 million. Table 1 is helpful for comparing the benefits per expected dollar expenditure created by the different subsidy contracts.

We do not report the results for the patent extension plan because for the example considered here it is completely ineffective at solving the small market problem. Applying our valuation technique we find that extending the patent protection to 1000 years does little to improve the value of the vaccine R&D; even under the most favorable patent protection, no developer would undertake this vaccine R&D. While increasing patent protection might be the cheapest way (in a fiscal sense only) for governments to provide incentives for vaccine R&D, for

the market failure considered here it is completely ineffective at solving the pharmaceutical under-investment problem.

Probability of Successful Vaccine Development—From Table 1, we see that the cost-sharing subsidy produces the greatest probability for producing a viable vaccine, followed by the hybrid contracts, then by the fixed and variable price purchase commitment plans. Under the cost-sharing subsidy the pharmaceutical company has the incentive, at time τ_1, to continue an R&D project even if it has a low expected final quality $Q(\tau_1)$, because it does not fully internalize the cost of Phase *II* R&D.[31] Not surprisingly then, the cost-sharing subsidy reports the highest probability (60.74%) of entering Phase *II* development. Ultimately, this leads to significantly higher probability of developing a successful vaccine.

Under a purchase commitment plan, the pharmaceutical company must internalize the full cost of the R&D. The firm tends to abandon early on when the expected efficacy at the end of Phase *I* is low.

For the hybrid contracts, the probabilities for advancing to Phase *II* and for producing a viable vaccine are increasing in the fraction of cost-sharing subsidy. That is, the more of the expected $40 million in sponsor cost is used to reduce the firm's R&D cost, the greater is the stimulated research activity.

Number of People Vaccinated when a Successful Vaccine is Identified—From Table 1 we find that the hybrid contracts produces the largest expected units of vaccine supplied, followed by the constant price purchase commitment contract, then the variable price purchase commitment contract, and finally the cost-sharing subsidy plan. The difference in the quantity supplied under a cost subsidy contract and a price subsidy contract is intuitive. The vaccine quantity supplied,

[31] The developer, under this plan, pays only 7.22% of the total R&D cost.

under a cost subsidy program, is the monopoly quantity; while the quantity supplied, under a price subsidy program, is the socially optimal quantity.

Consumer Surplus, Expected Number of Successful Vaccinations and Cost Per Successful Immunization—The consumer surplus is increasing with the average quantity of the vaccine supplied in Table 1. This result is intuitive and suggests that contracts designed to increase the probability of successful vaccine development and the quantity sold when a successful vaccine is developed would produce greater consumer surplus.

The expected number of successful vaccinations is useful statistic in evaluating the success of a particular subsidy contract. Under this measure, all persons successfully vaccinated are counted equal. The cost per individual successfully vaccinated (*CPISV*) provides a useful statistic for measuring the benefit provided by the subsidy relative to the cost. The *CPISV* also ignores the individual's valuation of the vaccine in the computation. Instead the statistic focuses on the efficacy of the vaccine and the number of people who receive the vaccination. The expected number of successful vaccination and the *CPISV* are the more useful statistics because of the large positive externality produced by each successful vaccination.[32]

In general, we find price subsidy contracts produce lower *CPISV*s and higher expected number of successful vaccination due to the larger vaccine productions they induce relative to cost subsidy contracts. For the hybrid contracts the *CPISV* is falling and the expected number of successful vaccination is increasing in the fraction of cost-sharing subsidy.

Project Present Value—The net present value of the project to the firm is essentially the transfer to the vaccine developer from the sponsor. Under the constant price purchase commitment, the firm expects to spend 32.28 million dollars of the 40 million dollars in expected subsidy to fund

[32] The positive externality could by interpreted cynically as the reduction in the probability of a uncontainable global outbreak of the disease, or as the comfort we derive in believing that all lives are valuable and that we are responsible for making lives better when we are able to do it.

research, leaving 7.72 million dollars as expected profit from accepting the R&D contract. Under the cost-sharing subsidy, the firm expects to spend 36.66 million dollars and expects to keep 3.34 million dollars as profit. The hybrid contracts are more effective at reducing the amount of the subsidy that becomes firm profit. We observe that firm expected profit falls monotonically as the cost-sharing subsidy ratio increases.

Hybrid Subsidy Contracts

The hybrid subsidy contracts appear to combine the benefits from push and pull subsidy programs. We see that by increasing the cost-sharing subsidy ratio of the hybrid subsidy the R&D activity increases, resulting in a higher probability of vaccine development. This arises because cost-sharing subsidy directly offsets the cost of the R&D expenditure. For every R&D investment dollar spent, the developer receives a rebate of X, regardless of the ultimate outcome of the research. The purchase commitment, on the other hand, only covers the developer's cost indirectly through price guarantees for a successful vaccine. The two mechanisms for offsetting R&D costs are clearly distinct in an important way even in our framework where risk sharing is not a motive! The mechanism through which the firm is subsidized in a cost-sharing subsidy scheme is more effective at encouraging R&D activities. Unfortunately, it is ineffective at encouraging an efficient quantity supplied once a successful vaccine is developed. However, the latter problem is alleviated when we combine a cost-sharing subsidy with a purchase commitment subsidy into a hybrid contract.

As far as we are aware these types of hybrid contracts have not been analyzed in the literature. Our framework allows for a quantitative evaluation of hybrid contracts with other incentive contracts and between different types of hybrid contracts.

Reading across Table 1, we see that the performance of the contract in the dimensions of consumer surplus, *CPISV,* expected number of successful vaccinations, as well as the probability of development is monotonically increasing in the cost-sharing subsidy ratio. The improvements over the standard price contracts are significant. Overall, we find the hybrid contracts most attractive,[33] followed by the fixed and variable price contracts, and followed by the cost-sharing subsidy contract.

How best to award more funding

In Table 2 and 3, we provide analyses on the different contracts when the expected present value of the sponsor cost is set at 60 million dollars and 80 million dollars. By and large, there are no surprises. What is noteworthy is that for purchase commitment plans without cost-sharing subsidy, roughly half of the increase in expected sponsor funding cost accrues to the pharmaceutical firm as expected profit. This seems undesirable. The problem, however, is easily alleviated if the additional funding is not provided as price incentives for a successful vaccine, but as cost-sharing subsidy on investment cost. That is, if a sponsor wishes to increase funding to a hybrid contract, it should increase the cost-sharing subsidy ratio rather than providing a richer purchase commitment contract.

To highlight comparisons between Table 1 and Table 2, Table 4 reports the increases in the output variables when the subsidy increases from $40 million to $60 million. This $20 million increase in subsidy brings about an increase in the probability of successful vaccine development of around 4% for all contracts and a decrease in the average vaccine efficacy of around 1.5%. The firms are induced to continue R&D on more marginal projects, but the increase in the expected number of successful immunizations per year is around 15%. The cost per individual successfully

[33] Batson and Ainsworth also posit that a combination of push and pull would likely deliver the best result in terms of stimulating research in the private sector.

vaccinated increases, especially for the cost-sharing subsidy plan. Note that the increase in subsidy is not captured entirely by the firms, though there is an increase in the project's NPV.

Examine in Table 3 the hybrid contract where the sponsor pays for 100% of the R&D and capacity building cost. Clearly, in this case the firm would never abandon at the end of Phase *I*; this results in the maximum probability of success that stands at 30.69%. Comparing this hybrid contract that costs an expected $80 million to the 95% cost-sharing subsidy hybrid contract with an expected cost of $60 million suggests that the additional $20 million in subsidy does not appear to buy much. This is because the limitation in the technology becomes the dominant issue (among the many issues which plague HIV/AIDS vaccine research) beyond a certain subsidy threshold.

Static Comparison and Robustness Analysis

The behaviors of the contracts do not change materially with other different demand function specifications or state variable dynamics. We examine some of the more interesting parameters and their impacts on the firm's decision process as well as on the different contracts.

$Q(\tau)$'s *beta distribution variance*—Reduction in the variance of the efficacy variable $Q(\tau)$ leads uniformly to higher CPISV, lower expected vaccine efficacy and lower probability of developing a viable vaccine. This is intuitive because the reduction in volatility also reduces the option value of the vaccine project. That means that at the same level of subsidy, the firm would need to reject more low-efficacy candidate vaccines to avoid losses.

Price elasticity γ—In calibrating the inverse demand function to data we assumed an elasticity of γ=1.2. We vary that assumption and recalibrate the demand function. This has surprisingly little impact on the contract analysis, except that the firm's ability to extract monopoly profits falls with increased price elasticity that makes pure cost-sharing subsidy plans less effective. We also varied

the efficacy preference parameters π from 0.507 to numbers greater than 1; this also does not have an impact on the contract analysis.

Ex ante candidate vaccine efficacy $Q(0)$ —The ex ante vaccine efficacy is assumed equal to 20%. Assuming a higher $Q(0)$ has the obvious effect that probability of producing a vaccine becomes higher. However, an interesting implication is that cost-sharing subsidy becomes relatively more attractive in this environment. This is because purchase commitments respond to the high ex ante efficacy by reducing the price paid for viable vaccines; this is the only way to keep the sponsor cost at $40 million. However, there is no change to the cost-sharing subsidy contract. As an illustration, when $Q(0)$ is raised from 20% to 50%, the probability of success goes from 25.6% to 80.5% for cost-sharing subsidy and from 17.2% to 34% for constant price purchase commitment. However, the comparison between the constant price contract and the variable price contract remain similar.

Summary and Conclusions

In this article, we develop an R&D valuation model and apply it to analyze research incentive contracts for sponsored pharmaceutical R&D's. We find that extending additional patent protection that is usually effective in stimulating R&D's in most environments and situations, is unlikely to induce vaccine R&D on diseases affecting the poor developing countries. The small market problem is simply too severe. A cost subsidy program, where the sponsor shares part of the R&D investment cost, is very effective at encouraging R&D activities and produces a higher probability of developing a successful vaccine. However, it performs poorly in supplying the vaccine in quantities once a successful development results.

Price subsidy, in the form of a purchase commitment, is comparably less effective at encouraging high amount of R&D activities, thus resulting in a lower probability of successful

development. However, the sponsor can contract the purchase commitment to induce a socially optimal quantity to be supplied, in the event that a successful vaccine is developed. These effects combined lead to a higher consumer surplus, a larger number of expected vaccination provided as well as lower cost per individual successfully vaccinated.

Refining the purchase commitment contract further with the incorporation of sponsor cost-sharing subsidy, we find that these hybrid contracts deliver even more desirable outcomes. Specifically, the hybrid contract with the highest cost-sharing subsidy ratio outperforms all other hybrid contracts; it also outperforms other non-hybrid contracts in all the effectiveness measures except for one (the probability of success for cost-sharing subsidy is higher). We are therefore led to conclude that hybrid contracts are preferred to purchase commitment contracts which are preferred to cost-sharing subsidy contracts. Additionally, we find patent extensions completely ineffective at inducing any R&D effort.

In this paper, we have assumed specific demand functions and stochastic processes. However, the valuation framework we have developed and the numerical solutions we have implemented are quite general. We could allow for any reasonable demand function and joint stochastic processes describing the conditional expected cost to completion and quality of the R&D output. More R&D phases can also be considered without much complication. In our analysis of the pharmaceutical R&D incentive designs, we have used specific functions and parameters, but we believe that the qualitative implications of the analysis are quite general.

There are important issues that we do not consider in our analysis. Specifically, we do not model the interesting and complicated issues of moral hazard and information asymmetry between the vaccine developer and the research sponsor. However, it does appear intuitive to us that the inclusion of moral hazard would make cost subsidy programs such as full discretionary research

grants and sponsor cost-sharing subsidy less effective relative to the purchase commitment program in producing the desired level of R&D activity in the targeted vaccine.

We also do not assume a utility function for the subsidy sponsors. There is little doubt that government health agencies and philanthropic foundations value greatly the potential human lives that can be saved through R&D subsidy programs. However there is insufficient data for us to construct an applicable sponsor utility function. As a consequence we do not address questions associated with first best contracting.

Another issue of interest is the analysis of competition in the development of vaccines. What is the impact on the expected cost to the research sponsor and the probability of vaccine development under the different incentive programs when more than one firm engages in the same vaccine R&D? How should the incentive contracts be modified to target sponsor cost and/or the probability of success? Answers to these questions will further aid world organizations to effectively solve the health care crises in the developing countries.

Appendix A

First Hitting Time Density

By definition, $K_1(\tau_1) = 0$, therefore, τ_1 is the first time the diffusion K_1 reaches zero. The first hitting time density (which is not normal) of an arithmetic Brownian motion with drift $-I_1$ and volatility σ_1 starting at $K_1(0)$ and reaching 0 is:[34]

$$\phi_1(\tau_1) = \frac{K_1(0)}{\sigma_1(2\pi)^{1/2}\tau_1^{3/2}} \exp\left\{-\frac{\left[K_1(0) - I_1\tau_1\right]^2}{2\sigma_1^2\tau_1}\right\} \tag{A1}$$

and the cumulative density function for the first hitting time is:

$$\Phi_1(\tau_1) = 1 - N\left(\frac{K_1(0) + I_1\tau_1}{\sigma_1\tau_1^{1/2}}\right) + \exp\left\{\frac{-2I_1K_1(0)}{\sigma_1^2}\right\} N\left(\frac{-K_1(0) + I_1\tau_1}{\sigma_1\tau_1^{1/2}}\right). \tag{A2}$$

Similarly, for τ_2, we have:

$$\phi_2(\tau_2) = \frac{K_2(\tau_1)}{\sigma_2(2\pi)^{1/2}\tau_2^{3/2}} \exp\left\{-\frac{\left[K_2(\tau_1) - I_2\tau_2\right]^2}{2\sigma_2^2\tau_2}\right\} \tag{A3}$$

$$\Phi_2(\tau_2) = 1 - N\left(\frac{K_2(\tau_1) + I_2\tau_2}{\sigma_2\tau_2^{1/2}}\right) + \exp\left\{\frac{-2I_2K_2(\tau_1)}{\sigma_2^2}\right\} N\left(\frac{-K_2(\tau_1) + I_2\tau_2}{\sigma_2\tau_2^{1/2}}\right). \tag{A4}$$

Since the firm invests with a constant intensity, the total realized research expenditure for Phase *I* R&D is $I_1\tau_1$. The unexpected Phase *I* research cost is defined as:

$$X_1 = K_1(0) - I_1\tau_1, \tag{A5}$$

which can be expressed as:

$$X_1 = \int_0^{\tau_1} \sigma_1 dW_1 . \tag{A6}$$

Similarly, the revision in the expected research cost for Phase *II* is defined as:

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[34] For details, see Karatzas and Shreve (1991).

$$X_2 = K_2(0) - K_2(\tau_1), \tag{A7}$$

which can also be expressed as:

$$X_2 = \int_0^{\tau_1} \sigma_2 dW_2 \,. \tag{A8}$$

Since dW_1 and dW_2 are correlated, we can decompose dW_2 into two orthogonal Brownian motions and rewrite (A8) as:

$$X_2 = \sigma_2 \int_0^{\tau_1} \left(\rho dW_1 + \sqrt{1-\rho^2}\, dZ_2 \right) = \rho \frac{\sigma_2}{\sigma_1} X_1 + \sqrt{1-\rho^2}\, \sigma_2 Z_2(\tau_1) \tag{A9}$$

where dW_1 and dZ_2 are orthogonal, and $Z_2(\tau_1)$ is a normal random variable with mean zero and variance τ_1. Rearranging (A7) and substituting (A5) and (A9), we have:

$$K_2(\tau_1) = K_2(0) - \rho \frac{\sigma_2}{\sigma_1} \left(K_1(0) - I_1 \tau_1 \right) - \sqrt{1-\rho^2}\, \sigma_2 Z_2(\tau_1) \,. \tag{A10}$$

Therefore $K_2(\tau_1)$ is conditionally normal with mean $K_2(0) - \rho \frac{\sigma_2}{\sigma_1} \left(K_1(0) - I_1 \tau_1 \right)$ and variance $\left(1-\rho^2\right) \cdot {\sigma_2}^2 \cdot \tau_1$.

Appendix B

Parameterization for Mean and Variance of Expected Quality Variable

The specific parameterization for the mean of the expected quality variable we adopt is:

$$\mu_Q(\tau_i) = 1 - \left(1 - Q(\tau_{i-1})\right) \left(\frac{\tau_i}{E_{\tau_{i-1}}[\tau_i]} \right)^{\eta_{\mu,i}}, \tag{A11}$$

where $Q(\tau_{i-1})$ is the expected final product quality prior to the start of phase *i*, and $\eta_{\mu,i}$ is the response parameter to the unexpected delay in research time.

Note that, for $\eta_{\mu,i} < 0$, the mean, $\mu_Q(\tau_i)$, of the quality variable is decreasing in the unexpected delay in research time, $(\tau_i - E_{\tau_{i-1}}[\tau_i])$. When the realized Phase *i* research time τ_i is

equal to the ex ante expected research time, $E_{\tau_{i-1}}[\tau_i]$, $\mu_Q(\tau_i)$ is equal to the ex ante expectation $Q(\tau_{i-1})$. However when $\tau_i > E_{\tau_{i-1}}[\tau_i]$, we have $\mu_Q(\tau_i) < Q(\tau_{i-1})$ and vice versa. Finally, we note that $\mu_Q(\tau_i)$ is bounded between 0 and 1.

The specific parameterization for the variance of the expected quality variable we adopt is:

$$\sigma_Q^2(\tau_i) = \mu_Q(\tau_i)\left(1-\mu_Q(\tau_i)\right)\left(1-\left(1-s(\tau_{i-1})\right)^{\left(\frac{\tau_i}{E[\tau_i]}\right)^{\eta_{\sigma,i}}}\right), \qquad \text{(A12)}$$

where $\mu_Q(\tau_i)\left(1-\mu_Q(\tau_i)\right)$ is the maximum admissible variance for the conditional expected quality variable, $\mu_Q(\tau_i)\left(1-\mu_Q(\tau_i)\right)\cdot s(\tau_{i-1})$ is the variance of the quality variable if there is no unexpected R&D delay, and $\eta_{\sigma,i}$ is the response parameter to the unexpected delay in research time. Note, $\sigma_Q^2(\tau_i)$ is defined as a fraction of the maximum admissible variance.

Consistent with the notion that the more time available for learning about the project the larger is the variance of the distribution of $Q(\tau_i)$, the variance ${\sigma_Q}^2(\tau_i)$ of the quality variable is increasing in the research time τ_i. When the phase *i* research time τ_i is equal to the ex ante expected research time $E_{\tau_{i-1}}[\tau_i]$, the variance of the conditional expected quality $\mu_Q(\tau_i)$ is equal to the ex ante variance $\mu_Q(\tau_i)\left(1-\mu_Q(\tau_i)\right)\cdot s(\tau_{i-1})$. However, for $\eta_{\sigma,i} < 0$, when $\tau_i > E_{\tau_{i-1}}[\tau_i]$, ${\sigma_Q}^2(\tau_i) > \mu_Q(\tau_i)\left(1-\mu_Q(\tau_i)\right)\cdot s(\tau_{i-1})$ and vice versa. Finally note that ${\sigma_Q}^2(\tau_i)$ is bounded between 0 and the maximum allowable variance value $\mu_Q(\tau_i)\left(1-\mu_Q(\tau_i)\right)$.

Appendix C

Longstaff and Schwartz Least-Squares Solution Procedure

We apply the least-squares technique developed by Longstaff and Schwartz (2001) to estimate the conditional expectation functions described in equation (13). These conditional expectations functions are needed to characterize the firm's abandonment policy functions that are required to evaluate the R&D project.

To proceed, we first simulate *N* independent paths (or evolutions) of the model state variables. Specifically, each path *j* has three nodes labeled by time 0, $\tau_1^{\,j}$, and τ^j, with the associated state vector $\{Q(0),\ K_1(0),\ K_2(0)\}$, $\{Q^j(\tau_1^{\,j}),\ K_2^j(\tau_1^{\,j}),\ \tau_1^{\,j}\}$, and $\{Q^j(\tau^j),\ \tau^j\}$.[35] Recall that $\tau_1^{\,j}$ and τ^j can be simulated using the distribution defined in (A1) and (A3); $K_2^j(\tau_1^{\,j})$ can be simulated using the conditional normal distribution defined in (A10); and $Q^j(\tau_1^{\,j})$ and $Q^j(\tau^j)$ can be simulated using the conditional Beta distribution with mean and variance defined in (A11) and (A12).

In the sections below, we solve first for the firm's policy functions. After the policy function at each decision node is determined, the valuation problem simplifies to an exercise in taking simulated sample averages. Throughout, we use *v*(t) to denote the present value of the project without the option to abandon at time *t* and *V*(t) to denote the value when the option to abandon exists.

After the state variables are simulated, we work backward and examine, first, the present value of the R&D at time τ^j for each of the *N* paths. As we mentioned before, the time τ^j

[35] Note that at the first node, all paths have the identical set of state variables $\{Q(0),\ K_1(0),\ K_2(0)\}$; since no time has elapsed for the state variables to evolve.

present value $V(\tau^j)$ can be computed using (11) and (12) without any complication. After computing $V(\tau^j)$ for each path *j*, we then proceed to compute:

$$\tilde{v}\left(Q(\tau^j), {\tau_2}^j\right) = V\left(\tau^j\right) \cdot e^{-(r+\lambda_2){\tau_2}^j} - \int_0^{{\tau_2}^j} I_2 e^{-(r+\lambda_2)t} dt\,, \qquad \text{(A13)}$$

which is a point estimate of the conditional expectation defined in equation (13) (which we present here again for clarity):

$$v\left({\tau_1}^j\right) = E\left[V\left(\tau^j\right) \cdot e^{-(r+\lambda_2){\tau_2}^j} - \int_0^{{\tau_2}^j} I_2 e^{-(r+\lambda_2)t} dt \middle| Q({\tau_1}^j), K_2({\tau_1}^j) \right]. \qquad \text{(A14)}$$

The $\tilde{v}\left(Q(\tau^j), {\tau_2}^j\right)$'s are then projected onto our chosen basis functions to construct an approximate function for the conditional expectation. Note that these basis functions $f_1\left(Q({\tau_1}^j), K_2({\tau_1}^j)\right), \cdots, f_k\left(Q({\tau_1}^j), K_2({\tau_1}^j)\right)$ may include higher moments, cross moments, logs and exponentials of the state variables. The larger the set of basis functions we use, and the more judiciously we select the basis functions, the more accurate is the approximation. To determine the coefficients on the basis functions selected, we regress the *N* (simulated) realized $\tilde{v}\left(Q(\tau^j), {\tau_2}^j\right)$'s onto these basis functions. The fitted value from the regression equation $\hat{v}(Q(\tau_1), K_2(\tau_1)) = X(Q(\tau_1), K_2(\tau_1))'\beta$ (where *X* is the vector of the basis functions and β is the vector of estimated OLS coefficients) provides a direct estimate of the conditional expectation $v({\tau_1}^j)$. The time τ_1 policy function is then approximated by:

$$\mathbf{1}\left\{v({\tau_1}^j) > 0\right\} \approx \mathbf{1}\left\{\hat{v}\left(Q({\tau_1}^j), K_2({\tau_1}^j)\right) > 0\right\}, \qquad \text{(A15)}$$

and the time τ_1 present value of the project is:

$$\hat{V}({\tau_1}^j) = \mathbf{1}\left\{\hat{v}\left(Q({\tau_1}^j), K_2({\tau_1}^j)\right) > 0\right\} \cdot \hat{v}\left(Q({\tau_1}^j), K_2({\tau_1}^j)\right). \qquad \text{(A16)}$$

To compute the time 0 policy function we need to compute first the point estimates for $v(0)$:

$$\tilde{v}\left(Q(\tau_1^{\,j}), K_2(\tau_1^{\,j}), \tau_1^{\,j}\right) = \hat{V}\left(\tau_1^{\,j}\right) \cdot e^{-(r+\lambda_1)\tau_1^{\,j}} - \int_0^{\tau_1^{\,j}} I_1 e^{-(r+\lambda_1)t} dt \ . \qquad \text{(A17)}$$

The same least-square projection technique is again applied to approximate the conditional expectation from a set of basis functions of the state variables. However, we note that at time 0, the values of the state variables do not vary across the N paths; no time has elapsed for the state variables to evolve. Therefore the regression trivially regresses the (simulated) realized $\tilde{v}\left(Q(\tau_1^{\,j}), K_2(\tau_1^{\,j}), \tau_1^{\,j}, Q(\tau_2^{\,j}), \tau_2^{\,j}\right)$'s onto a constant. Consequently, the expected discounted present value at time 0 is just the mean of the N $\tilde{v}\left(Q(\tau_1^{\,j}), K_2(\tau_1^{\,j}), \tau_1^{\,j}\right)$'s:

$$\hat{v}\left(Q(0), K_1(0), K_2(0)\right) = \frac{1}{N} \cdot \sum_{j=1}^{N} \tilde{v}\left(Q(\tau_1^{\,j}), K_2(\tau_1^{\,j}), \tau_1^{\,j}\right). \qquad \text{(A18)}$$

The time 0 policy function is then approximated by:

$$\mathbf{1}\{v(0) > 0\} \approx \mathbf{1}\left\{\hat{v}\left(Q(0), K_1(0), K_2(0)\right) > 0\right\}. \qquad \text{(A19)}$$

With the firm's abandonment policy functions solved, we can evaluate the time 0 value of the R&D project by Monte Carlo. Since we have created N simulated paths already, the Monte Carlo approach can be executed with almost no additional effort:

$$\begin{aligned} & V\left(Q(0), K_1(0), K_2(0)\right) \\ & = \mathbf{1}\left\{\hat{v}\left(Q(0), K_1(0), K_2(0)\right) > 0\right\} \cdot \tilde{v}\left(Q(\tau_1^{\,j}), K_2(\tau_1^{\,j}), \tau_1^{\,j}, Q(\tau^{j}), \tau_2^{\,j}\right), \end{aligned} \qquad \text{(A20)}$$

where:

$$\tilde{v}\left(Q(\tau_1^{\,j}), K_2(\tau_1^{\,j}), \tau_1^{\,j}, Q(\tau^{j}), \tau_2^{\,j}\right) = \tilde{V}\left(\tau_1^{\,j}\right) \cdot e^{-(r+\lambda_1)\tau_1^{\,j}} - \int_0^{\tau_1^{\,j}} I_1 e^{-(r+\lambda_1)t} dt \ , \qquad \text{(A21)}$$

where:

$$\tilde{V}(\tau_1^{\,j}) = \mathbf{1}\left\{\hat{v}\left(Q(\tau_1^{\,j}), K_2(\tau_1^{\,j})\right) > 0\right\} \cdot \tilde{v}\left(Q(\tau^j), \tau_2^{\,j}\right), \qquad \text{(A22)}$$

and :

$$\tilde{v}\left(Q(\tau^j), \tau_2^{\,j}\right) = V\left(\tau^j\right) \cdot e^{-(r+\lambda_2)\tau_2^{\,j}} - \int_0^{\tau_2^{\,j}} I_2 e^{-(r+\lambda_2)t} dt\,. \qquad \text{(A23)}$$

We have assumed throughout the discussion only three phases in the project lifecycle. However, the extension to a more general case with *M* phases is quite natural. The time 0 and τ valuation and abandonment would remain identical to the procedures described above. For the intermediate τ_i valuation and abandonment, where *i* = 1 to *M*-1, we can apply the same procedure described above for the time τ_1 valuation and optimal abandonment.

Appendix D

Parameters of Demand Function

The inverse demand function we assume is:

$$P = \alpha \cdot \max(Q - Q_{\min}, 0)^{\pi} \cdot q^{-1/\gamma}, \qquad \text{(A24)}$$

We are given the following information on the demand for vaccines in the Sub-Saharan Africa region, when the vaccines are supplied at cost.

Low~Moderate Efficacy (40% efficacy): 7.4 million units

High Efficacy (85% efficacy): 17.2 million units

We rewrite (A24) as:

$$\frac{P}{\alpha} = \max(Q_L - Q_{\min}, 0)^{\pi} \cdot q_L^{\,-1/\gamma} = \max(Q_H - Q_{\min}, 0)^{\pi} \cdot q_H^{\,-1/\gamma} \qquad \text{(A25)}$$

Plugging in the point estimates on vaccine demand we have:

$$\frac{1}{\alpha} = 0.15^{\pi} \cdot 7.4^{-1/\gamma} = 0.6^{\pi} \cdot 17.2^{-1/\gamma} \qquad \text{(A26)}$$

Since we do not have enough data points to estimate all three parameters, we assume a value of 1.2 for γ, which then suggest α =13.87 and π = 0.507.

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Timeline of the R&D Process

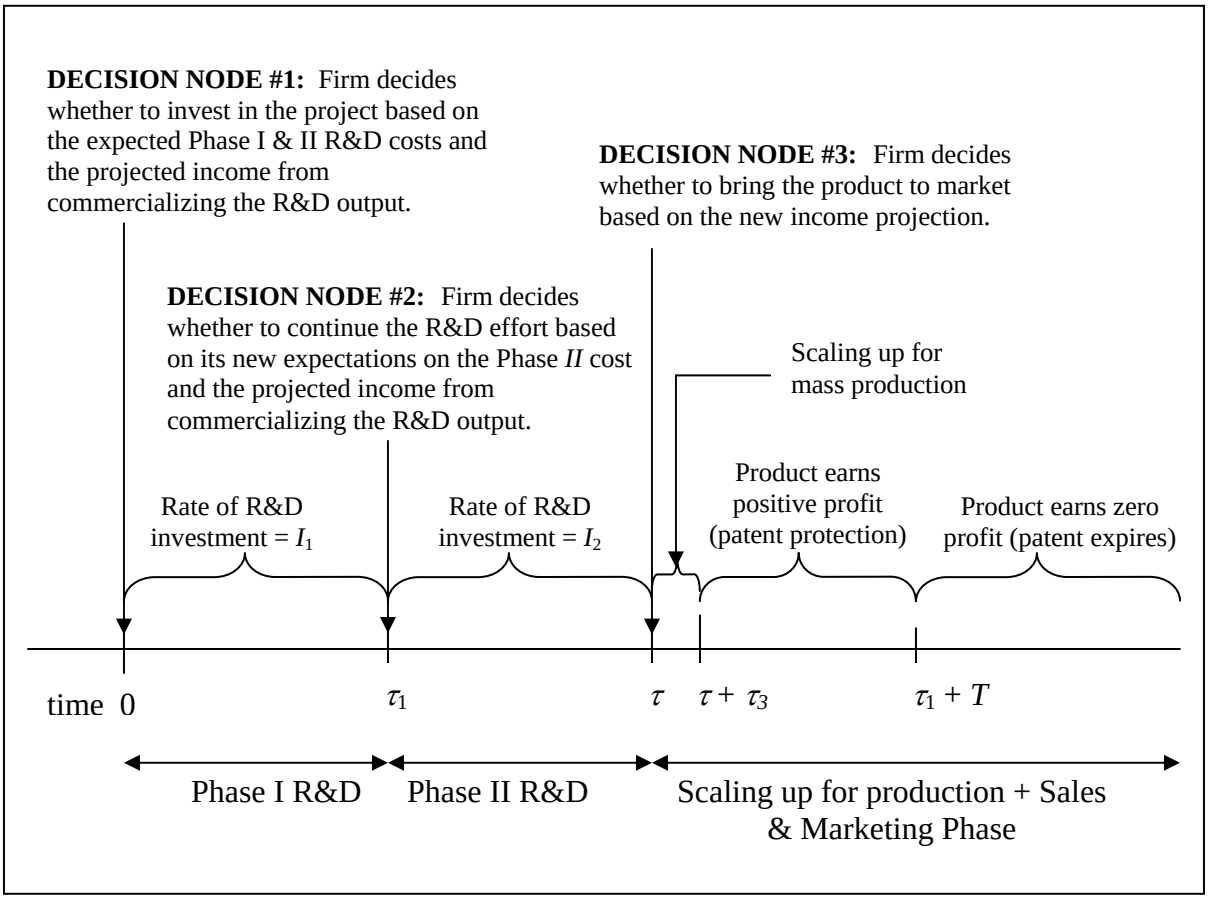

Figure 1. At time 0, the firm forms expectations on the cost to complete Phase *I* R&D, Phase *II* R&D, and the quality of the R&D output. When Phase *I* R&D is completed, the firm learns (partially) about its ability to develop the product profitably. With this knowledge, it revises its expectation on the cost to complete Phase *II* R&D and the quality of the R&D output. The decision to continue is then formed based on these new expectations. If the R&D is continued into Phase *II*, upon its completion, the firm observes the exact quality of the R&D output. Income from bringing the product to market is forecasted, and the firm makes decision to shelf or to commence production.

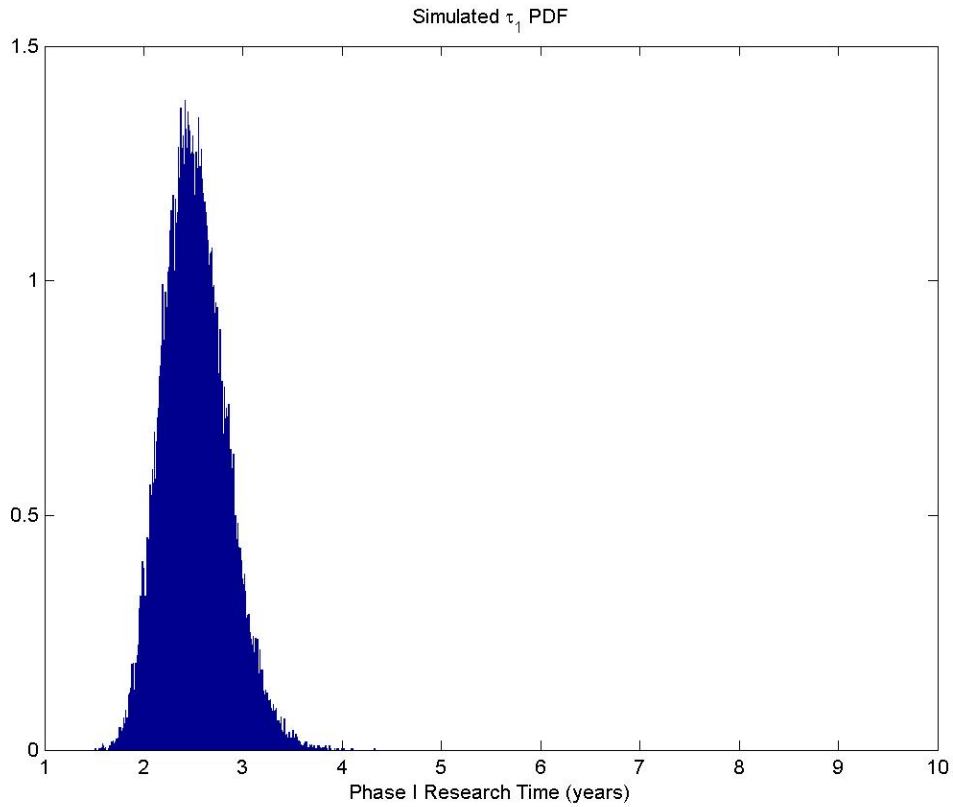

Figure 2. The simulated probability density function of the Phase *I* R&D time τ_1 is plotted here. The mean of the distribution is 2.5 years, and the standard deviation is 0.32 years. The skewness of the distribution is 0.39 (right skewed) and the excess kurtosis is 0.26 (more peaked with fatter tails than normal distribution).

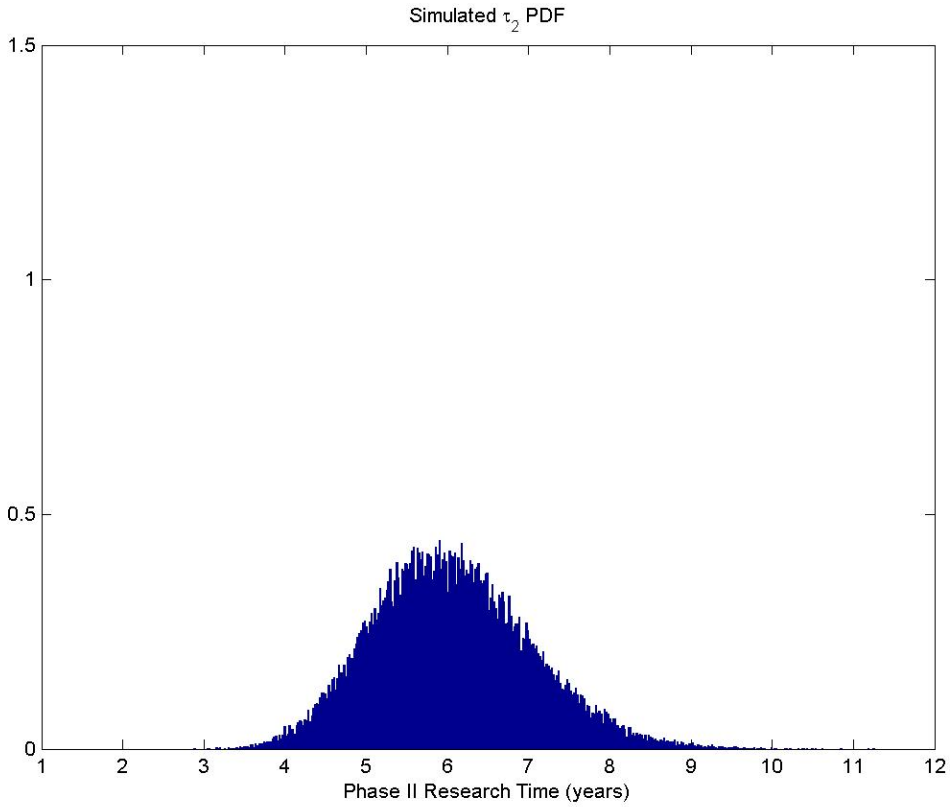

Figure 3. The simulated probability density function of the Phase *II* R&D time τ_2 is plotted here. The mean of the distribution is 6.25 years, and the standard deviation is 0.98 year. The skewness of the distribution is 0.36 (right skewed) and the excess kurtosis is 0.18 (more peaked with fatter tails than normal distribution).

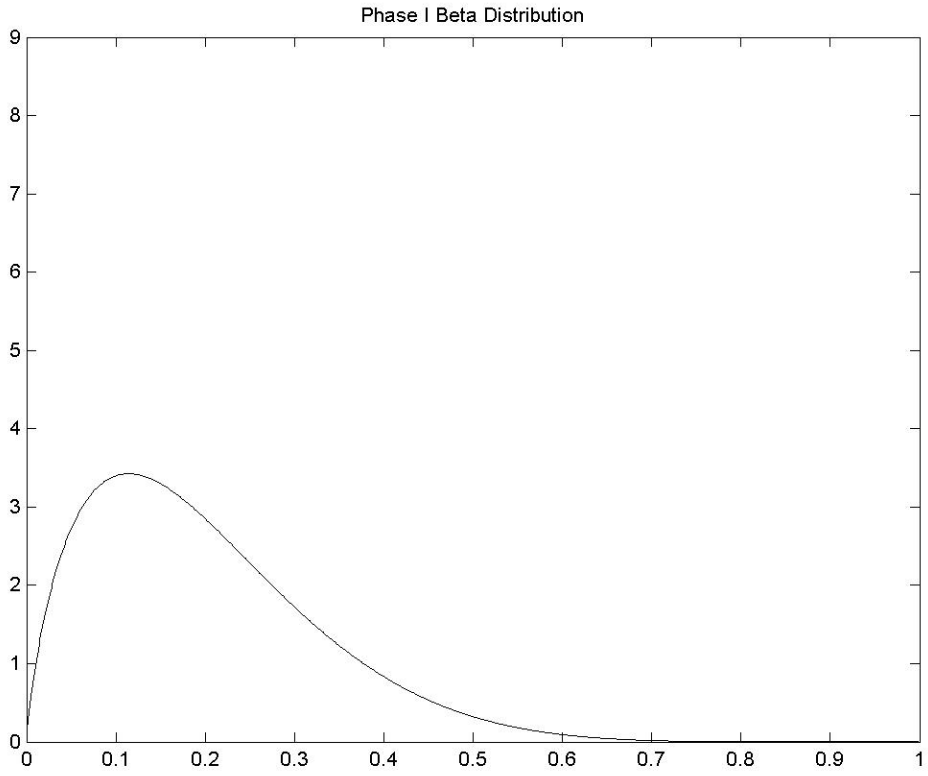

Figure 4. The time τ_1 probability density function of the expected efficacy of the vaccine, $Q(\tau_1)$, is plotted here. The spread of the distribution corresponds to how much can be learned about the efficacy of the vaccine at the conclusion of Phase *I* research. If the variance is very small, then the conditional expectation on the final vaccine efficacy at time τ_1 would not change very significantly.

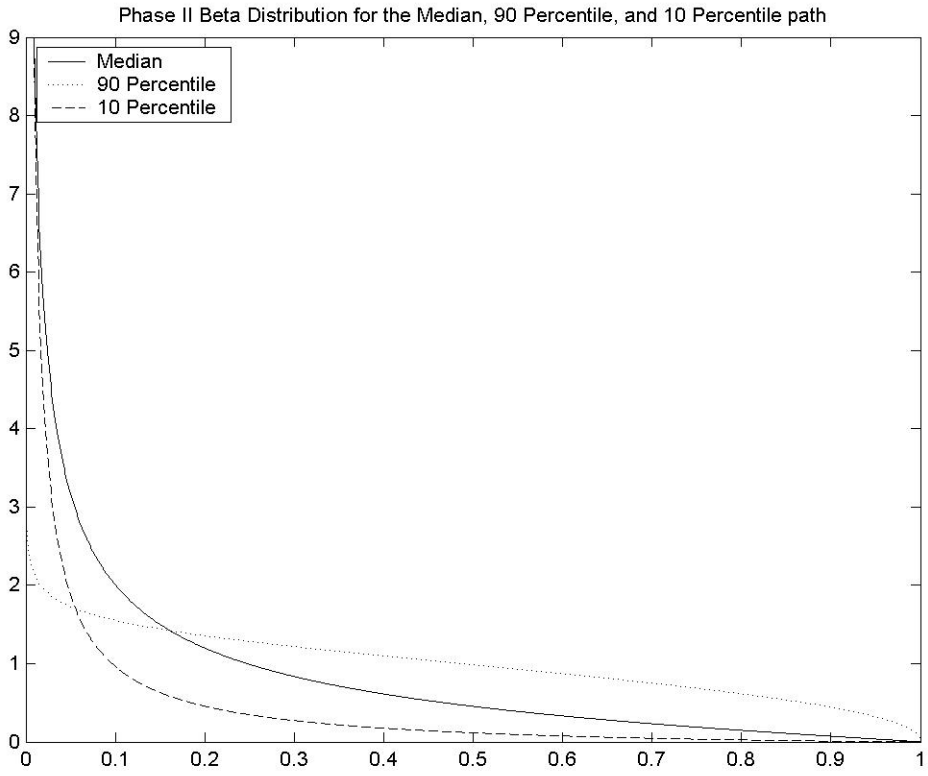

Figure 5. The time τ probability density function of the efficacy of the vaccine, $Q(\tau)$, is plotted here for the median prior expectation $Q(\tau_1)$ and the bottom 10 percentile and 90 percentile $Q(\tau_1)$. The 90 percentile $Q(\tau_1)$ naturally has a higher expected quality than the median and the bottom 10 percentile. Note that there is significant probability that the final vaccine efficacy is 0, meaning that the developed vaccine is no better than a placebo.

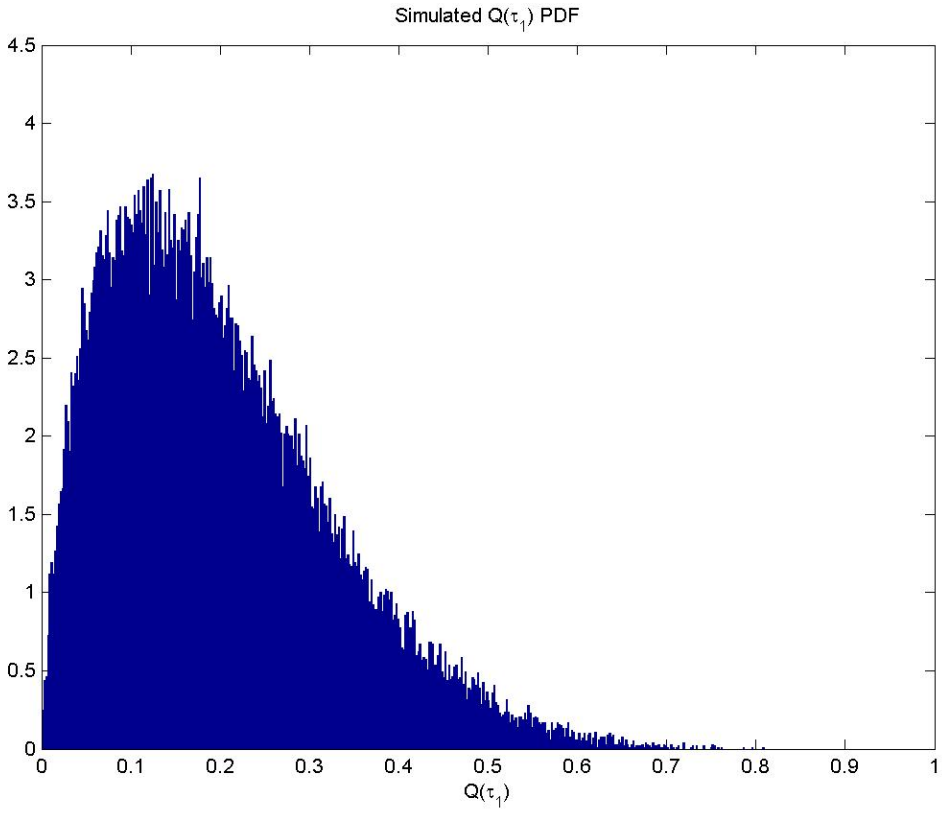

Figure 6. The simulated unconditional probability density function of the quality of the final product, $Q(\tau_1)$, is plotted here. The mean of the distribution is 0.20, and the standard deviation is 0.1264. The skewness of the distribution is 0.8560 (right skewed) and the excess kurtosis is 0.4821 (more peaked and fatter tails than normal distribution).

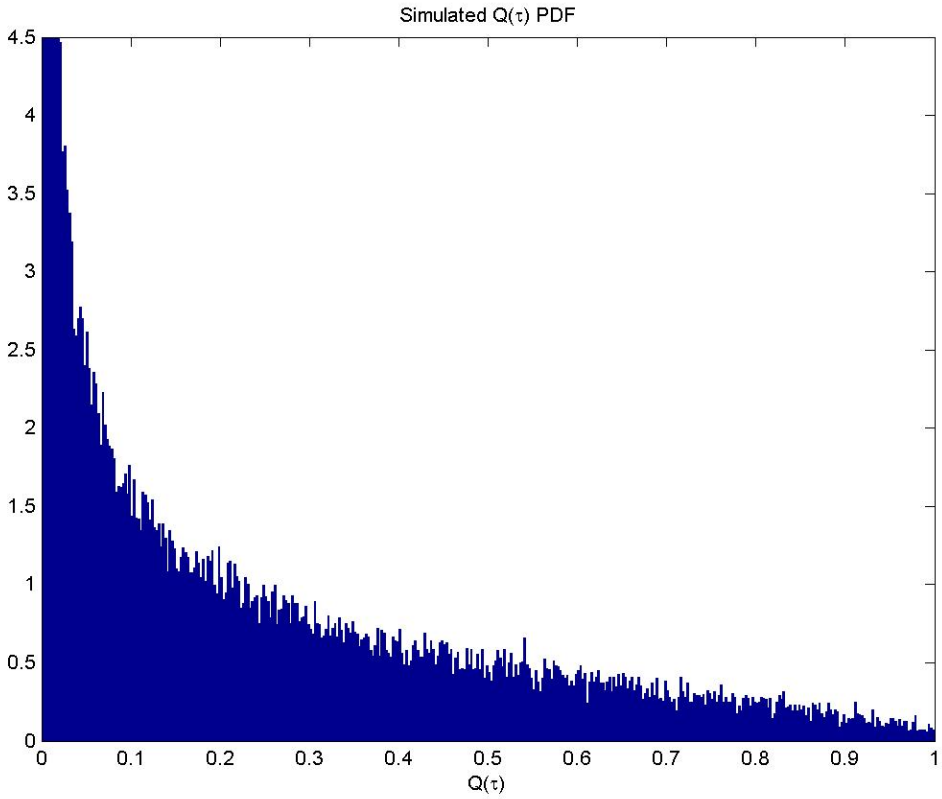

Figure 7. The simulated unconditional probability density function of the quality of the final product, $Q(\tau)$, is plotted here. The mean of the distribution is 0.2, and the standard deviation is 0.2429. The skewness of the distribution is 1.30 (right skewed) and the excess kurtosis is 0.7462 (more peaked and fatter tails than normal distribution).

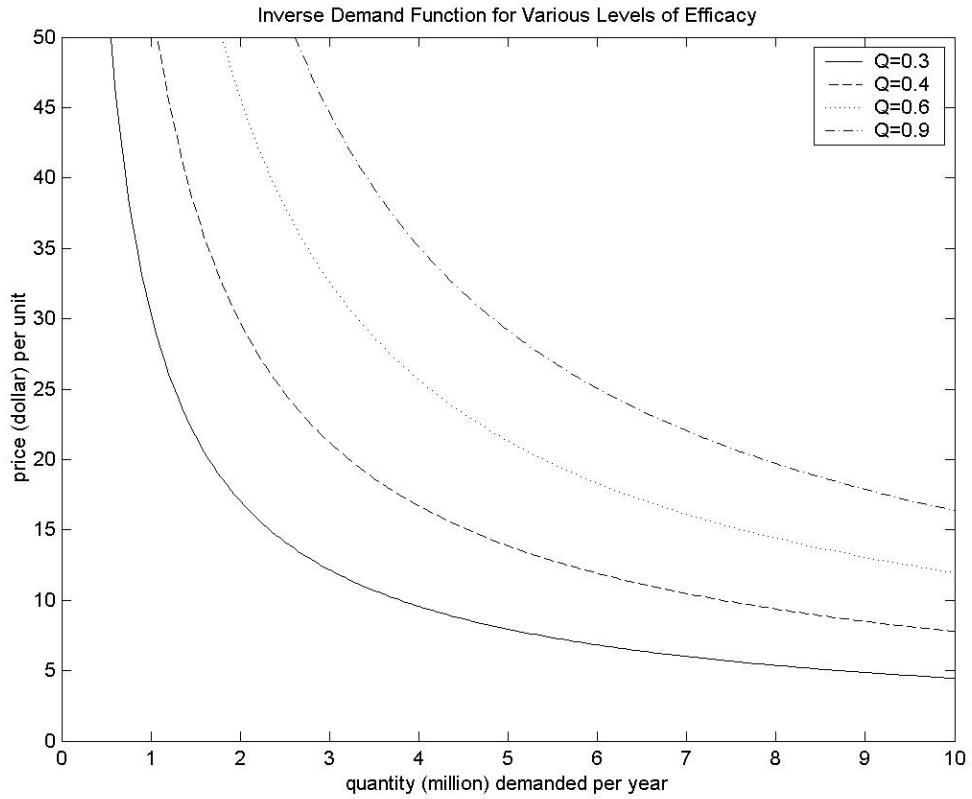

Figure 8. The inverse demand functions, $P = \alpha \cdot \max(Q - Q_{\min}, 0)^{\pi} \cdot q^{-1/\gamma}$, with α =138.7, π = 0.507, $Q_{\min}$ =0.25, and the demand elasticity γ =1.2 is plotted for four different final product qualities are plotted here. In general lower quality products have lower market clearing prices given the same quantity. In addition, note that this market is unwilling to pay significantly more for better quality products. At a quantity of 10 million units supplied, the marginal consumer is only willing to pay $3.5 additional for an increase in quality from 30% to 40%. However, he is willing to pay $4.5 additional for an increase in quality from 60% to 90%.

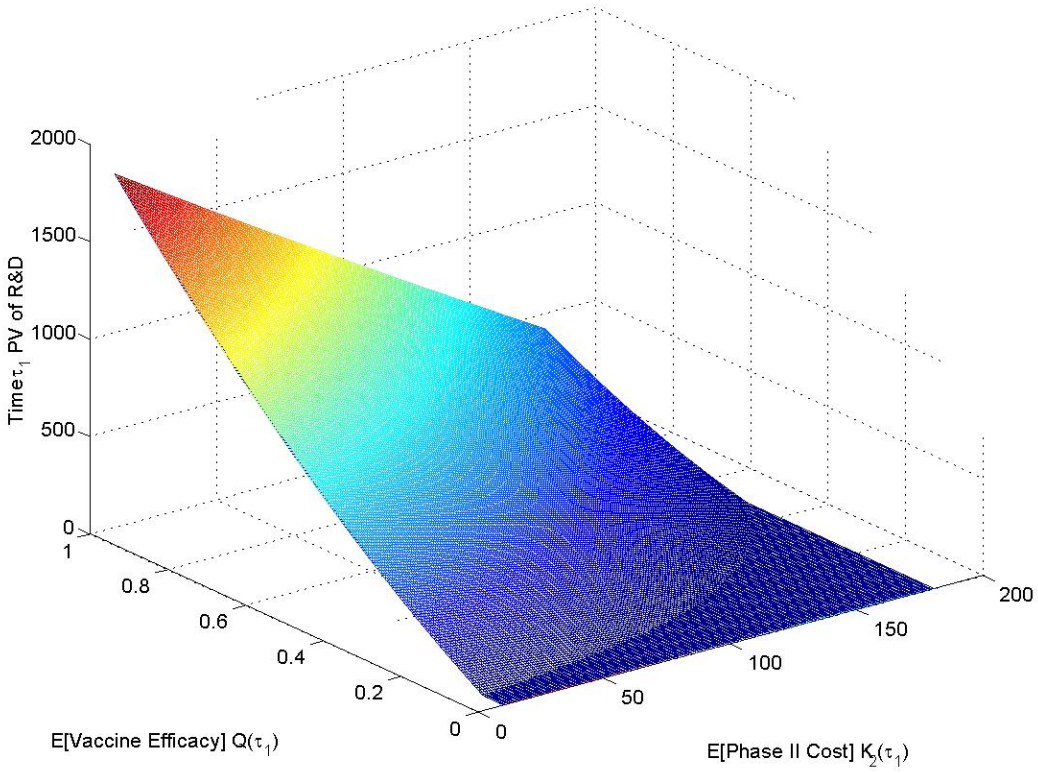

Figure 9. The pharmaceutical firm's project value at the end of the Phase *I* R&D is plotted here. Note that the project value depends on both the expected vaccine efficacy $Q(\tau_1)$ as well as the expected Phase *II* cost $K_2(\tau_1)$. Note further that $Q(\tau_1)$ and $K_2(\tau_1)$ are unconditionally negatively correlated—a higher than expected τ_1 tends to lower $Q(\tau_1)$ but increase $K_2(\tau_1)$.

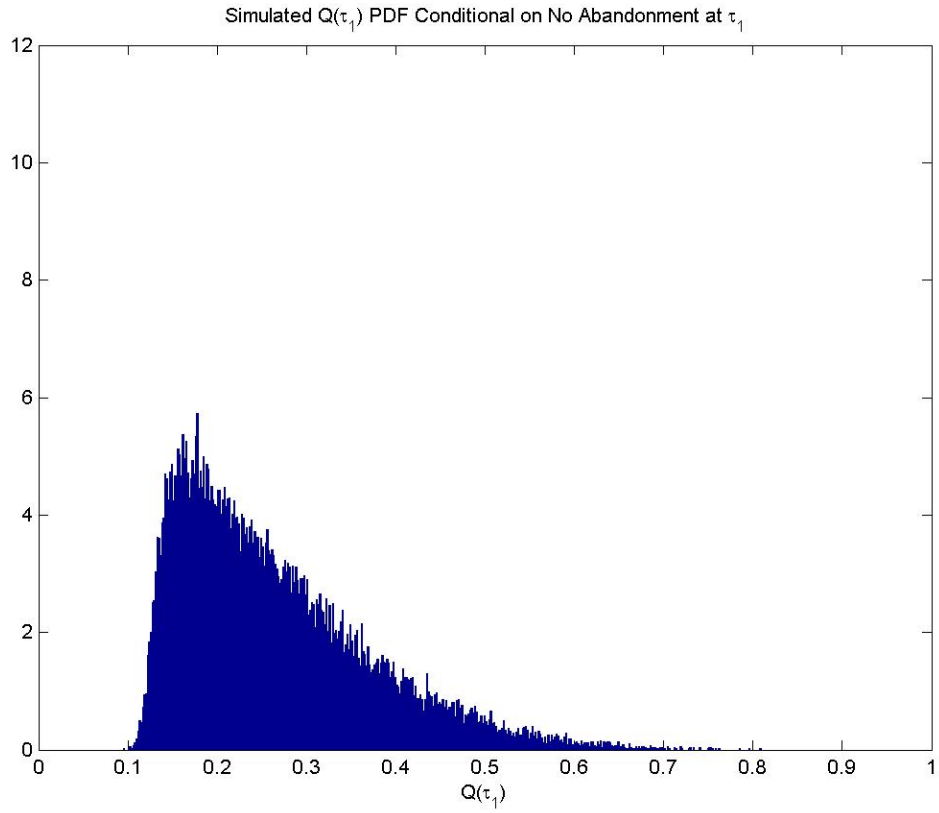

Figure 10.1. The simulated conditional (conditional on no abandonment at the end of Phase *I* R&D) probability density function of the quality of the final product, $Q(\tau_1)$, is plotted here. Recall that the minimum quality demanded by the market is 25%. However, the variance of $Q(\tau_2)$ is sufficiently large that the option value from continuing is significant. Therefore, even vaccine projects which are assessed to be very low efficacy will be continued at the end of Phase *I* R&D.

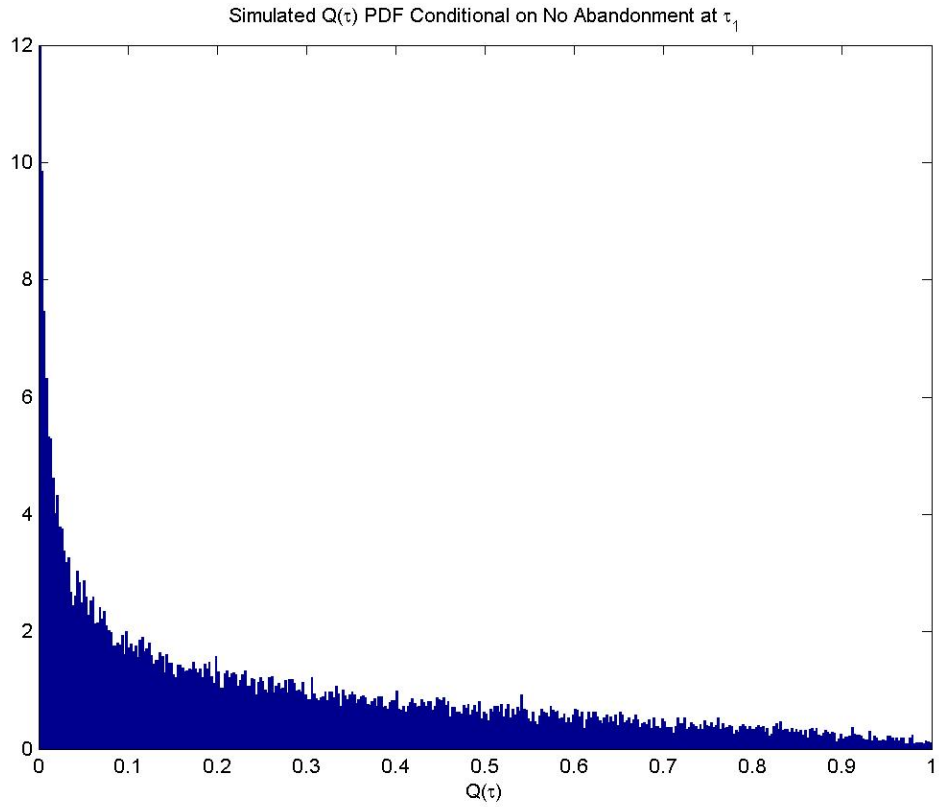

Figure 10.2. The simulated conditional (conditional on no abandonment at the end of Phase *I* R&D) probability density function of the quality of the final product, $Q(\tau)$, is plotted here. Note that there is still significant probability for a vaccine that enters Phase *II* R&D to turn out to be unmarketable (efficacy lower than 25%). Specifically, note that there is a point mass at 0% efficacy.

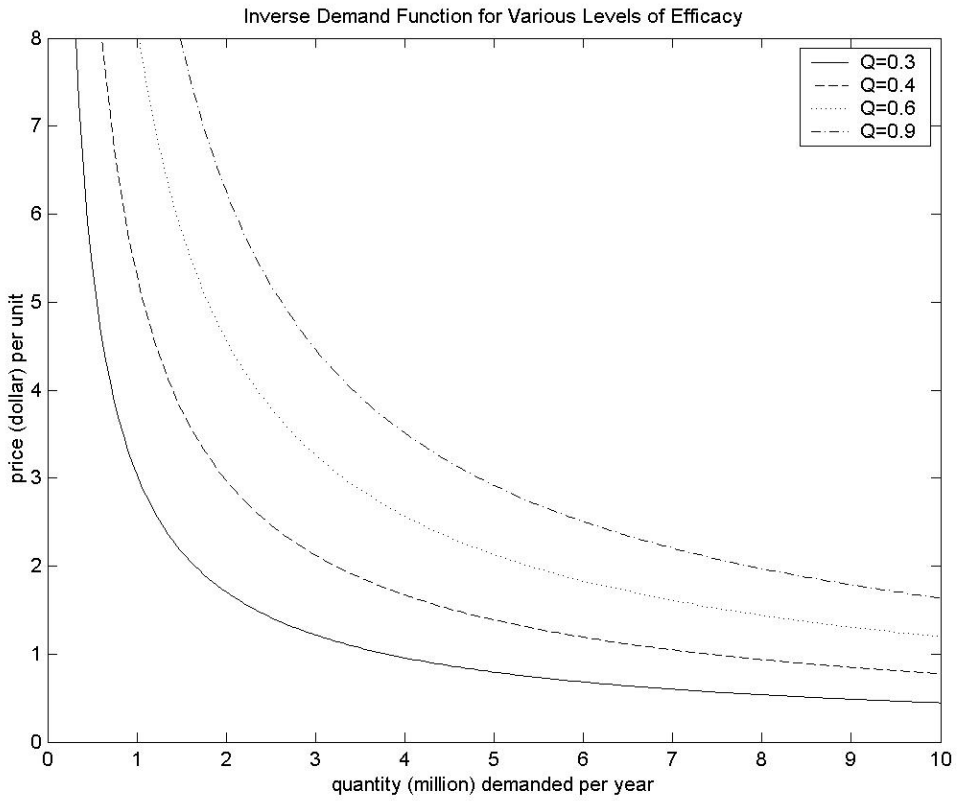

Figure 11. The inverse demand functions, $P = \alpha \cdot \max(Q - Q_{\min}, 0)^{\pi} \cdot q^{-1/\gamma}$, with α =13.87, π = 0.507, $Q_{\min}$ =0.25, and the demand elasticity γ =1.2 is plotted for four different final product qualities are plotted here. In general lower quality products have lower market clearing prices given the same quantity. In addition, note that this market is unwilling to pay significantly more for better quality products. At a quantity of 10 million units supplied, the marginal consumer is only willing to pay $0.35 additional for an increase in quality from 30% to 40%. However, he is willing to pay $0.45 additional for an increase in quality from 60% to 90%.

Table 1. Subsidy Contracts: sponsor award equal to $40 million

	Cost-sharing Plan (92.88% sponsor share)	Constant Price Purchase Commitment Plan	Variable Price Purchase Commitment Plan	Hybrid (Constant Price with 50% Cost-share)	Hybrid (Variable Price with 50% Cost-share)	Hybrid (Constant Price with 95% Cost-share)	Hybrid (Variable Price with 95% Cost-share)
Sponsor PV Cost	-$40 M	-$40 M	-$40 M	-$40 M	-$40 M	-$40 M	-$40 M
Firm's Project PV	$3.34 M	$7.72 M	$8.57 M	$6.63 M	$7.33 M	$1.53 M	$1.73 M
CPISV	-$15.31	-$2.407	-$2.455	-$2.175	-$2.206	-$1.888	-$1.896
Expected Consumer Surplus per year	$9.02 M	$9.226 M	$9.011 M	$10.32 M	$10.13 M	$12.09 M	$12.01
Expected No. of Successful Immunization per year	0.1866 M	1.187 M	1.164 M	1.313 M	1.295 M	1.513 M	1.507 M
Expected No. of Immunizations per year	0.3007 M	1.847 M	1.8 M	2.064 M	2.026 M	2.419 M	2.402 M
Average Quantity Supplied per year (if successful)	1.167 M	10.73 M	11.07M	10.51 M	10.83 M	10.17 M	10.41 M
Probability of Successful Vaccine Development	25.76%	17.19%	16.27%	19.65%	18.70%	23.78%	23.07%
Average Vaccine Efficacy (if successful)	52.78%	55.60%	56.72%	54.70%	55.78%	53.37%	54.14%
Probability of Vaccine Reaching Phase *II*	60.74%	31.57%	30.57%	38.13%	37.15%	52.44%	52.09%
Phase *II* Efficacy Cutoff	18.86%	30.18%	29.22%	27.36%	27.47%	21.88%	22.95%
Average Price Charged to Sponsor (if successful)	$0.00	$5.38	$5.492	$3.5	$3.578	$1.337	$1.356
Average Price Charged to Target Population (if successful)	$6.00	$1.00	$1.00	$1.00	$1.00	$1.00	$1.00

Table 2. Subsidy Contracts: sponsor award equal to $60 million

	Cost-sharing Plan (97.96% sponsor share)	Constant Price Purchase Commitment Plan	Variable Price Purchase Commitment Plan	Hybrid (Constant Price with 50% Cost-share)	Hybrid (Variable Price with 50% Cost-share)	Hybrid (Constant Price with 95% Cost-share)	Hybrid (Variable Price with 95% Cost-share)
Sponsor PV Cost	-60 M	-60 M	-60 M	-60 M	-60 M	-60 M	-60 M
Firm's Project PV	$6.40 M	$18.24 M	$19.43 M	$15.78 M	$16.86 M	$5.73 M	$6.19 M
CPISV	-$20.54	-$3.082	-$3.14	-$2.82	-$2.858	-$2.471	-$2.479
Expected Consumer Surplus per year	10.24 M	11 M	10.75 M	12.15 M	$11.95 M	$14.12 M	$14.07 M
Expected No. of Successful Immunization per year	0.2086 M	1.391 M	1.365 M	1.52 M	1.5 M	1.734 M	1.729 M
Expected No. of Immunizations per year	0.3414 M	2.2 M	2.15 M	2.431 M	2.39 M	2.825 M	2.813 M
Average Quantity Supplied per year (if successful)	1.127 M	10.38 M	10.7 M	10.16 M	10.42 M	9.781 M	9.917 M
Probability of Successful Vaccine Development	30.29%	21.20%	20.10%	23.92%	22.93%	28.88%	28.37%
Average Vaccine Efficacy (if successful)	51.50%	54.19%	55.22%	53.32%	54.17%	51.88%	52.29%
Probability of Vaccine Reaching Phase *II*	89.89%	43.03%	41.56%	53.05%	51.47%	77.10%	76.33%
Phase *II* Efficacy Cutoff	4.84%	25.39%	24.72%	21.65%	22.20%	12.47%	12.61%
Average Price Charged to Sponsor (if successful)	$0.00	$6.528	$6.659	$4.414	$4.514	$1.678	$1.714
Average Price Charged to Target Population (if successful)	$6.00	$1.00	$1.00	$1.00	$1.00	$1.00	$1.00

Table 3. Subsidy Contracts: sponsor award equal to $80 million

	Constant Price Purchase Commitment Plan	Variable Price Purchase Commitment Plan	Hybrid (Constant Price with 50% Cost-share)	Hybrid (Variable Price with 50% Cost-share)	Hybrid (Constant Price with 95% Cost-share)	Hybrid (Variable Price with 95% Cost-share)	Hybrid (Constant Price with 100% Cost-share)	Hybrid (Variable Price with 100% Cost-share)
Sponsor PV Cost	-80 M	-80 M	-80 M	-80 M	-80 M	-80 M	-80 M	-80 M
Firm's Project PV	$30.41 M	$31.94 M	$27.54 M	$28.76 M	$16.60 M	$16.94 M	$12.69 M	$12.49 M
CPISV	-$3.779	-$3.843	-$3.498	-$3.541	-$3.188	-$3.192	-$3.163	-$3.163
Expected Consumer Surplus per year	$12.09 M	$11.83 M	$13.19 M	12.99 M	14.67 M	$14.65 M	$14.8 M	14.8 M
Expected No. of Successful Immunization per year	1.512 M	1.487 M	1.634	1.614 M	1.792 M	1.79 M	1.806 M	1.806 M
Expected No. of Immunizations per year	2.417 M	2.365 M	2.639 M	2.599 M	2.934 M	2.929 M	2.961 M	2.961 M
Average Quantity Supplied per year (if successful)	10.17 M	10.46 M	9.966M	10.18 M	9.678 M	9.745 M	9.648 M	9.648 M
Probability of Successful Vaccine Development	23.76%	22.61%	26.48%	25.52%	30.32%	30.06%	30.69%	30.69%
Average Vaccine Efficacy (if successful)	53.38%	52.32%	52.57%	53.26%	51.49%	51.69%	51.39%	51.39%
Probability of Vaccine Reaching Phase *II*	52.38%	50.40%	63.93%	62.11%	90.35%	89.75%	100%	100%
Phase *II* Efficacy Cutoff	21.94%	22.56%	17.70%	18.54%	4.81%	4.85%	0%	0%
Average Price Charged to Sponsor (if successful)	$7.72	$7.867	$5.428	$5.541	$2.495	$2.521	$1.933	$1.922
Average Price Charged to Target Population (if successful)	$1.00	$1.00	$1.00	$1.00	$1.00	$1.00	$1.00	$1.00

Table 4. Comparison of Subsidy Contracts: increases in R&D outputs when Sponsorship increases from $40 to $60 million.

	Co-payment Plan	Constant Price Purchase Commitment Plan	Variable Price Purchase Commitment Plan	Hybrid (Constant Price w/ 50% Co-payment)	Hybrid (Variable Price w/ 50% Co-payment)	Hybrid (Constant Price w/ 95% Co-payment)	Hybrid (Variable Price w/ 95% Co-payment)
Increase in Sponsor PV Cost	20 M	20 M	20 M	20 M	20 M	20 M	20 M
Increase in Firm's Project PV	$3.06 M	$10.52 M	$10.86 M	$9.15 M	$9.52 M	$4.26 M	$4.46 M
Increase in *CPISV*	-$5.23	-$0.675	-$0.705	-$0.645	-$0.652	-$0.583	-$0.583
Increase in Expected Consumer Surplus per year	1.22 M	1.774 M	1.639 M	1.83 M	$1.82 M	$2.03 M	$2.06 M
Increase in Expected No. of Successful Immunization per year	0.0220 M	0.2041 M	0.201 M	0.207 M	0.205 M	0.221 M	0.222 M
Increase in Probability of Successful Vaccine Development	4.53%	4.01%	3.83%	4.27%	4.23%	5.10%	5.30%
Increase in Average Vaccine Efficacy (if successful)	-1.28%	-1.41%	-1.50%	-1.38%	-1.61%	-1.49%	-1.85%