GENERAL RESEARCH

Real Options Based Analysis of Optimal Pharmaceutical Research and Development Portfolios

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This paper presents a stochastic optimization model (OptFolio) of pharmaceutical research and development (R&D) portfolio management using a real options approach for making optimal project selection decisions. A method is developed to model new product development as a series of continuation/abandonment options, deciding at each stage in pharmaceutical R&D whether to proceed further or stop development. Multistage stochastic programming is utilized to model the flexibility afforded by the abandonment option. The resulting mixed-integer linear programming formulation is applied to a case study involving the selection of the optimal product portfolio from a set of 20 candidate drugs at different stages in the developmental pipeline over a planning horizon of 6 years. This proposed framework provides a road map for future decisions by tracking the decision of abandonment over time and calculating the minimum market value above which development is continued under changing resource constraints and estimated market and technical uncertainty. Results indicate that the riskier the project is, the larger the minimum market value required for continuing testing in future stages. Consequently, the value of the abandonment option increases with rising market uncertainty or decreased probability of clinical trial success. In addition, a framework for incorporating additional managerial choices to the OptFolio model is discussed.

1. Introduction and Background

The new product pipelines of pharmaceutical companies have largely fueled the current growth in the pharmaceutical sector. These product pipelines are in a constant state of flux as new drug leads are identified and products reach the market or are discontinued during development because of safety/efficacy concerns. As a result, the optimal management of the new product pipeline has emerged at the forefront of all strategic planning initiatives of a pharmaceutical company.

Every drug in a pharmaceutical pipeline undergoes a well-defined developmental process comprised of a number of distinct, sequential stages (see Figure 1). Following the drug discovery process in which the drug lead is identified, optimized, and tested in animals, the drug candidate is taken through three phases of clinical testing. Phase I studies are aimed at determining the toxicity levels and are usually carried out in a small population of subjects. Following the successful completion of phase I trials, phase II trials are undertaken in which the efficacy of the drug is determined. Finally, large-scale phase III trials are conducted to establish the potential effectiveness of the drug. This is achieved by comparing the therapeutic potential of the drug with an existing treatment. Once sufficient evidence regarding the safety and efficacy of the drug is collected, a new drug application (NDA) is filed with the Food and Drug Administration (FDA). Approval of the NDA culminates in the commercialization and large-scale production of the drug. Figure 1 summarizes the life cycle of a drug from preclinical development through FDA filing and product launch.[1] A drug may spend 6−10 years in the developmental process and cost, on average, $300 million to bring to market.[2]

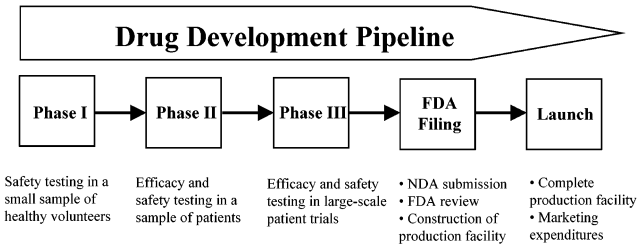

Figure 1. Pharmaceutical pipeline from clinical trials through launch.

The financial value of pharmaceutical drug developmental projects is difficult to assess because they are subject to considerable uncertainty. Pharmaceutical research and development (R&D) projects face both technological and market/demand uncertainties during the drug developmental process. Technological uncertainties stem from the inability of researchers to guarantee a priori safe and effective products that can pass clinical trial hurdles and gain FDA approval. Unforeseen side effects or lack of efficacy in a developing drug may prematurely terminate development in any one of

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the three clinical phases. For every approved drug, roughly 10 000 molecules have started development and have been abandoned along the way.[2] The chances of failure are significant even at the FDA approval stage in light of ever-changing and tightening regulatory restrictions. Market uncertainties concern the volatility of the future value of a product as forecasted during R&D, which may involve market reduction, entrance of branded competitor drugs, or an economic downturn. Incomplete information regarding the cost of producing the drug, the eventual pricing structure, and the captured market share translates into significant uncertainty in the drug's market value. Therefore, market side uncertainty implies that a drug's technical success is no guarantee of commercial revenues. In fact, very few commercial drugs reach the status of a "blockbuster", which has peak sales that are roughly 20 times higher than the peak sales of an average drug.[3]

During the course of pharmaceutical R&D planning, managerial flexibility is available to shape the uncertainty of the drug developmental process. If an initial investment in pharmaceutical research is successful, the company has the option of proceeding with each of the three stages of clinical testing followed by an application to gain FDA approval. At any point in the developmental process, the company reserves the right to abandon the project because of changing market conditions or internal budgetary limitations. Thus, the risk profile of a project can be altered considerably by controlling downside risk (e.g., abandoning the project in response to adverse market conditions) and increasing upside potential (e.g., continuing development under favorable market conditions).

In the context of managerial flexibility, determining the priority of potential investments is vital in pharmaceutical drug developmental planning. Traditionally, capital budgeting issues are resolved by discounted cash-flow techniques using the classic net present value (NPV) rule for choosing the best investment opportunity.[4] One obvious shortcoming of the NPV approach is that it assumes that all future cash flows are static, neglecting the real-world choices to stop investing in the project or change course because of market circumstances. The NPV analysis can be extended to account for uncertainty and managerial flexibility through the decision tree analysis (DTA) framework, which maps out all alternative future actions contingent on all possible future states of nature.[5] Subsequently, NPV estimates, in the face of uncertainty, can be obtained by working backward through the decision tree and applying the standard discounted cash flow (DCF) methodology. The key challenge in applying the DCF and DTA techniques lies in the determination of the appropriate discount rate used for translating future cash flows into their present value equivalents. In principle, the appropriate discount rate is determined by the rate of return offered in the financial market by securities that have the same risk profile as the project under consideration. Because the risk profile of a project can be altered considerably with managerial flexibility by controlling downside risk and increasing upside potential, use of a constant discount rate could clearly misevaluate the project. The only way the DCF and DTA techniques can deal with this risk effect is through ad hoc adjustment of the discount rate. In fact, Myers and Howe[1] have illustrated that the weight-adjusted cost of capital of pharmaceutical programs changes dramatically over the course of the project.

In view of this limitation of the DCF and DTA methods, a more appropriate technique for capital budgeting is real options valuation (ROV) or contingent claims analysis.[6] This methodology is based on the option pricing principles developed by Black and Scholes[7] in finance literature. To understand the impact of project volatility, an analogue of the Black−Scholes options pricing formula has been proposed to capture the value of managerial flexibility.[8] Myers[9] and Dixit and Pindyck[4] recognized that traditional DCF methods inadequately value R&D projects because the total worth of R&D investments includes the option value of future opportunities to alter course as more information becomes available. Consequently, they classified R&D investment opportunities as *real options* best captured within the options analysis framework. Faulkner[10] and Trigeorgis[11] have provided excellent surveys on the use of the options approach to project valuation. Morris et al.[12] discussed an R&D example in which the NPV is the same for all projects, but there are varying levels of risk and uncertainty. Within a real options framework, they showed that a riskier project can be more valuable because it has a larger upside while still maintaining a fixed, staged level of potential loss. Recently, a number of applications of real options pricing to the valuation of individual pharmaceutical projects have been discussed.[13,14]

Within the framework of a pharmaceutical company's pipeline, valuing one drug at a time is not sufficient. Instead, R&D managers must consider the entire portfolio in the face of market and technological uncertainty and resource constraints. Recognizing this, we address the pharmaceutical pipeline management problem by viewing it as a multistage stochastic portfolio optimization problem embedded within the ROV framework:

Given a set of candidate drugs in various stages of development, estimates of the probability of clinical success, duration, and investment required for the remaining stages and forecasts for the future market values determine the optimal drug developmental portfolio that maximizes ROV.

A stochastic programming approach giving rise to a mixed-integer linear programming (MILP) formulation is introduced for selecting the optimal product portfolio from a set of candidate drugs at different stages in the developmental pipeline and subject to varying levels of market and technical uncertainty over the desired planning horizon. This stochastic framework provides a road map for future decisions by tracking the decision of abandonment over time and calculating the minimum market value above which development is continued under changing resource constraints and estimated market and technical probabilities.

Next, a brief literature review of pharmaceutical planning is presented in section 2, while section 3 introduces the theory behind financial options using the Black−Scholes equation, followed by a discussion on how this approach is extended to real options evaluation. The problem of valuing individual candidate drugs is then expanded to formulate an optimal drug portfolio in view of managerial flexibility. A stochastic programming-based algorithm (OptFolio) is developed in section 4 to value the uncertainty of candidate drugs and handle portfolio selection. A stochastic programming-based algorithm (OptFolio) is developed in Section 4 to value

the uncertainty of candidate drugs and handle portfolio selection. In addition, a framework for incorporating additional managerial choices in the model to enhance the flexibility of the decision structure is discussed. In Section 5, the case study of selecting optimal drug portfolios is explored and real options valuation is applied to the problem. Finally, section 6 provides concluding remarks on the results of the OptFolio portfolio valuation and selection technique and highlights opportunities to expand the work.

2. Product Planning Literature

Capacity management and planning under uncertainty have been studied extensively in the process systems literature. Ierapetritou and Pistikopoulos,[15] Subrahmanyam et al.,[16] and Clay and Grossmann[17] explored the allocation of resources in the face of variable product demand. Gupta and Maranas[18] addressed multiperiod, multisite supply chain integration under demand uncertainty. Only recently, however, has stochastic optimization been applied to the problem of pharmaceutical planning and capacity management.[19,20] In the pharmaceutical industry, a firm needs to consider its entire product portfolio in the context of market and technological uncertainty, budgetary constraints, and the desire to balance the portfolio across many drug-type classifications. Traditionally, portfolio selection decisions were based on R&D costs and the estimated value of these products for several forecasted scenarios. To date, many R&D managers are displeased with existing portfolio selection models.[21] In a benchmarking study of R&D decision making "best practices", Matheson et al.[22] report that a majority of R&D executives mention the need for better portfolio selection methods as their most critical requirement for improving R&D performance.

Existing work on new product development in the process systems engineering community has focused on the technical outcome of R&D stages instead of including a more holistic view of market risk. Schmidt and Grossmann[23] discussed an elegant optimization model for scheduling tasks in new product development, analogous to the screening process used to discover new products in the agricultural, chemical, and pharmaceutical industries. They developed a MILP to find the nonsequential testing schedule that maximizes the expected NPV of the new products. While the model incorporated some of the technical uncertainty in the R&D process, it did not provide a valuation method for selecting what products should begin this testing process. In subsequent papers,[24,25] they addressed the resource-constrained scheduling of testing tasks and integrated an approach to account for product selection and capacity investments. Papageorgiou et al.[26] developed a MILP model of a pharmaceutical company's supply chain given deterministic demand. They examined capacity management of a product portfolio through the consideration of R&D costs, demand forecasts, manufacturing costs, and resource allocation. In a follow-up paper,[27] they formulated an optimization model for capacity planning and capital investment strategy subject to the uncertainty of clinical trials for a given product portfolio. In both of these cases, a traditional NPV analysis was used as the financial metric and the focus was on capacity planning decisions that occur at the onset of production as opposed to project valuation and selection. While the stochastic model contained several possibilities for future demand, it did not take into account the existence of financial markets for estimating a project's risk.

The key idea that distinguishes the proposed ROV approach from existing work is the explicit tracking of the uncertainty in the market value of the drug through market-traded securities. The basis of ROV is that a company can use a portfolio consisting of cash and market-traded securities whose volatility is correlated with the market value of the R&D project in question to make internal planning decisions. Using the arbitrage-free principle and the concept of a replicating portfolio of securities, this technique allows for strategic decision making by utilizing hedging opportunities present in the financial markets. Intuitively, the value of a real option to continue/abandon new product development is higher for more volatile projects if the uncertainty can be resolved before decisions are made and costs are incurred. Although the risks of research projects are typically project-specific, a trend toward the securitization and development of nontraditional markets, such as telecommunications bandwidth trading, suggests that this is a viable strategy as "what is private risk today may well be securitized in the future".[28] For example, suppose a pharmaceutical company is developing a cancer drug. Schwartz and Moon[29] argued that the market value of this drug can be approximately tracked with a portfolio of small biotechnology firms specializing in developing cancer treatments, because frequently these firms have only one product in revenue. Ultimately, the viability of a tracking portfolio for pharmaceutical products in development is decided in conjunction with empirical data as more markets are completed and the distance between private risks and market-priced risks decreases over time.[28]

3. Financial Options Valuation

An option is the right, but not the obligation, to buy/sell an asset (e.g., security) at a future date at a predetermined price. There are two basic types of options: *call* (right to buy) and *put* (right to sell). The price in the option contract is known as the *exercise price* or the *strike price*; the date in the contract is known as the *expiration date* or *exercise date*. American options can be exercised at any time up to the expiration date, while European options can be exercised only on the expiration date.[30] The payoffs for the call and put options are given by

$$\text{net payoff (call)} = \max(S_T - K, 0) - C \qquad (1)$$

$$\text{net payoff (put)} = \max(K - S_T, 0) - P \qquad (2)$$

where S_T is the price of the underlying security on the expiration date T, K is the strike price, and C/P are the call/put premiums paid to obtain the corresponding options. If $S_T - K \geq 0$ for a call option, then it is exercised by paying the strike price K and receiving the underlying security in return. If $S_T - K < 0$, then the call option is allowed to expire because the holder is under no obligation to buy the security.

The sequential nature of investments in pharmaceutical R&D is analogous to options evaluation. Typically, a drug is commercialized after 8−10 years of screenings, toxicology studies, and clinical testing phases so these R&D investments are not undertaken for immediate returns but rather for the future opportunities of

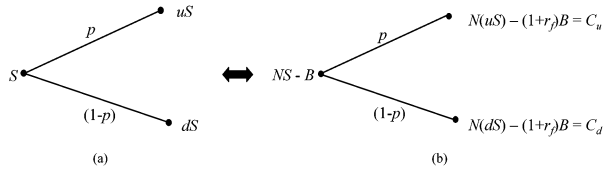

Figure 2. Binomial pricing tree for stock price (a) and replicating portfolio (b).

commercialization. The initial investment decision to begin phase I clinical trials is undertaken with an expectation of future cash flows. However, future investments are only made if preceding R&D is deemed promising. Ultimately, the drug is commercialized if it is technologically successful (gains FDA approval), has promising market potential, and fits the overall strategy of the company. Each sequential R&D investment is analogous to a call option involving a future decision to invest in further development or commercialize when the R&D outcome is successful. At any point in the development, the drug can be abandoned so that only the sunken investment is lost. On the basis of this comparison, Herath and Park[31] argued that an R&D investment can be viewed as the cost of a real option that is exercised only if the R&D stage is successful. The investment cost of the current stage of R&D development is the call option premium C, the investment cost of the subsequent stages of R&D followed by product launch is the exercise price K, and the present value of the future cash flows from product launch is the asset value S_T.

3.1. Arbitrage-Free Principle and the Binomial Pricing Model. The option pricing problem involves determination of the option premium given the uncertainty in the value of the underlying security, the strike price, and the time to expiration. To facilitate the evaluation of the option premium, Black and Scholes[7] proposed the key idea of *arbitrage-free markets* or the *law of one price*. This principle states that all securities having the same risk/return profiles should be identically priced so that there are no arbitrage opportunities. An arbitrage opportunity corresponds to an opportunity of making a risk-free profit. Black and Scholes[7] analyzed the option pricing problem in a continuous-time framework by assuming that the underlying stock price follows a geometric Brownian motion. The geometric Brownian motion assumption corresponds to assuming a log-normal distribution for the stock price with the additional feature that the standard deviation of the logarithm of the stock price is proportional to the square root of the time horizon.[30] Thus, the level of uncertainty, as captured by the standard deviation, increases with the length of the future time horizon considered. A simpler, discrete time analysis, which in the limit of very small time steps yields the continuous-time results obtained by Black−Scholes, was proposed by Cox et al.[8] This approach, known as the binomial pricing approach, is adopted in this work and is briefly discussed next. The key assumption on which this methodology is based is that the stock price follows a multiplicative binomial process as shown in Figure 2. Thus, as Figure 2a demonstrates, if the current stock price is S, then the stock price at the end of the period will be either uS ($u \geq 1$) with probability p or dS ($d \leq 1$) with probability $1 - p$. The existence of a risk-free security is also assumed with the corresponding risk-free rate of return given by r_f. In a real market setting, the risk-free asset would correspond to the Treasury Bills issued by the U.S. government. Assuming that the current value of the call option on the security is C, its value after one period would be given by either C_u or C_d.

Subsequently, consider a portfolio that is formed by (i) buying N shares of the underlying security at the current price of $\$S$ per share and (ii) borrowing $\$B$ at the risk-free rate (borrowing at the risk-free rate corresponds to taking a short position on the risk-free asset). The "out-of-pocket" cost for constructing such a portfolio is $NS - B$. At the end of the period, the worth of this portfolio is as shown in Figure 2b, where the value of the security follows a binomial process and the $(1 + r_f)B$ term corresponds to repayment of the $\$B$ borrowed initially with interest. Next, suppose that the above portfolio is constructed such that the payoff of the portfolio exactly matches the payoff of the call option, that is,

$$N(uS) - (1 + r_f)B = C_u \tag{3}$$

$$N(dS) - (1 + r_f)B = C_d \tag{4}$$

These two equations are solved for the two variables N and B to yield

$$N = \frac{C_u - C_d}{uS - dS} \tag{5}$$

$$B = \frac{1}{1 + r_f}\left(\frac{dC_u - uC_d}{u - d}\right) \tag{6}$$

On the basis of expressions for N and B, the current value of the replicating portfolio is calculated as

$$NS - B = \frac{1}{R}\left[\left(\frac{R - d}{u - d}\right)C_u + \left(\frac{u - R}{u - d}\right)C_d\right] \tag{7}$$

where $R = 1 + r_f$.

Now, because the replicating portfolio's payoff is (by construction) exactly the same as that of the call option, its current value must equal the value of the call option to avoid any arbitrage opportunities. Therefore,

$$C = NS - B = \frac{1}{R}[qC_u + (1 - q)C_d] \tag{8}$$

where

$$q = \frac{R - d}{u - d} = \frac{1 + r_f - d}{u - d} \tag{9}$$

is known as the *risk neutral* probability. The value of the call option is thus obtained by discounting the expected value of the option with respect to the risk neutral probability q (not the actual probability p) and using the risk-free rate r_f (not the actual discount rate) as the appropriate discount factor. From a risk management perspective, the key feature of an option is its asymmetrical payoff. Because the contract does not imply any obligation to buy the underlying product, the holder of the contract profits from favorable price changes while being protected from adverse ones. In return for this downside protection, the option holder has to pay a premium to the option-issuing authority. Buying an option is similar to purchasing insurance, in which the "insured" pays an insurance premium to avoid losses. This central idea of options pricing can be applied to the valuation of *real options* as discussed next.

3.2. ROV Based on the Quadranomial Approach. The *ROV* framework is obtained by extending the option pricing framework to account for real assets. This requires generalization of the definition of an option as a financial vehicle that allows the exchange of one asset, whose value evolves stochastically over time, for another.[4] In a financial (call) option setting, the stock value evolves stochastically over time and the holder of the option can exchange the exercise price for the underlying stock. In the same spirit, the flexibility offered in the staged investment in the development of a new drug can also be interpreted as an option by recognizing that (i) the future cash flows generated by the drug once it is commercialized evolve stochastically over time and (ii) management has the flexibility of (a) continuing with the development, (b) abandoning the project, (c) attempting to accelerate the clinical testing, or (d) conducting additional tests to expand the possible market of the drug as information becomes available. Consequently, a one-to-one correspondence can be established between the option pricing problem and the flexibility valuation problem, implying that the tools utilized to address the former could be used for addressing the later. Using real options, we postulate that a pharmaceutical company's individual project could be traded as a security (instead of trading stock in the company as a whole) and look to the external financial markets to estimate the project's payoffs in different states of nature. The arbitrage-free principle provides a framework for evaluating the "fair" value of the call option premium to undertake a stage of R&D based on estimates of the current value of the project and its associated volatility. If the "fair" value of the investment opportunity is greater than the actual cost of the investment and the firm has the necessary resources, the decision is made to exercise the R&D investment option.

Because of the presence of technological and market uncertainties, real options in pharmaceutical drug development can be evaluated using the quadranomial approach, which allows for the simultaneous resolution of uncertainties.[32] The commonly used binomial model for pricing options uses a tree representation to depict the evolution of a single uncertain variable over discrete time.[11] An advantage of the binomial modeling approach is that it provides a numerical solution to complex real-world investment decisions (e.g., staged investment decisions that may include the options of deferral, abandonment, expansion, or contraction of a project) when exact formulas are not available. The quadranomial approach, which considers two sources of uncertainty, is a two-variable binomial tree. In the case of a pharmaceutical company, it is assumed that market/demand uncertainty is correlated with the economy while technological uncertainty is independent of it. Both forms of uncertainty evolve simultaneously over time. In lieu of an external twin security that exactly matches the payouts of the project, real-options practitioners often use the present value of the project itself, without flexibility, as the underlying risky asset V_0.[32] Assuming that the estimated starting value of a project is V_0, its multiplicative up and down movements are u and d when driven by the market uncertainty. The upward market movement u occurs with probability q, while the downward movement occurs with probability $1 - q$. Here, q refers to the risk-neutral probability obtained by hedging the project with securities and risk-neutral Treasury Bonds. Technological success occurs with probability ϕ, while failure of a particular testing phase occurs with probability $1 - \phi$. Technological uncertainty is estimated from historical clinical trial data and is assumed to be independent of the economy so it does not contribute to a change in the project's value. However, if a project fails a trial within a clinical phase, the project's value goes to zero. Let C_t^s represent the value of the project at time t and state s. The event tree has four possible outcomes at the end of one period as shown in Figure 3: (1) $C_1^4 = uV_0$, technological success and market upward movement, occurring with probability ϕq; (2) $C_1^3 = dV_0$, technological success and market downward movement, occurring with probability $\phi(1 - q)$; (3) $C_1^2 = 0$, technological failure and market upward movement, occurring with probability $(1 - \phi)q$; (4) $C_1^1 = 0$, technological failure and market downward movement, with probability $(1 - \phi)(1 - q)$. Note that the third and fourth possibilities result in a project value of zero regardless of the anticipated demand for the product because the drug is a technological dead-end.

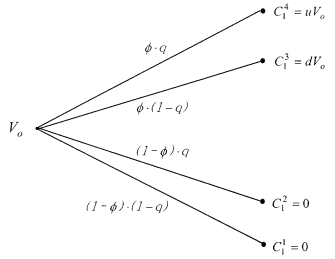

Figure 3. Quadranomial tree showing resolution of the market and technical uncertainty for one period.

When the decision tree framework is applied over discretized time intervals of 1 year, four branches emanate from every node if the process is extended over multiple time periods. The values of u, d, and q are computed using the formulas for pricing stock options based on the binomial model:[8]

$$u = e^{\sigma\sqrt{\Delta T}} \tag{10}$$

$$d = e^{-\sigma\sqrt{\Delta T}} = 1/u \tag{11}$$

$$q = \frac{e^{r_f \Delta T} - d}{u - d} \tag{12}$$

Here, ΔT is the discrete time interval, r_f is the risk-free interest rate, and σ is the volatility in the market demand as estimated by historical data and market research. These formulas follow from a discrete approximation to the Black−Scholes continuous-time model, which is valid for small enough values for ΔT. Having developed an approach to value individual pharmaceutical R&D projects, we next move to describing the problem of valuing multiple candidate drugs and formulating an optimum drug portfolio under consideration of managerial flexibility.

4. Mathematical Problem Representation

The starting point of the pharmaceutical planning problem is the candidate portfolio P, a set of products that are being considered for development. Figure 1 describes the five phases of pharmaceutical R&D included in the set S of drug developmental stages: three clinical trial phases, FDA approval, and product launch.[1] In practice, a pharmaceutical company may elicit expert,

though subjective, estimates of stage duration for each research phase of a project and calculate the single-point probabilistic time to complete each stage. The duration of each phase of clinical development is postulated as follows: phase I, 1 year; phase II, 1 year; phase III, 2 years; FDA approval, 2 years.

Following a successful FDA approval phase, the product can be immediately commercialized under the assumption that capacity investments and production preparations are made during the 2 years spent awaiting FDA approval. The proposed OptFolio formulation uses the following sets and parameters to describe the pharmaceutical portfolio optimization problem.

Sets

i = product ($i = 1, 2, ..., P$)
s = stage of drug development ($s = 1, 2, ..., S$)
t = year of the portfolio planning horizon ($t = 0, 1, ..., T$)

For each candidate drug i, portfolio selection decisions made at the present time ($t = 0$) classify the impending stage as $s = 1$ regardless of where the candidate drug is in its development. Subsequent development stages are numbered in ascending order until termination at product launch.

The key parameters of the problem formulation are identified and defined as follows.

Parameters

V_{0_i} = current value of drug i at $t = 0$
σ_i = estimated annual market volatility for drug i
ΔT = duration in years of each discrete time interval for value movements
r_f = risk-free interest rate
u_i = upward movement in value for drug i during each discrete time interval
d_i = downward movement in value for drug i during each discrete time interval
q_i = risk-neutral probability of upward movement in value for drug i during each discrete time interval
T_{is} = length in years of stage s of drug development for drug i
I_{is} = investment cost of developmental stage s for drug i
ϕ_{is} = probability of technical success in stage s of development for drug i
B_t = budgetary constraint for year t

The parameter V_{0_i} represents the estimated value of drug i, based on the NPV of all cash flows that result if the drug is commercialized, at time $t = 0$ of the planning horizon. This value is an aggregate of the projected sales revenue of the drug minus production, distribution, and marketing costs and all other expenses. The market volatility σ_i is the estimated annual standard deviation in the value of product i if it is commercialized. The estimation of the current value of a project and its associated volatility is typically based on market forecasts, the historical sales data of similar products, and the qualitative risk of the project.[32] The risk-free interest rate r_f, set at 5%, corresponds to an average observable market rate (e.g., U.S. Treasury Bills) that allows for the use of a hedging portfolio to replicate the value of the R&D project. Here, we assume that no risk premium is applied to any specific project and opportunity costs are not incurred even in the presence of budgetary limitations.

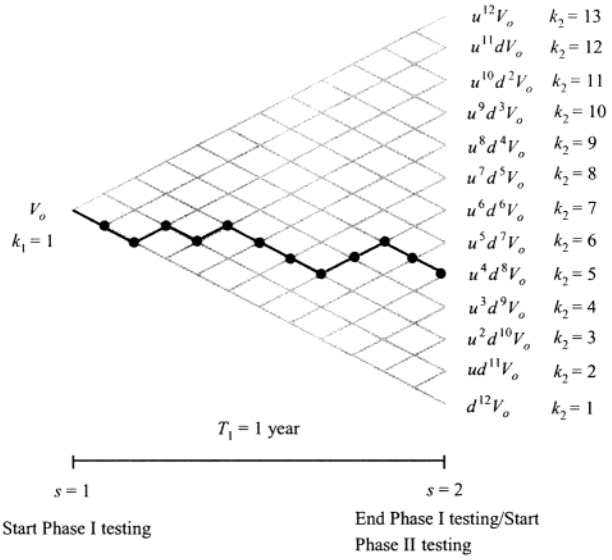

Figure 4. Binomial pricing tree showing possible value scenarios for a product at the end of phase I testing.

The binomial pricing lattice is generated using the discrete approximation to the Black−Scholes model given by eqs 10−12.[8] As market and technical uncertainty are resolved, the binomial pricing tree spans all possible future outcomes represented as nodes of project value as shown in Figure 4 for a time period of 1 year. A *value scenario* is an outcome that occurs at the beginning of a developmental stage, where the continue/abandon decision is available. Here, the index $k_s \in \{1, 2, ..., N_{is}\}$ corresponds to a specific value scenario of a candidate drug as given by the binomial pricing tree where N_{is}, the number of value scenarios available at the beginning of stage s for drug i, is given as $N_{is} = 1 + \sum T_{i,s-1}/\Delta T$. The binomial coefficients, their respective probabilities, and the discrete value distributions for drug i at the beginning of stage s of clinical testing are given by the binomial formula

$$\text{coef}_{ik_s} = \binom{N_{is} - 1}{k_s - 1} = \frac{(N_{is} - 1)!}{(k_s - 1)!(N_{is} - k_s)!} \quad \forall\, i \in P,\ s \in S,\ k_s = 1, ..., N_{is} \tag{13}$$

$$V_{ik_s} = u_i^{k_s - 1}\, d_i^{Nis - k_s} V_{0_i} \quad \forall\, i \in P,\ s \in S,\ k_s = 1, ..., N_{is} \tag{14}$$

$$\omega_{ik_s} = q_i^{k_s - 1}(1 - q_i)^{N_{is} - k_s} \frac{(N_{is} - 1)!}{(k_s - 1)!(N_{is} - k_s)!} \quad \forall\, i \in P,\ s \in S,\ k_s = 1, ..., N_{is} \tag{15}$$

where coef_{k_s} is the binomial coefficient for a product beginning stage s with value scenario k_s, V_{ik_s} is the value of drug i at the beginning of developmental stage s for scenario k_s, and ω_{ik_s} is the probability that drug i will follow scenario k_s at the beginning of stage s. The number of value scenarios available at the beginning of each stage is based on the discrete time interval ΔT. For a candidate drug about to begin phase I testing, the binomial pricing tree will have $N_2 = 1 + 1/\Delta T$ value scenarios available at the end of the 1-year interval, with the index k_2 ranging from 1 to N_2.

Figure 4 demonstrates this procedure for the case of a 1-month discrete time interval ($\Delta T = {}^1/_{12}$) for a candidate drug that has completed phase I clinical

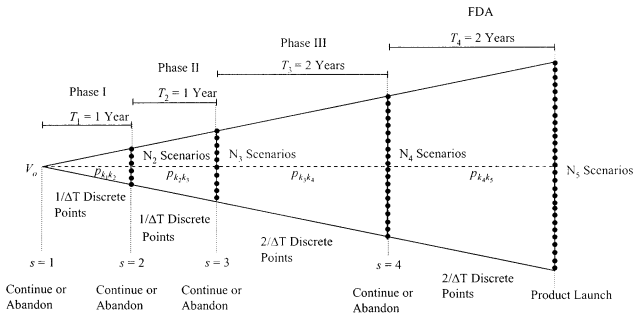

Figure 5. Market uncertainty for a candidate drug beginning phase I.

testing. Here, N_2 represents 13 value scenarios, or nodes, available at the beginning of stage 2 after phase I testing is complete. The value scenarios are numbered in ascending order of the project's value at the beginning of a stage, classifying the lowest node on the binomial tree as value scenario one and continuing to the topmost node. Each intersection point, or node, of the binomial tree shown in Figure 4 represents the value of the candidate drug at the end of a time interval. The value scenarios correspond to the nodes that exist at the end of the developmental stage. Value scenario $k_2 = 1$ is the result of 12 consecutive downward price movements during the year-long phase I clinical trials, giving the candidate drug an estimated value of $V_{k_2=1} = d^{12}V_0$ at the beginning of phase II clinical trials. Value scenario $k_2 = 5$ corresponds to four upward price movements and eight downward price movements, giving the candidate drug an estimated value of $V_{k_2=5} = u^4d^8V_0$ at the beginning of phase II clinical trials. A possible path through the pricing tree to value scenario $k_2 = 5$ is marked in Figure 4 and is analogous to the log-normal price distribution of a tracking stock in the securities market. Note that the order in which these price movements occur does not affect the final value scenario because there are numerous paths that consist of four upward value movements and eight downward value movements through the binomial tree to this node.

Using this same method, discrete value distributions are generated each time a drug i is about to enter another phase of clinical testing and the binomial coefficients and probabilities are used to determine the probability of moving from a given value scenario to another scenario in the subsequent phase of drug development. Consequently, a candidate drug beginning phase I testing in stage $s = 1$ will have $2^{N_{i,s=5}-1}$ potential paths leading to stage $s = 5$, each with a certain probability of $\omega_{ik_s=5}$.

For a drug i beginning phase I testing at $t = 0$, these calculations are performed to enumerate the scenarios available at the end of phase I testing ($t = 1$), phase II testing ($t = 2$), phase III testing ($t = 4$), and phase IV FDA approval/product launch ($t = 6$). The aggregate value of the candidate drug i at product launch for scenario k_5 is given by

$$V_{ik_5} = u_i^{k_5-1}d_i^{N_{is}-k_5}V_{0_i} \qquad \forall\, i \in P,\ k_5 = 1, 2, ..., N_{i5} \tag{16}$$

Note that upper and lower bounds on the value of the candidate drug at commercial launch could easily be imposed to keep expected payoffs within a realistic range. The conditional probability $P_{ik_sk_{s+1}}$ of moving from scenario k_s to scenario k_{s+1} in the next stage of development is given by the binomial probability of a value movement as follows:

$$p_{ik_sk_{s+1}} = q_i^{l-1}(1-q_i)^{1+(T_{is}/\Delta T)-l}\frac{(T_{is}/\Delta T)!}{(l-1)!\left(1+\frac{T_{is}}{\Delta T}-l\right)!}$$

$$\forall\, i \in P,\ s \in S,\ l = 1, ..., 1+\frac{T_{is}}{\Delta T};$$

$$k_s \le k_s+1 \le k_s+\frac{T_{is}}{\Delta T} \tag{17}$$

Given a stage s beginning scenario of k_s, k_{s+1} must have a lower bound of k_s, which occurs if all value movements are downward for the length T_{is} of the stage, and an upper bound of $k_s + T_{is}/\Delta T$, which occurs if all value movements are upward for the duration of the stage. Note also that

$$\sum_{k_s=1}^{N_{is}} P_{ik_sk_{s+1}} = 1 \qquad \forall\, i \in P,\ s \in S,\ k_s = 1, ..., N_{is} \tag{18}$$

The OptFolio model formulation utilizes binary variables to track the selection and abandonment of candidate drugs through the planning horizon. The key decision variables of the model are chosen as follows.

Binary Variables. $y_{isk_s} = 1$ if drug i is selected to undergo stage s of development while in value scenario k_s and $y_{isk_s} = 0$ otherwise.

The binary variables y_{isk_s} control the product selection decisions at the beginning of developmental stages. If it is favorable under value scenario k_s to begin the next stage s of development, the drug will be selected to continue and y_{isk_s} will equal 1. However, if it is favorable to abandon the drug in this given value scenario, the binary variable will be set to 0. The optimal drug developmental portfolio is selected based on R&D investment constraints and the probabilities of future revenue streams. As market and technical uncertainty are resolved, the developmental portfolio can be reconfigured to account for this new information.

Figure 5 highlights the market uncertainty inherent in the drug discovery process for a drug beginning phase I clinical testing. Assuming that a candidate drug successfully completes the prior stage of clinical testing, two decisions are available at the beginning of the next stage of clinical development: continue with development or abandon the project. This translates into a four-stage problem with four decision points as shown in Figure 5. If the candidate drug successfully passes the FDA approval phase (developmental stage 4), the drug is commercially launched in stage 5. Figure 5 represents the cone of market uncertainty for candidate drugs beginning phase I at developmental stage $s = 1$. Over the course of the planning horizon, the number of available value scenarios increases and the spread between these values increases as a function of the volatility of the candidate drug. Figure 6 displays the cones of market uncertainty for two products. Product $i = 1$ has successfully completed phase I clinical testing and is a candidate to enter phase II testing. Product $i = 2$ is a candidate to begin phase I testing. Using $t = 0$ as a basis, stage $s = 1$ corresponds to phase II testing for product 1 and phase I testing for product 2. The number of available scenarios at the beginning of each stage differs based on the lengths of these respective

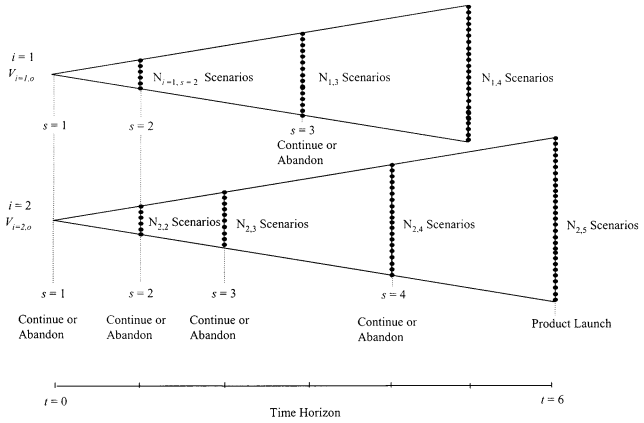

Figure 6. Market uncertainty of products at different points in the developmental cycle.

stages. The binary parameters w_{ist} account for the differences in stage durations for products at various points in the developmental cycle. For example, $w_{i=1,s=3,t=3} = 1$, while $w_{i=1,s=3,t=4} = 0$ to denote that stage $s = 3$ for product $i = 1$ begins at period $t = 3$ years. In this manner, products at different points in the developmental pipeline can be compared to formulate the optimal portfolio for that given time.

In addition to market uncertainty, candidate drugs in the developmental pipeline are subject to technical uncertainty. Figure 7 shows the technical uncertainty for candidate drugs beginning phase I clinical testing at developmental stage $s = 1$. The technical uncertainty of a stage of drug development has two possibilities: success or failure. The probability of success for a stage of drug development for a candidate drug is given as ϕ_{is}. Thus, the total probability of a drug i reaching a given value scenario at the beginning of a stage includes both the cumulative technical success probability and the risk-neutral probability of price movement derived from the market volatility and the risk-free interest rate.

Drug Precedence Constraints. If a candidate drug i is not selected for development in stage $s = 1$ of clinical testing, then this drug should be excluded from any future phases of clinical testing. Mathematically, this is expressed as

$$y_{isk_s} \le y_{i,s=1,k_{s=1}} \qquad \forall\, i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is} \quad (19)$$

Furthermore, it is necessary to prevent a drug from being selected in a particular phase of clinical testing if it has been abandoned in a prior stage, which translates into constraints expressed as

$$y_{i,s+1,k_{s+1}} \le \sum_{k_s} y_{isk_s}$$

$$\forall\, i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is},\ k_s \le k_{s+1} \le k_s + \frac{T_{is}}{\Delta T} \quad (20)$$

Value Monotonicity Constraints. In the binomial pricing tree, the value scenarios are numbered in ascending order of the project's value at the beginning of a stage, classifying the lowest node on the binomial tree as value scenario 1 and continuing to the topmost node. A characteristic of the solution to the OptFolio problem is that once y_{isk_s} equals 1 for a given scenario k_s, y_{isk_s} equals 1 for all scenarios of a higher index k_s. Clearly, if a candidate drug is chosen to continue development in a stage s under a given value scenario k_s, it will also be chosen in the more valuable scenarios that are arranged above k_s in the binomial pricing tree. Similarly, if y_{isk_s} equals 0 for a given scenario k_s, y_{isk_s} equals 0 for all scenarios of a lower index k_s. Mathematically, this is expressed as

$$y_{i,s,k_s-1} \le y_{isk_s} \qquad \forall\, i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is} \quad (21)$$

Investment Constraints. Decisions to include a drug in the pharmaceutical company's portfolio or abandon it are made before each phase of clinical testing begins. However, these decisions may be "out of synch" with the decision points of drugs at different locations in the developmental pipeline. Assuming an aggregate budgetary constraint for every year t in the planning horizon that limits the investment in subsequent stages of development, the binary parameters w_{ist} ensure that only those drugs beginning a stage of development at time t will be included in the budgetary constraint. The investment constraints regarding drugs i under consideration to begin stages at time t are expressed as

$$\sum_{i,s}^{N_{is}} \sum_{k_s} p_{ik_{s-1}k_s} I_{is} y_{isk_s} w_{ist} \le B_t \qquad \forall\, t \quad (22)$$

To satisfy the budgetary constraints, it may be necessary to reduce the number of value scenarios in which a drug's development is continued. Consequently, the

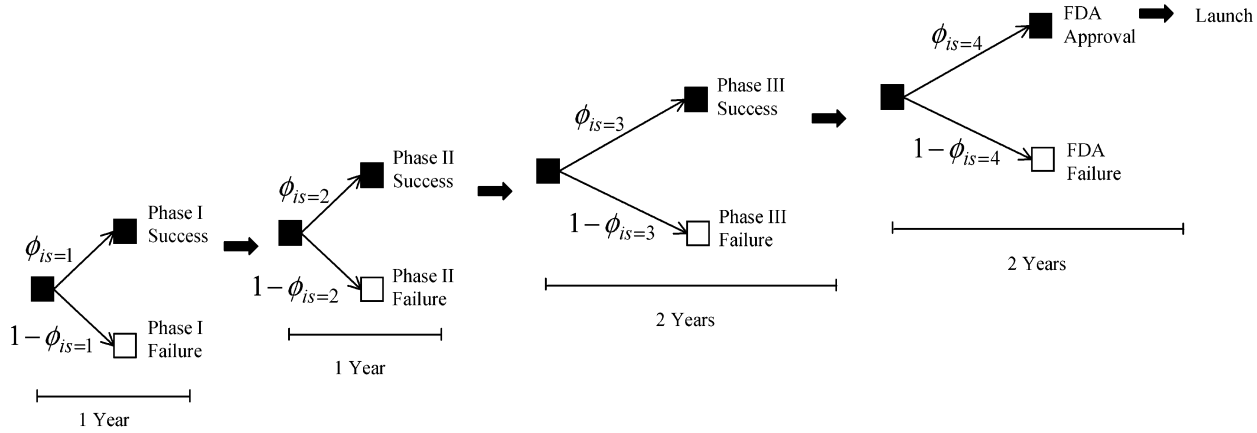

Figure 7. Technical uncertainty of drug development.

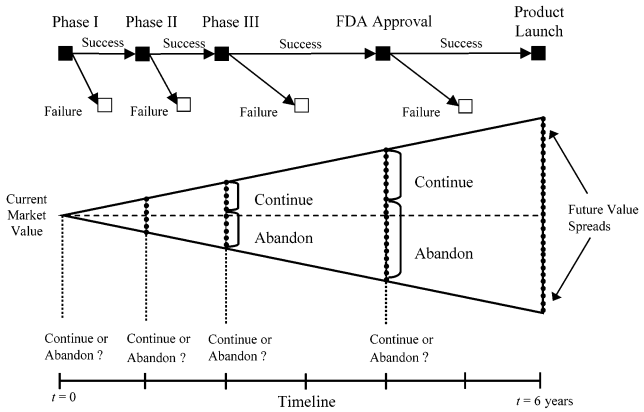

Figure 8. Portfolio selection decisions under uncertainty.

road map of future continuation/abandonment decisions is dependent on the resource constraints. Note that the R&D investment limit B_t does not have a dependence on the success probabilities of the current R&D projects. The optimal portfolio at $t = 0$ may be substantially different (i.e., it may contain more candidate products or show a preference toward low-risk, low-reward products over high-risk, high-reward products) when the need to guarantee revenue to fund future R&D efforts is included.

Real Options Decision Tree. The sequential decision process described in Figure 8 is evaluated by using backward recursion to make continuation/abandonment decisions at each market scenario of the binomial decision tree based on the future revenue streams obtained by market launch. The value M_{isk_s} for each market scenario is formulated as a stochastic dynamic program

$$M_{isk_s} = \mathrm{Max}\left\{-I_{is} + \frac{\sum_{k_{s+1}=1}^{N_{i,s+1}} [\phi_{is} p_{ik_sk_{s+1}} M_{i,s+1,k_{s+1}}]}{(1+r_f)^{T_{is}/\Delta T}}, 0\right\} \quad (23)$$

beginning from the expected payoff V_{isk_s} received during commercial launch where M_{isk_s} are continuous variables that represent the value of candidate product i in stage s of development following value scenario k_s. In this form, the optimal decision policy chooses continuation whenever M_{isk_s} is positive. To account for the possibility that continuation may not be chosen because of resource limitations, the optimal decision rule is expressed in terms of the binary selection variables y_{isk_s}:

$$M_{isk_s} = \left[-I_{is} + \frac{\sum_{k_{s+1}=1}^{N_{i,s+1}} [\phi_{is} p_{ik_sk_{s+1}} M_{i,s+1,k_{s+1}}]}{(1+r_f)^{T_{is}/\Delta T}}\right] y_{\mathrm{isk_s}} \quad (24)$$

If the future value of the drug, discounted to the time when the current stage s begins using the risk-free interest rate r_f, less the investment cost of the stage is positive, the decision is made to continue development, assuming that the appropriate resource constraints are not violated. If this quantity is negative, the decision is made to abandon development of this drug for the given market scenario k_s. Successive substitutions working backward through eq 24 result in an explicit expression for $M_{i,s=1,k_{s=1}}$, the ROV for candidate drug i at $t = 0$.

By resolving this recursion, $M_{i,s=1,k_{s=1}}$ is expanded for the case where all drugs are under consideration to begin phase I clinical testing at developmental stage $s = 1$:

$$\sum_i M_{i,s=1,k_{s=1}} = \sum_i \left[-I_{i1} y_{i1k_1} - \frac{1}{(1+r_f)^{1/\Delta T}} \sum_{k_2=1}^{N_{i2}} \left[\phi_{i1} p_{ik_1k_2} I_{i2} y_{i2k_2}\right] y_{i1k_1} - \frac{1}{(1+r_f)^{2/\Delta T}} \sum_{k_2=1}^{N_{i2}} \left[\phi_{i1} p_{ik_1k_2} \sum_{k_3=1}^{N_{i3}} \left[\phi_{i2} p_{ik_2k_3} I_{i3} y_{i3k_3}\right] y_{i2k_2}\right] y_{i1k_1} + \frac{1}{(1+r_f)^{2/\Delta T}} \sum_{k_2=1}^{N_{i2}} \left[\phi_{i1} p_{ik_1k_2} \sum_{k_3=1}^{N_{i3}} \left[\phi_{i2} p_{ik_2k_3} \sum_{k_4=1}^{N_{i4}} \left[\phi_{i3} p_{ik_3k_4} \left[\frac{1}{(1+r_f)^{2/\Delta T}} \sum_{k_5=1}^{N_{i5}} \left[\phi_{i4} p_{ik_4k_5} V_{ik_5}\right] - I_{i4}\right] y_{i4k_4}\right] y_{i3k_3}\right] y_{i2k_2}\right] y_{i1k_1}\right] \quad (25)$$

Upon linearizing the binary−binary products found in eq 25, the expression comprises a large number of binary variables, which makes the model size prohibitively large as more products or managerial choices are added. A more tractable approach is to express the selection variables in terms of the current stage of development and the future stage of development instead of including *all* stages to reduce the number of variables in the model formulation.

The objective function of the OptFolio model is expressed as the ROV for the candidate portfolio at $t = 0$:

$$\max \mathrm{ROV} = \sum_i M_{i,s=1,k_{s=1}} \quad (26)$$

where the values of M_{isk_s} for all other decision nodes are defined as continuous variables in the form of eq 24 and added as constraints to the problem. In addition, the following constraints are also needed to ensure that the M_{isk_s} continuous variables are always nonnegative:

$$M_{isk_s} \geq 0 \quad (27)$$

The continuous−binary products $M_{i,s+1,k_{s+1}} y_{isk_s}$ that appear in eq 24 can be linearized using continuous variables $z_{ik_sk_{s+1}}$ as follows:

$$M_{isk_s} = \left[-I_{is} \cdot y_{isk_s} + \frac{\sum_{k_{s+1}=1}^{N_{i,s+1}} [\phi_{is} p_{ik_sk_{s+1}} z_{ik_sk_{s+1}}]}{(1+r_f)^{T_{is}/\Delta T}}\right] \quad (28)$$

$$0 \leq z_{ik_sk_{s+1}} \leq M^{\mathrm{upper}}_{i,s+1,k_{s+1}} y_{isk_s} \quad (29)$$

$$M_{i,s+1,k_{s+1}} - M^{\mathrm{upper}}_{i,s+1,k_{s+1}}(1 - y_{isk_s}) \leq z_{ik_sk_{s+1}} \leq M_{i,s+1,k_{s+1}} + M^{\mathrm{upper}}_{i,s+1,k_{s+1}}(1 - y_{isk_s}) \quad (30)$$

where $M^{\mathrm{upper}}_{i,s+1,k_{s+1}}$ are parameters that represent upper bounds on the continuous scenario values of $M_{i,s+1,k_{s+1}}$. These upper bounds are generated by solving the

problem with no budgetary restrictions using the following model formulation:

$$\min \sum_{i,s} \sum_{k_s=1}^{N_{is}} [M_{isk_s}] \tag{31}$$

subject to

$$M_{isk_s} \geq -I_{is} + \frac{\sum_{k_{s+1}=1}^{N_{i,s+1}} [\phi_{is} p_{ik_sk_{s+1}} M_{i,s+1,k_{s+1}}]}{(1 + r_f)^{T_{is}/\Delta T}}$$

$$M_{isk_s} \geq 0$$

This procedure is identical with the dynamic recursive program described by eq 23. The optimal scenario values obtained in the unconstrained problem represent upper bounds of $M^{\text{upper}}_{i,s+1,k_{s+1}}$ on the values of $M_{i,s+1,k_{s+1}}$ that can be realized in the constrained problem. When the investment constraints are relaxed, the scenario values of a given candidate drug correspond to the maximum revenue potential available when resources are not scarce. An unconstrained scenario value of M_{isk_s} must characterize the best possible result that is obtainable in the constrained problem; otherwise, the unconstrained scenario value is not optimal. Similarly, if a given scenario value of M_{isk_s} is equal to 0 in the unconstrained problem, its value should remain equal to 0 when investment constraints are imposed.

Model Formulation. The complete model formulation of the problem is

$$\max \text{ROV} = \sum_i M_{i,s=1,k_{s=1}} \qquad \text{(OptFolio)}$$

subject to

$$M_{isk_s} = \left[-I_{is} \cdot y_{isk_s} + \frac{\sum_{k_{s+1}=1}^{N_{i,s+1}} [\phi_{is} p_{ik_sk_{s+1}} z_{ik_sk_{s+1}}]}{(1 + r_f)^{T_{is}/\Delta T}} \right]$$

$$0 \leq z_{ik_sk_{s+1}} \leq M^{\text{upper}}_{i,s+1,k_{s+1}} y_{isk_s}$$

$$M_{i,s+1,k_{s+1}} - M^{\text{upper}}_{i,s+1,k_{s+1}} \cdot (1 - y_{isk_s}) \leq z_{ik_sk_{s+1}}$$

$$z_{ik_sk_{s+1}} \leq M_{i,s+1,k_{s+1}} + M^{\text{upper}}_{i,s+1,k_{s+1}} \cdot (1 - y_{isk_s})$$

$$y_{isk_s} \leq y_{i,s=1,k_{s=1}} \qquad \forall\, i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is}$$

$$y_{i,s+1,k_{s+1}} \leq \sum_{k_s} y_{isk_s} \qquad \forall\, i \in P,\ s \in S,\ k_s = 1, \ldots,$$

$$N_{is},\ k_s \leq k_{s+1} \leq k_s + \frac{T_{is}}{\Delta T}$$

$$y_{i,s,k_s-1} \leq y_{isk_s} \qquad \forall\, i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is}$$

$$\sum_{i,s} \sum_{k_s}^{N_{is}} p_{ik_{s-1}k_s} I_{is} y_{isk_s} w_{ist} \leq B_t \quad \forall\, t$$

$$M_{isk_s} \geq 0$$

$$y_{isk_s} \in \{0, 1\}$$

To enhance the flexibility of the decision framework, the OptFolio model can be modified to incorporate additional managerial choices. These choices could include deferring an R&D investment decision until more information becomes available, expanding or contracting the scale of the investment in response to changing market conditions, using third-party companies that specialize in managing clinical trials in an attempt to accelerate a developmental stage, or conducting phase IV indication tests to increase the therapeutic claims of the drug. In most situations, these additional decision choices would create path-dependent routes through the decision tree that would have different volatilities and risk-neutral probabilities. Here, a decision node in a given binomial tree may be the starting point for one or more different binomial trees that result if a certain course of action is chosen. The combination of many options creates a *nonrecombining* decision tree with a large state space.[32] The inclusion of more choices in the model alters the values of M_{isk_s} that control the optimal decision made at each value scenario node:

$$M_{isk_s} = \text{Max}(A, B, C, \ldots) \tag{32}$$

where A, B, and C represent the payoffs from the choices that are available in the current value scenario and binary selection variables represent each additional decision. Working back through time from the end points of the different binomial trees, the OptFolio model makes the value-maximizing decision at each node, based on the choices available, and determines the optimal road map of decisions.

The OptFolio model could also be modified to incorporate a stochastic Monte Carlo simulation of the development and commercialization for each candidate drug to determine how the portfolio ROV and composition change over simulated outcomes.[33] The purpose of the simulation is to gauge the variance of the ROV outcomes based on varying model input parameters in order to calculate the risk of each candidate drug. To account for the emergence of competitors' products, the model framework could include "leakage" in the value of the underlying asset as in the option to buy a stock that pays dividends. In the absence of dividends, the optimal course of action is to defer the start of a stage of the project until the last possible moment. With this leakage of value due to competition and lost patent protection, it may be optimal to invest early. In addition, real options analysis could be embedded into a game theory situation where competing firms recognize each other's behavior and adjust their strategies accordingly.

5. Pharmaceutical Portfolio Case Study

As an illustrative example of the OptFolio model, we consider a pharmaceutical company that has 20 candidate products (P1−P20) in R&D along six developmental classifications: six products beginning phase I testing (type I, P1−P6), five products beginning phase II testing (type II, P7−P11), three products beginning phase III (type III, P12−P14), two products in the second year of phase III testing (type IV, P15 and P16), two products beginning phase IV FDA review (type V, P17 and P18), and two products in the second year of FDA review (type VI, P19 and P20). In general, candidate products with high probabilities of technical success and a high current value to future investment ratios are preferable. Conversely, the ability to control downside risk with the abandonment option means that

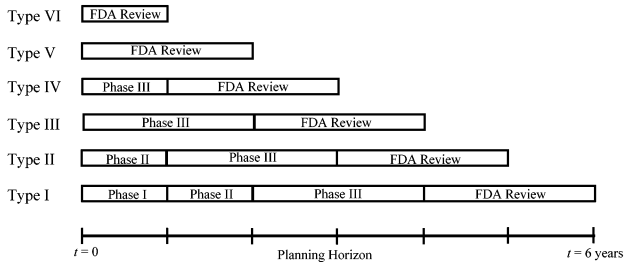

Figure 9. Developmental schedule for available drugs in the pharmaceutical pipeline.

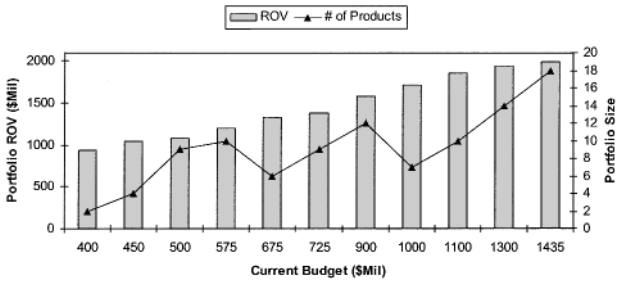

Figure 10. Optimal portfolio ROV and size as a function of the $t = 0$ R&D budget.

the ROV increases with increasing market volatility. Constrained by an R&D budget, the pharmaceutical company must decide which candidate products to fund for further development during the upcoming year.

The candidate products fall into one of six types depending on the remaining length of their developmental schedule as shown in Figure 9. Products under consideration to begin phase I clinical testing are assumed to be 6 years away from product launch, so selection decisions are made over a planning horizon of 6 years. A discretization time interval of 1 month is used in the mathematical model, resulting in 73 possible value scenarios at product launch for each candidate drug that is beginning phase I development. Required model parameters include the current value of the drug, probabilities of technical success for each stage of development, the investment costs for each stage of development, and the estimated annual volatility in the candidate drug's value. Realistic values, based on historical studies of the pharmaceutical industry,[3,34−37] are chosen for the data used in this example as summarized in Table 1. In practice, these time-dependent parameters would be based on historical data, market research, and qualitative estimates made by R&D management at the present time of the analysis.

The set of 20 candidate drugs represents a variety of product characteristics. Volatility estimates range from 20% for low-risk drugs to 100% for high-risk drugs, with a typical market volatility of 50%/year. The probabilities of technical success also vary to reflect the risk of each candidate drug during drug development. The estimated investment costs needed to begin subsequent phases of development are loosely related to the current value of each candidate drug to indicate that valuable drugs usually cost more to develop and produce. The above example is modeled using the GAMS modeling system accessing CPLEX 7.0 for the MILP optimization part. The budgetary constraint for $t = 0$ is varied while holding the budgetary constraints for all future years constant at \$800M. The linearization procedure described in eqs 28−30 used continuous variables $z_{ik_sk_{s+1}}$ to linearize the continuous−binary products $M_{i,s+1,k_{s+1}}y_{isk_s}$ that appear in the formulation. Using this approach, the mathematical model of the case study was reduced to include only 893 binary variables and 12 843 continuous variables and solved to optimality in 268 CPU s using an IBM RS/6000-270 workstation. If the objective function would have included the explicit expression for $M_{i,s=1,k_{s=1}}$ given by eq 25, the resulting linearization of the binary−binary products would have yielded 101 042 binary variables and would have required far greater computational time to find even a suboptimal solution within a 2−3% tolerance of optimality.

Figure 10 summarizes the results of the portfolio selection case study. The figure shows how the portfolio size and ROV change as a function of the budgetary constraint $B_{t=0}$. In general, products at later stages of development, having survived several phases of clinical testing, are more valuable because they are more likely to reach commercial launch. However, the capital investment and marketing costs associated with product launch during phase IV FDA review are substantial, limiting the number of products the pharmaceutical company can bring to market. Thus, the size of the optimal portfolio balances the desire to launch valuable products in phase IV FDA review with the investment in potentially valuable drugs in early stages of development.

Table 1. Candidate Product Parameters

	V_0 (\$ million)	σ (%)	$\phi_{s=1}$	$\phi_{s=2}$	$\phi_{s=3}$	$\sigma_{s=4}$	$I_{s=1}$ (\$ million)	$I_{s=2}$ (\$ million)	$I_{s=3}$ (\$ million)	$I_{s=4}$ (\$ million)
P1	50	80	0.6	0.7	0.8	0.95	2	10	20	30
P2	100	70	0.65	0.55	0.75	0.9	3	10	40	45
P3	200	50	0.7	0.8	0.9	0.9	10	15	60	100
P4	200	60	0.5	0.7	0.8	0.9	5	15	50	170
P5	600	50	0.6	0.6	0.7	0.9	20	40	45	200
P6	100	20	0.85	0.9	0.9	0.95	15	15	25	45
P7	80	50	0.6	0.8	0.95		10	25	30	
P8	100	70	0.6	0.8	0.95		20	35	50	
P9	180	55	0.75	0.7	0.85		20	55	80	
P10	380	35	0.6	0.8	0.95		30	55	120	
P11	80	45	0.6	0.8	0.95		10	25	30	
P12	100	80	0.8	0.9			30	60		
P13	400	30	0.8	0.9			75	180		
P14	700	40	0.6	0.85			90	280		
P15	500	35	0.8	0.95			50	100		
P16	300	100	0.7	0.9			80	150		
P17	350	60	0.75				180			
P18	550	30	0.9				220			
P19	800	60	0.7				250			
P20	1150	20	0.9				350			

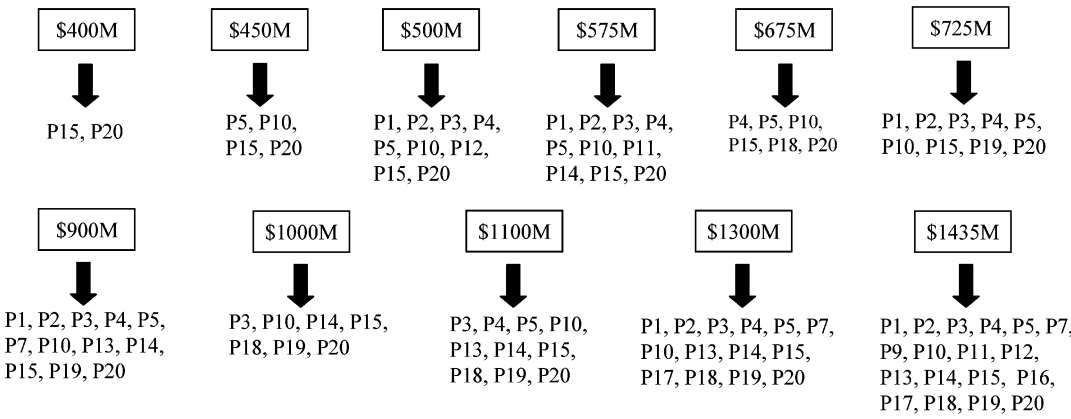

Figure 11. Composition of the optimal portfolio as a function of $B_{t=0}$.

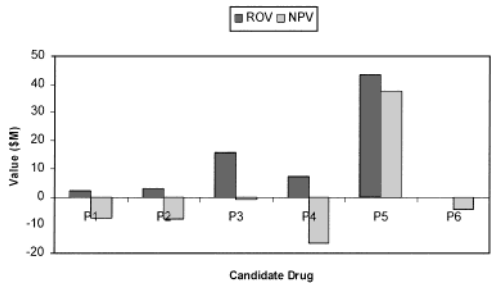

Figure 12. Comparison of ROV and NPV values of type I candidate drugs.

Figure 11 describes how the composition of the optimal drug portfolio changes with the R&D budgetary constraint. P20 is selected in every budgetary scenario because it has the largest V_0 of any product in the set of candidate drugs and has a 90% chance of being successfully launched in the following year. Similarly, P15, which is entering the final year of phase III clinical testing, is chosen in every scenario because it has a large V_0 in relation to the investment costs of subsequent developmental stages and a 76% chance of being successfully launched in 3 years. As the budgetary constraint increases, the OptFolio model chooses type I and II drugs that have commercial promise but relatively low investment costs for the current year. Under the ROV metric, these products, though 5 or 6 years away from market launch, are considered valuable because of their *potential* future value. When $B_{t=0} =$ \$675M, the OptFolio model drops several type I−III candidate products for the opportunity to select P18, a product 2 years away from commercial launch. Similarly, six products are dropped from the optimal portfolio at $B_{t=0} =$ \$900M to add P18 at $B_{t=0} =$ \$1000M. From a management perspective, candidate drugs that have made it through the first two stages of clinical testing are only excluded if the pharmaceutical company cannot afford to launch multiple products. These results are consistent with the analysis of Amram and Kulatilaka,[28] who viewed pharmaceutical investment as a two-part decision structure consisting of (i) information-gathering investments in phase I and II testing to identify the most valuable products and (ii) the progression of these products into phase III testing, where development continues unless deterred by a negative scientific or regulatory result.

Figure 12 illustrates the difference in valuation of type I candidate drugs using ROV and the NPV metric. Here, we consider ROV to include the abandonment option and NPV to assume that future cash flows are static, essentially fixing all binary selection variables to 1. These financial metrics are substantially different for drugs in early stages of development, having large technical and market uncertainties. The NPV technique undervalues these risky projects because of its inability to capture managerial flexibility: product selection is not a commitment to proceed all of the way to commercial launch but only to start with a "wait-and-see" approach until some of the uncertainty is resolved.[14] In contrast, the real options approach recognizes project volatility and the flexibility of management to react to arising circumstances by continuing a project under favorable conditions and abandoning disappointing projects. The difference between the ROV and NPV gives the value of the abandonment option to control downside risk and increase upside market potential. Intuitively, candidate products with high probabilities of technical success and high current value/investment ratios are relatively low risk and should have similar valuations under the ROV and NPV metrics. Candidate drug P5 is fairly low risk because its V_0 of \$600M is high relative to future investment costs so the product is abandoned less frequently than more risky candidates, making it the only type I candidate with a positive NPV. As a result, the ROV and NPV of this candidate drug are very close, giving it an abandonment option worth \$6.0 M. For P4, a more risky candidate drug with only a 50% probability of phase I clinical success but just a \$5M phase I investment cost, the value of this abandonment option is \$23.6M. In this case, the low phase I investment cost encourages preliminary R&D, but the phase IV investment cost of \$170M is only undertaken when market conditions are encouraging. Consequently, the value of the abandonment option is large for risky projects because of the presence of managerial flexibility to control downside loss in drug development.

In this analysis, five of the six type I candidate drugs have positive ROVs, but only one candidate has a positive NPV. The key result of this analysis is the value of gathering information at the beginning stages of drug development to determine whether the investment in later, more expensive stages is justified and using the abandonment option to terminate disappointing candidates. Thus, the ROV technique is more appropriate to value the uncertainty inherent in pharmaceutical portfolio management as companies strive to identify blockbuster products and avoid the large late-stage costs of marginal products.

As described before, the OptFolio model generates a road map of future "what if" decisions by tracking the

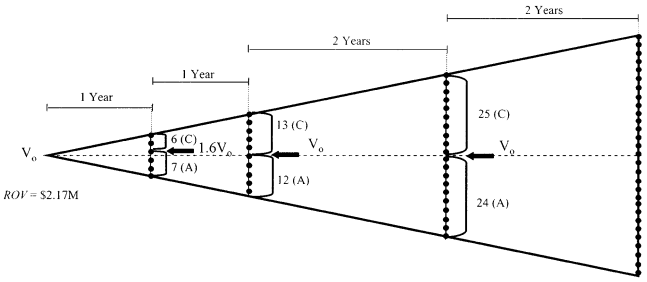

Figure 13. Optimal developmental schedule showing abandonment scenarios (A), continuation scenarios (C), and cutoff values for P1.

decision of abandonment for individual candidate products over time under changing market conditions and calculating the minimum market value above which development is continued. To illustrate this result, consider candidate drug P1. Figure 13 shows the optimal developmental schedule for candidate product P1 in the absence of R&D resource constraints. The OptFolio model calculates an ROV of $2.17M and chooses to abandon R&D in 7 of the 13 value scenarios at the beginning of phase II testing, 12 of the 25 value scenarios at the beginning of phase III testing, and 24 of the 49 value scenarios at the beginning of phase IV FDA review. In addition, it determines that the value of P1 must be at least $79.4M ($1.6V_0$) at the beginning of phase II testing in order to justify continued investment in drug development. The minimum cutoff values for the beginning of phase III and IV testing return to $50M, the original V_0, as uncertainty in R&D is resolved.

Candidate product parameters can be varied for each individual drug to determine the sensitivity of the optimal developmental schedule. For example, if the current value V_0 of candidate drug P1 is increased from $50M to $150M, the ROV would be expected to increase, causing the cutoff value for continued R&D investment to decrease. With P1 being less risky, the OptFolio model calculates an ROV of $42.75M and chooses to abandon R&D in 4 of the 13 value scenarios at the beginning of phase II testing, 10 of the 25 value scenarios at the beginning of phase III testing, and 21 of the 49 value scenarios at the beginning of phase IV FDA review. In addition, the minimum cutoff value for continued R&D decreases to $0.4V_0$ at the beginning of phase II clinical trials because of the lower risk of future drug revenues failing to break even with R&D expenditures. Similarly, we investigate how the optimal developmental schedule changes if P1 is more of a technical risk. As shown in Table 1, drug P1 has a 31.9% chance ($0.6 \times 0.7 \times 0.8 \times 0.95$) of reaching commercial launch. Changing the technical success parameters to $\phi_{s=1} = 0.5$, $\phi_{s=2} = 0.5$, $\phi_{s=3} = 0.6$, and $\phi_{s=4} = 0.7$ gives a cumulative probability of 10.5% for a successful commercial launch. As a result, the ROV for the more risky candidate product P1 is equal to 0 at a volatility of 80% and does not become positive until $\sigma = 150\%$. With $\sigma = 200\%$, the minimum market value of P1 needs to be at least $158.7M ($3.2V_0$) at the beginning of phase II testing to justify continued investment in drug development. The minimum cutoff value for the beginning of phase III stays at $3.2V_0$, while for phase IV testing, it returns to $50M, the original V_0, as uncertainty in R&D is resolved. The results of the sensitivity analysis of P1 indicate that the minimum market value needed to continue development in future stages of R&D is significantly larger for risky projects. Incorporating the flexibility of the continue/abandon option into the model formulation allows for the determination of these cutoff values to guide the future decisions of portfolio managers. Within the stochastic valuation framework, decisions to adopt a "wait-and-see" approach for risky projects by initiating a phase of clinical testing can be coupled with the future results needed to justify further R&D efforts.

To illustrate the impact of R&D resource constraints, we consider a portfolio that contains only candidate drugs P1 and P2. In the absence of any resource constraints, the optimal portfolio has an ROV of $5.23M. This result could also be obtained by evaluating each drug individually using backward recursion and adding the results. When $B_{t=0} = B_{t=1} =$ $5M and the other budgetary constraints are left unrestricted, the ROV of the optimal portfolio decreases to $4.22M. The OptFolio model reduces the number of value scenarios in which P1 and P2's development is continued to satisfy the resource constraints. These results demonstrate the importance of evaluating candidate drugs within a multistage framework that optimizes the portfolio ROV subject to budgetary limitations as opposed to using the standard recursive methods to value projects in isolation.

6. Concluding Remarks

The main objective of this paper was to develop a stochastic programming model of pharmaceutical R&D using a real options decision tree approach for making optimal project selection decisions in response to market and technical uncertainty and changing R&D budgetary limitations. In this context, drug development is viewed as a series of continue/abandon investment options to value managerial flexibility in deciding at each stage in pharmaceutical R&D whether to proceed further or stop development. The overall problem is formulated as an MILP model whose applicability is demonstrated by a portfolio selection case study that involves the selection of the optimal product portfolio under varying resource constraints.

The key idea that distinguishes the proposed ROV approach from existing work is the explicit tracking of the uncertainty in the market value of a candidate drug for R&D through external financial market information. From a management perspective, the model proposed in this paper provides a road map for a "what if" analysis of future R&D decisions by tracking the decision of abandonment over time and calculating the minimum market value above which pharmaceutical development is continued. In addition, the OptFolio model serves as a decision-support tool in making portfolio selection decisions based on uncertain project and market characteristics as candidate products compete for limited resources. The key insight of this approach, quantified by the stochastic programming model, is that it is worth exploring uncertain candidate molecules in staged R&D investments until additional information is learned about product performance (through clinical testing) and market potential. In realistic case studies, a probabilistic simulation of model parameters such as phase success probabilities, market volatility, and phase duration/cost uncertainties would allow for the integration of a formal risk management strategy and provides an interesting extension to this work.[33] Ultimately, a real options framework could be

linked to capacity planning decisions within the strategic supply chain.

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