Valuation and Design of Pharmaceutical R&D Licensing Deals

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In today's intensely competitive business environment, pharmaceutical companies are augmenting their product pipelines by both developing drugs on their own and in-licensing proprietary compounds or drug discovery–related technologies from smaller biotechnology companies. In this work, the OptFolio model of pharmaceutical R&D portfolio management is extended to evaluate partnership opportunities as real options and determine the optimal timing and investment policy for proposed alliances in the face of technological and market uncertainties and budgetary restrictions. Licensing deals are modeled within a decision tree as a series of continuation/abandonment options for the pharmaceutical company, deciding at each stage of R&D whether to make a predetermined milestone payment to continue the alliance or terminate the alliance because of unfavorable market conditions and/or internal resource limitations. Results indicate that early stage alliances become more valuable as market uncertainty and the ability of pharmaceutical companies to enhance the value of the licensed drug increase because of the ability to control downside risk by the abandonment option. © 2004 American Institute of Chemical Engineers *AIChE J,* 51: 198–209, 2005
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Introduction

As pharmaceutical companies strive to maintain their annual revenue-growth rates, the emphasis is on improving the flow of new drugs into the developmental pipeline and increasing the number of significant commercial launches each year. To achieve these goals, a growing number of pharmaceutical companies are licensing proprietary compounds or drug discovery–related technologies from other companies to bolster their internal R&D efforts. These licensing agreements typically involve combinations of initial payments, milestone payments based on the successful completion of an R&D stage, and royalty payments upon product commercialization. As of June 2003, there were a total of 5103 reported pharmaceutical alliances based on 2941 drug compounds, a reflection that multiple alliances can be formed for each drug (such as, marketing rights to different parts of the world).[1] For example, consider the following terms of the deal struck between the Public Health Research Institute and Vysis, Inc. in 1994 for licensing the diagnostic use of DNA probes.[2] The deal involved a \$50K up-front payment, \$1.55M in total research payments, \$3.15M in total maintenance fees starting year 4 through year 10, \$1.05M in total development milestone payments, \$2M in total sales milestone payments, and, finally, royalty on net sales based on prespecified rules (0.875% for sales $\leq$ \$100M; 1.0% for \$100M $<$ sales $\leq$ \$200M; 1.5% for \$200M $<$ sales $\leq$ \$300M; 2.0% for sales $>$ \$300M).

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Pharmaceutical companies commonly enter into partnerships to license developmental drugs from biotechnology companies. These collaborations provide pharmaceutical companies access to promising compounds while offering biotechnology companies, who may be reluctant to take the risks and assume the costs of clinical trials themselves, the manufacturing and marketing expertise of the large pharmaceutical companies that can greatly enhance the value of the drug. For example, the 2002 licensing agreement between Hoffmann La-Roche and Kosan BioSciences for the phase I cancer drug Epothilone D consisted of $30M in initial payments, $180M in milestone payments, and a royalty percentage of sales.[2] In addition, the licensing agreement provided Kosan BioSciences a "buy-in" option at the end of Phase II clinical testing to reimburse a portion of the development costs for an increased royalty share, indicative of the option nature of licensing agreements.

A critical component in pharmaceutical pipeline planning is determining the financial value of a developmental compound in light of the substantial technical and market-based uncertainty inherent in pharmaceutical R&D. Despite many significant contributions on new product development, most existing work from the process systems engineering community has used the traditional net present value (NPV) metric as the financial basis for decision making, which does not include the flexibility to shape market risk during development.[3-9] In contrast, many researchers in the management science community have applied real options valuation (ROV) to R&D investment decisions.[10-13] In view of this, Rogers et al.[14] introduced a stochastic optimization model (OptFolio) of pharmaceutical R&D portfolio management to make resource-constrained portfolio selection decisions in the face of uncertainty. The selection model views new product development as a series of continuation/abandonment options, embedded within a decision tree that reflects the market and technical uncertainty of each candidate project, and decides before each stage of R&D whether to proceed further or abandon the project.

Most work on evaluating pharmaceutical licensing agreements has used probabilistic techniques to examine the factors that influence licensing deals to provide strategic insight into how they should be managed. Arnold et al.[15] performed a regression analysis of historical licensing data to identify the factors that most affect a deal's financial terms. Kalamas et al.[16] used Monte Carlo simulation of hypothetical compounds to calculate the NPV distribution of drug development and suggest trends in when pharmaceutical companies should partner. Although these research efforts have provided strategic direction in managing licensing agreements, a systematic valuation tool is clearly needed for valuing and designing a portfolio of drug alliances in the presence of uncertainty and resource limitations.

Although many qualitative factors affect the valuation of licensing deals, "options-based techniques can help a prospective licensee judge the full value of an asset by quantifying the effects of its uncertain future and of the licensee's ability to bail out should things go badly." [17] Nichols[18] described Merck's analysis of biotechnology partnerships using the Black–Scholes options-pricing model to compare the market value of a licensing opportunity to the up-front cost of entering into the alliance. The hierarchical option nature of drug development projects is derived from the fact that projects have tremendous upside potential with downside risk limited to the amount invested at each stage of R&D. After an initial up-front payment to the biotechnology company to license a candidate drug, the pharmaceutical company has the right—but not the obligation—to make at each stage of development a predetermined milestone/sponsored research payment to continue the alliance. At every point in this sequential investment process, the pharmaceutical company may reserve the right to terminate the alliance because of unfavorable market conditions and/or internal budgetary priorities.

In this article, the OptFolio mathematical programming model is augmented to evaluate partnership opportunities as real options and determine the optimal timing and payment structure (allocation of up-front payments, milestones, and royalties) for proposed alliances in the face of both technological and market/demand uncertainties. This extension gives the OptFolio framework the capability to guide not only internally focused R&D planning decisions but also to evaluate and design external opportunities such as licensing of drug development. The resulting multistage stochastic optimization model captures the impact of managerial flexibility in the context of a portfolio of licensed drugs. The key advantage of this real options–based portfolio approach is that newly arriving information about product performance and market potential is used to manage proactively portfolio selection and R&D development decisions within the entire drug development pipeline.

To gain insight into the selection of potential alliances, the licensing payments are risk-adjusted to equalize the net present value of the deal for the biotechnology company under all choices referred to herein as the *indifference condition*. This biotechnology company choice equalization ensures that the biotechnology company is indifferent to when the alliance is formed, while allowing the pharmaceutical company to select the optimal deal based on the flexibility afforded by the abandonment option. The indifference condition is used to relate the cost to license complete or partial ownership of a biotech drug to the ability of the pharmaceutical company to amplify the value of the drug (that is, *amplification factor*) because of its advanced manufacturing and marketing capabilities. By adjusting the cost of the deal to reflect the technical uncertainty of a given drug and its initial estimated commercial value, the preferred licensing time becomes dependent on only the drug's market uncertainty and the pharmaceutical company's amplification factor. These two factors are then used to provide insight into the design and selection of drug alliances. The proposed framework addresses the following research questions:

(1) What is the optimal stage for the pharmaceutical company to enter into a licensing deal for a given candidate drug?

(2) What is the pharmaceutical company's optimal R&D investment policy under changing market uncertainty and amplification factors?

(3) Within a given therapeutic area, what is the optimal portfolio of alliances and their respective timing and investment policies under time-varying resource constraints?

The article is organized as follows. The OptFolio framework is modified to value the optimal timing of a licensing opportunity by linking the payment structure of all available deals within a hierarchy of real options. The indifference condition is then used in a case study to generate a contour map depicting how the timing of the optimal deal changes as a function of market volatility and the value added by the alliance with the pharmaceutical company. The case study of selecting optimal licensing opportunities is extended to illustrate how changing budgetary levels impact the pharmaceutical company's portfolio composition. Finally, concluding remarks are given on the results of the alliance valuation technique and opportunities to expand the work are highlighted.

Model Development

Originally, a complex mathematical technique used for valuing market traded securities, *options analysis* has emerged as a powerful tool in R&D project planning. An advantage of real options valuation is that it accounts for the strategic flexibility to make midproject corrections as uncertainty is resolved without the flawed assumption of a constant discount rate, used to translate future cash flows into their present value equivalents, as with standard decision tree analysis.[19] With decision tree analysis, the payoffs resulting from different strategic choices have different risks, which require the calculation of a unique market risk-adjusted discount rate at every decision node. In real options analysis, the risk-neutral probability of an event occurring is used instead of the objective probability, providing an accurate way to determine the present value of future cash flows that avoids the computation of discount rates that change over the course of the project.

Although individual R&D projects are not yet traded in the financial markets, Schwartz and Moon[20] argued that the market value of a pharmaceutical R&D project can be approximately tracked using a portfolio of small biotechnology firms specializing in developing similar treatments as a market proxy. Alternatively, many real options practitioners instead use the net present value of the project itself, without flexibility, as the underlying risky asset.[21] Instead, management assumptions about the distribution of outcomes that result upon commercialization, based on estimates of production costs, sales revenue, gross margin, and the probability of achieving high, average, or low sales volumes, are captured using Monte Carlo simulation. From the simulation, the net present value of the project, without decision flexibility, and the volatility of the project's value are determined. Using the project's volatility, a binomial lattice event tree is constructed to depict the uncertainty in the value of the project. Real options analysis does not assume that all chance market events and their associated probabilities can be predicted in advance as with decision tree analysis, but rather that the uncertainty in the market value of the project is resolved over time and the strategic choices optimally exercised in response to this updated information. The arbitrage-free principle of real options valuation thus provides a framework for evaluating the "fair" value of the option to undertake a stage of R&D based on estimates of the current value of the project and its associated volatility.

Model assumptions and limitations

In the context of our modeling framework[14] for licensing deals, a pharmaceutical company is assumed to have many biotechnology companies that are actively seeking partnerships. With the market power residing largely with the pharmaceutical company, a biotechnology company will license its developmental drug to a pharmaceutical company provided that this leads to the licensor's expected net present value remaining constant in both the licensed and unlicensed cases. Note that this indifference condition holds throughout the entire decision-making horizon so that access to a project is unaffected by competition from rival pharmaceutical companies. The biotechnology company manages the research and development of the candidate project once the alliance is formed to alleviate manpower/facility limitations for the pharmaceutical company. Furthermore, the pharmaceutical company's contribution to the alliance affects only the market potential of the candidate compound without changing the technical probabilities of R&D success.

The pharmaceutical company is assumed to be risk-neutral so that it will choose the licensing deal, from the set of available deals, that maximizes the real options value for a given candidate project. An agreement can be signed to acquire a percentage of the candidate drug immediately *or* at a future stage in the developmental pipeline with payments to the biotechnology company beginning at the onset of the licensing deal. Furthermore, the model is constructed such that the pharmaceutical company *can abandon the alliance at the start/end of a particular clinical phase at no cost.* Clearly, abandonment costs could be specified and included in the model to reflect the actual terms of an intellectual property agreement. Note that the entire modeling development described here is constructed from the pharmaceutical company's perspective. Alternatively, the problem could be formulated from the perspective of the biotechnology company.

Looking forward from the present time, the decision model provides the pharmaceutical company the opportunity to license with a biotechnology company at the following points in the developmental pipeline: (1) preclinical development; (2) phase I development; and (3) phase II and (4) phase III clinical trials. Note that the original OptFolio planning horizon has been expanded to include preclinical development as shown in Figure 1, which summarizes the development cycle of a drug from preclinical development through FDA filing and product launch.[22] Reasonable estimates of stage duration for each research phase of a project can be used to calculate the mean time of completion for each stage. Each one of these developmental periods, belonging to the set S of drug development stages, is assumed to require 2 years to complete with another 2 years spent in production scale-up while awaiting FDA approval, bringing the total time horizon from preclinical development to commercial launch to 10 years.

It is important to note that the above-stated assumptions are introduced to provide generalized managerial insights into the optimal timing and investment policy of licensing deals. Traditional financial analysis systematically undervalues risky projects, which may in part explain the current reluctance of pharmaceutical companies to pursue early-stage licensing deals until much of the uncertainty is resolved. Our proposed model seeks to address the risk–reward trade-offs of pharmaceutical

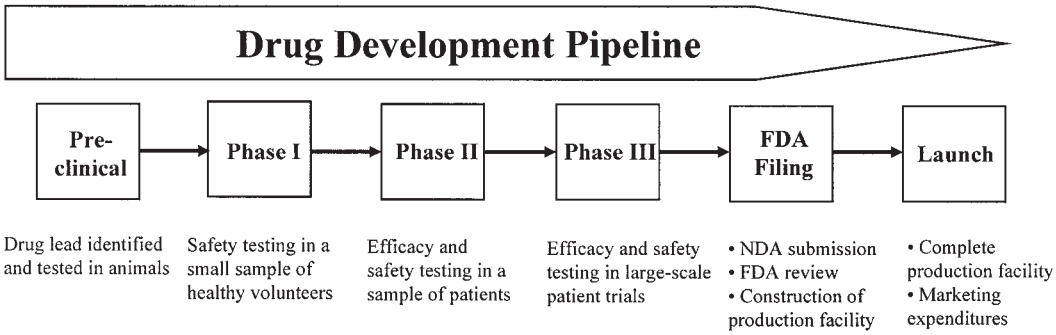

Figure 1. Pharmaceutical pipeline from preclinical development through launch.

in-licensing to quantify the option nature of research and development projects. The aim of this article is to provide an adaptable real options framework to guide managerial thinking on the design and valuation of pharmaceutical alliances. Nevertheless, the model maintains the flexibility to evaluate realistic deal terms as a decision-support tool for licensing negotiations. Restrictive assumptions can be relaxed and the set of available decisions expanded to reflect the unique conditions of proposed pharmaceutical alliances.

The model formulation makes use of the following sets and parameters to describe the problem, which are explained in greater detail in the original OptFolio publication.[14]

Sets

i = product, $i = 1, 2, \ldots, P$
s = stage of drug development, $s = 1, 2, \ldots, S$
t = year of the portfolio planning horizon, $t = 0, 1, \ldots, T$
j = alliance structure in terms of timing and investment allocation, $j = 1, 2, \ldots, J$

For each candidate drug i, portfolio selection decisions made at the present time ($t = 0$) classify the impending stage as $s = 1$ and 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 candidate 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^j_{is} = milestone payment made to biotechnology company under alliance opportunity j at the start of development stage s for drug i
ϕ_{is} = probability of technical success in stage s of development for drug i
B_t = expected in-licensing budgetary allocation for year t

The parameter V_{0_i} represents the estimated value of drug i, based on the net present value of all cash flows that result if the drug is commercialized, at time $t = 0$ of the planning horizon. The market volatility σ_i is the estimated annual standard deviation of the rates of return of product i based on this distribution of cash flows that may result if the product reaches the market. The product value is assumed to follow a geometric Brownian motion, giving rise to a lognormal distribution for the product value with the additional feature that the standard deviation σ_i of the logarithm of the rates of return of the product is proportional to the square root of the time horizon.[23]

The volatility can be estimated by using a Monte Carlo approach to incorporate the multiple uncertainties that affect the cash-flow calculations as described by Copeland and Antikarov[21] and Mun.[19] The calculated volatility remains constant with respect to time because it combines all of the uncertainties in the forecasted business case into a single measure of the market uncertainty of the project. Alternatively, one could estimate the volatility that corresponds to each stage of R&D independently and model the dynamics of the project using separate binomial lattices if evidence suggests that the market uncertainty changes over time.[19] The risk-free interest rate r_f, set at 5%, corresponds to an averaged observable market rate (such as U.S. Treasury Bills). A discrete time step of $\Delta T = 1/2$ is used to represent a 6-month time interval for value upward/downward changes. This chosen interval allows for the market value of a project to move up or down by several scenario nodes within successive decision points, which corresponds to the standard practice of updating market estimates, usually on a quarterly or semiannual basis, during a stage of development.[13]

Given that the complexity of the problem makes it impossible to obtain a closed-form solution, the quadrinomial approach is used to generate an event tree that incorporates the simultaneous resolution of market and technological uncertainties, assuming that these uncertainties are independent of one another.[21] If the estimated starting value of a project without flexibility 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 risk-neutral probability q, whereas the downward movement occurs with probability $(1 - q)$. Again note that the risk-neutral probabilities, not the objective probabilities, are used so that future revenue can be discounted using the risk-free rate of return instead of an event-

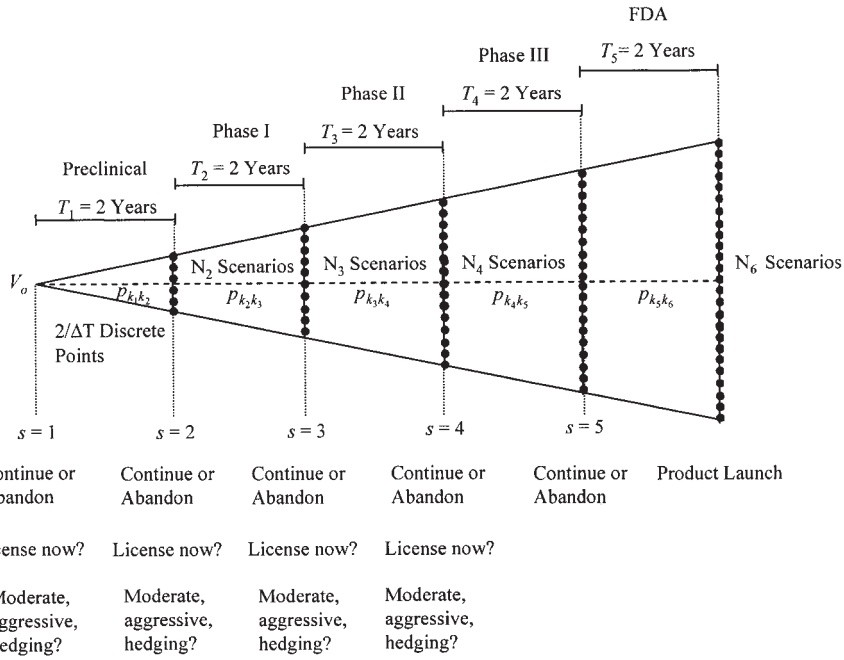

Figure 2. Decision tree for a Candidate Drug Beginning Preclinical Development.

specific, risk-adjusted discount rate. Technological success occurs with probability ϕ_s, whereas failure of a particular testing phase s occurs with probability $(1 - \phi_s)$.

Applying the decision tree framework over discretized time intervals, four branches emanate from every scenario node to represent the possible outcomes in market uncertainty (up/down movements) and technological uncertainty (success/failure). The values of u, d, and q are computed using the formulae for pricing stock options based on the binomial model of Cox et al.[23]

$$u = e^{\sigma\sqrt{\Delta T}} \tag{1}$$

$$d = e^{-\sigma\sqrt{\Delta T}} = 1/u \tag{2}$$

$$q = \frac{e^{r_f\Delta T} - d}{u - d} \tag{3}$$

A *value scenario* corresponds to the resolution of market and technical uncertainty that occurs at the beginning of a developmental stage, where the continue/abandon decision is available. The index $k_s \in \{1, 2, \ldots, N_{is}\}$ 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 equal to $N_{is} = 1 + [(\sum T_{i,s-1})/\Delta T]$. The aggregate commercial value of the candidate drug i for a given value scenario k_s is given by

$$V_{ik_s} = u_i^{k_s-1} d_i^{N_{is}-k_s} V_{0i} \qquad \forall\ i \in P,\ s \in S,\ k_s = 1, 2, \ldots, N_{is} \tag{4}$$

This translates into a five-stage decision tree as shown in Figure 2, with the spread between the available value scenarios increasing as a function of the volatility of the candidate drug. 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 a binomial probability distribution

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

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

$$k_s \le k_{s+1} \le k_s + \frac{T_{is}}{\Delta T} \tag{5}$$

The OptFolio model formulation utilizes binary variables to track the selection/continuation and abandonment of licensing opportunities through the planning horizon. Specifically, $y^j_{isk_s} = 1$ if the alliance for drug i continues into stage s of development, whereas in value-scenario k_s for alliance opportunity j and 0, otherwise. If it is both favorable and feasible under value-scenario k_s to begin the next stage s of development, the drug will be selected to continue with $y^j_{isk_s}$ set equal to one and the pharmaceutical company will make the predetermined milestone payment I^j_{is} to the biotechnology company. However, if it is favorable to abandon the drug alliance in this given value-scenario, the binary variable will be set equal to zero.

Indifference condition

To gain insight into how the real options framework exerts an impact on the selection of potential alliances, the licensing payments are risk-adjusted to equalize the net present value of

the deal for the biotechnology company under all conditions. Specifically, we introduce the concept of the indifference condition to account for technical uncertainty so that the biotechnology company is indifferent to when the licensing agreement is formed.[16] A large pharmaceutical company with advanced marketing resources may generate at least twice the value from a licensed product than would a smaller biotechnology company, depending on the pharmaceutical company's particular expertise in a given therapeutic area.[15] The *expected amplification factor* δ is a parameter thus defined as the measure of the value-added contribution made by the pharmaceutical company to the value of the project, which has an expected value of $V_0\delta$ if an alliance is formed. Alternatively, we can view this parameter as a measure of the biotechnology company's incentive to partner, with a larger δ signifying a higher potential for revenues and a lower cost to license the drug because of the synergy the pharmaceutical company brings to the partnership.

Given that the biotechnology company has the resources to develop the candidate drug i independently, the net present value of the project at $t = 0$ is defined as

$$NPV(Biotech)_{\text{no license}} = \prod_s \phi_s V_0 - E(development\ costs) \quad (6)$$

where the initial value of the drug is multiplied by the technical probability of success for each stage of development that remains and the expected development costs incorporate the time value of money and the technical probabilities that they will be incurred. If the biotechnology company instead chooses to license during alliance opportunity j with the pharmaceutical company, the biotechnology company transfers a percentage of ownership α^j to the pharmaceutical company in return for some combination of up-front payments, sponsored research, and milestone payments. The net present value of the project for the biotechnology company if an alliance is formed is

$$NPV(Biotech)_{\text{license}} = \prod_s \phi_s V_0 \delta(1 - \alpha^j) - E(development\ costs) + E(pharma\ payments^j) \quad (7)$$

where the value of the drug is multiplied by the pharmaceutical company's amplification factor and $(1 - \alpha^j)$ corresponds to the percentage of royalties paid to the biotechnology company upon the commercialization of the licensed product. By invoking the indifference condition, we have

$$E[NPV(Biotech)]_{\text{no license}} = E[NPV(Biotech)]_{\text{license}} \quad \text{(indifference condition)}$$

This yields the following relationship for the pharmaceutical company's payment requirements

$$E(pharma\ payments^j) = \prod_s \phi_s V_0(1 - \delta + \delta\alpha^j) \quad (8)$$

where $1 - \delta + \delta\alpha^j > 0$. Note that Eq. 8 groups expected sponsored research and milestone payments into a single quantity because, often, part of the clinical trial cost is assumed by the pharmaceutical company under a licensing agreement. Given the indifference condition, the net present value of the alliance to the pharmaceutical company becomes equal to

$$NPV(pharma) = \prod_s \phi_s V_0 \delta\alpha^j - \prod_s \phi_s V_0(1 - \delta + \delta\alpha^j) = \prod_s \phi_s V_0(\delta - 1) \quad (9)$$

which interestingly is independent of the percentage of ownership α^j that is negotiated. Therefore, although the biotechnology company, given this description, is indifferent to the timing of the alliance, the pharmaceutical company may not be because of the abandonment option. The net present value expressed by Eqs. 6, 7, and 9 relies solely on information that is available at the present time to give a single expectation of project value based on the conventional discounted cash flow business case. This metric does not reflect the volatility in the market value of the project, which is resolved as R&D is conducted and market conditions change, or the flexibility that the pharmaceutical company has to respond to newly arriving information. Thus, the above-described conditions are next embedded within a real options framework, which identifies a preferred time to license the candidate drug because of the pharmaceutical company's abandonment option.

Investment policies

For each stage in the developmental pipeline when an alliance can be formed, we assume that the pharmaceutical company has three different investment strategies that exemplify the following three postures: (1) moderate, (2) hedging, and (3) aggressive (see Figure 3). In the moderate strategy, the pharmaceutical payments to the biotechnology company are distributed in equal amounts based on their expected values under consideration of the technical risks and the time value of money. The hedging investment policy consists of smaller up-front payments and larger milestone payments in later stages of development, whereas the aggressive investment policy consists of larger up-front payments and smaller late-stage milestone payments. By assuming more risk through an aggressive investment strategy, the pharmaceutical company acquires a larger percentage of product ownership. Alternatively, a hedging investment policy consists of less risk in return for a smaller percentage of product ownership. The distribution of payments, as specified by a contractual licensing agreement, for any type of alliance j is given by

$$I_{is}^j = \prod_s \phi_{is} V_{0_i}(1 - \delta_i + \delta_i\alpha_i^j)(1 + r_f\Delta T)^{\sum_{s=1}^{s-1} T_{is}/\Delta T}\lambda_s^j \qquad \sum_s \lambda_s^j = 1 \quad (10)$$

where the parameter λ_s^j is the fraction of the total licensing payments made to the biotechnology company in stage s of development under alliance choice j and the payments are adjusted for the technical success probabilities and the time value of money. Note that only a payment made at $t = 0$ is contractually guaranteed to the biotechnology company.

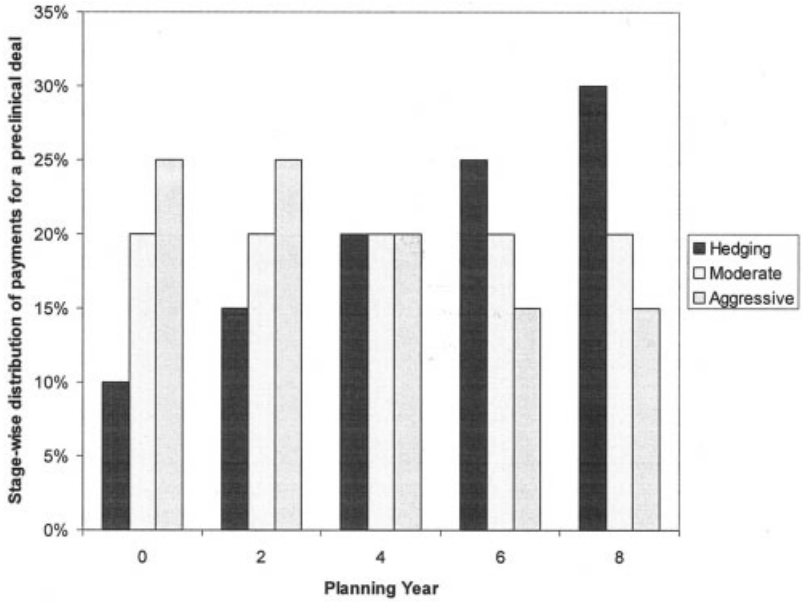

Figure 3. Distribution of licensing payments in R&D investment policies for acquiring a preclinical candidate drug.

To avoid having to specify a hard to estimate analytical expression relating the distribution of payments across stages (λ_s^j) and the percentage of product ownership that is acquired (α^j), we treat the λ_s^j values as parameters and not continuous variables that are a function of ownership percentage. The λ_s^j values could be freely varied in the OptFolio model given such a relationship between payment distribution and ownership percentage. To yield representative payment scenarios, historical data[2] is used to fix a typical percentage of ownership for a given licensing phase to the moderate investment policy. The distribution of payments in the aggressive and hedging strategies is varied to correspond to a slight increase/decrease in product ownership from this fixed value. The combination of four available licensing stages and three investment policies yields 12 possible alliance choices for a preclinical project, as detailed in Table 1. Nevertheless, the OptFolio framework has the versatility to accommodate additional choices if required. To ensure that licensing payments are not made to the biotechnology company until the alliance is formed, the λ_s^j parameters are set equal to zero for stages of drug development when the drug has yet to be licensed. However, the real options valuation of alliances formed at future dates is still affected by the technical uncertainty of prior R&D stages because these later opportunities are only available *if* the entire previous technical development hierarchical chain succeeds.

Model formulation

By considering the definitions and concepts described above, the multistage stochastic optimization model of pharmaceutical R&D portfolio management is formulated as follows:

$$\max ROV = \sum_{i,j} M^j_{i,s=1,k_{s=1}}$$

subject to

$$M^j_{isk_s} = \left[\begin{array}{l} \displaystyle\sum_{k_{s+1}=1}^{N_{i,s+1}} [\phi_{is} p_{ik_s k_{s+1}} z^j_{ik_s k_{s+1}}] \\ -I^j_{is} y^j_{isk_s} + \dfrac{}{(1 + r_f \Delta T)^{T_{is}/\Delta T}} \end{array} \right] \quad \text{(i)}$$

$$0 \le z^j_{ik_s k_{s+1}} \le M^{upper}_{i,s+1,k_{s+1}} y^j_{isk_s} \quad \text{(ii)}$$

Table 1. Description of Alliance Choices

Alliance Choice j	Alliance Type	$\lambda^j_{s=1}$	$\lambda^j_{s=2}$	$\lambda^j_{s=3}$	$\lambda^j_{s=4}$	$\lambda^j_{s=5}$	α^j (%)
1	Preclinical Moderate	1/5	1/5	1/5	1/5	1/5	95
2	Preclinical Hedging	1/10	3/20	1/5	1/4	3/10	85
3	Preclinical Aggressive	1/4	1/4	1/5	3/20	3/20	100
4	Phase I Moderate	0	1/4	1/4	1/4	1/4	85
5	Phase I Hedging	0	1/5	1/5	3/10	3/10	75
6	Phase I Aggressive	0	3/10	3/10	1/5	1/5	90
7	Phase II Moderate	0	0	1/3	1/3	1/3	75
8	Phase II Hedging	0	0	4/15	1/3	2/5	65
9	Phase II Aggressive	0	0	2/5	1/3	4/15	80
10	Phase III Moderate	0	0	0	1/2	1/2	65
11	Phase III Hedging	0	0	0	2/5	3/5	55
12	Phase III Aggressive	0	0	0	3/5	2/5	70

$$M^{j}_{i,s+1,k_{s+1}} - M^{j\_upper}_{i,s+1,k_{s+1}}(1 - y^{j}_{isk_s}) \le z^{j}_{ik_sk_{s+1}} \quad \text{(iii)}$$

$$z^{j}_{ik_sk_{s+1}} \le M^{j}_{i,s+1,k_{s+1}} + M^{j\_upper}_{i,s+1,k_{s+1}}(1 - y^{j}_{isk_s}) \quad \text{(iv)}$$

$$\sum_{j} y^{j}_{i,s=1,k_{s=1}} \le 1 \qquad \forall\ i \in P \quad \text{(v)}$$

$$y^{j}_{isk_s} \le y^{j}_{i,s=1,k_{s=1}} \qquad \forall\ i \in P,\ s \in S,\ j \in J,\ k_s = 1, \ldots, N_{is} \quad \text{(vi)}$$

$$y^{j}_{i,s+1,k_{s+1}} \le \sum_{k_s} y^{j}_{isk_s} \qquad \forall\ i \in P,\ s \in S,\ j \in J,\ k_s = 1, \ldots, N_{is},\ k_s \le k_{s+1} \le k_s + \frac{T_{is}}{\Delta T} \quad \text{(vii)}$$

$$y^{j}_{i,s,k_s-1} \le y^{j}_{isk_s} \qquad \forall\ i \in P,\ s \in S,\ j \in J,\ k_s = 1, \ldots, N_{is} \quad \text{(viii)}$$

$$\sum_{i,s,j} \sum_{k_s}^{N_{is}} p_{ik_{s-1}k_s} I^{j}_{is} y^{j}_{isk_s} \le B_t \qquad \forall\ t \quad \text{(ix)}$$

$$M^{j}_{isk_s} \ge 0 \quad \text{(x)}$$

$$y^{j}_{isk_s} \in \{0, 1\} \quad \text{(xi)}$$

The objective function describes a stochastic dynamic program that starts from the expected payoff received during commercial launch for a given value scenario as defined by Eq. 4. $M^{j}_{isk_s}$ are continuous variables that denote the value of candidate product i in stage s of development following value scenario k_s for alliance opportunity j. The future value of the drug is discounted to the time when the current stage s begins, and the dynamic program described by constraint i defines the value-maximizing decision subject to the appropriate resource limitations. Constraints ii–iv recast as equivalent linear expressions the continuous-binary products $M^{j}_{i,s+1,k_{s+1}} y^{j}_{isk_s}$ using continuous variables $z^{j}_{ik_sk_{s+1}}$, where $M^{j\_upper}_{i,s+1,k_{s+1}}$ are upper bounds on the scenario values of $M^{j}_{i,s+1,k_{s+1}}$ obtained by relaxing the resource constraints and solving the model formulation as an unconstrained recursive LP problem. Because an unconstrained scenario value must characterize the best possible result that is obtainable in the constrained problem, this procedure provides tight bounds on the scenario values and reduces the computational effort required to solve to optimality. Constraint v guarantees that only one licensing opportunity j is chosen for each candidate drug at the initial point of the decision process, with abandonment chosen if all of the binary variables for a given candidate drug are set equal to zero. Constraints vi–viii describe drug precedence and value monotonicity constraints, whereas constraint ix represents budgetary constraints limiting R&D investment. Figure 2 pictorially outlines the hierarchical decision process that determines the optimal stage to license each candidate drug, the optimal investment policy to structure the alliance, and the continuation/abandonment decisions for each possible decision tree.

Case Study Examining Licensing Timing and Structure

In this section, we examine how the preferred licensing time and R&D investment policy change based on the drug's market uncertainty and the pharmaceutical company's amplification factor to provide guidance into the design and selection of drug alliances. It is important to note that for a given drug, the indifference condition makes the preferred licensing time and investment policy dependent only on the market volatility and the amplification factor as the licensing payments are adjusted to reflect the technical risks of the project and its initial commercial value. Thus, the technical success probabilities and initial project value V_{0_i} affect only the magnitude of the deal valuations while preserving the valuation ratios between all possible deals for a specific project (that is, for a given σ_i and δ_i the optimal licensing time and R&D investment policy remain unchanged for any technical success parameters and initial project value V_{0_i}). This enables the construction of contour maps delineating the optimal stage to license and the optimal R&D investment policy by varying only the candidate drug's market uncertainty and the pharmaceutical company's amplification factor. Both of these examples are modeled using the GAMS modeling system accessing CPLEX 7.0 for the MILP optimization part.

Determination of the optimal stage to license

In general, a preclinical deal offers a larger percentage of product ownership to the pharmaceutical company but assumes a greater risk that the project will fail. Looking forward from the present time, the pharmaceutical company must decide whether to license the preclinical candidate drug at $t = 0$ to acquire a percentage of the drug immediately or to license at a future stage in the developmental pipeline ($t = 2$, 4, or 6 years) with payments to the biotechnology company beginning at this licensing stage. As Figure 4 illustrates, preclinical deals for a "moderate" investment policy (alliance choices 1, 4, 7, and 10) become optimal as the amplification factor increases because the pharmaceutical company can enter into the alliance at relatively low cost as a result of the value-enhancing synergy it contributes to the partnership while still obtaining a large percentage of product ownership. Conversely, as the potential benefit of licensing the drug decreases (amplification factor decreases) it becomes more valuable to delay the alliance until market uncertainty is resolved. High volatility favors earlier partnerships because the pharmaceutical company obtains large upside market potential at a lower cost while retaining the ability to control downside risk by the abandonment option. Both the "hedging" and "aggressive" investment policies follow these same trends in license timing.

These results signify that, although early licensing deals are subject to considerable risk of product failure, this risk may be offset by the large percentage of ownership that may lead to a sizeable stake in a blockbuster product. As Figure 4 shows, an amplification factor of 2.2 or more favors preclinical and phase I licensing agreements in a market setting when the biotech-

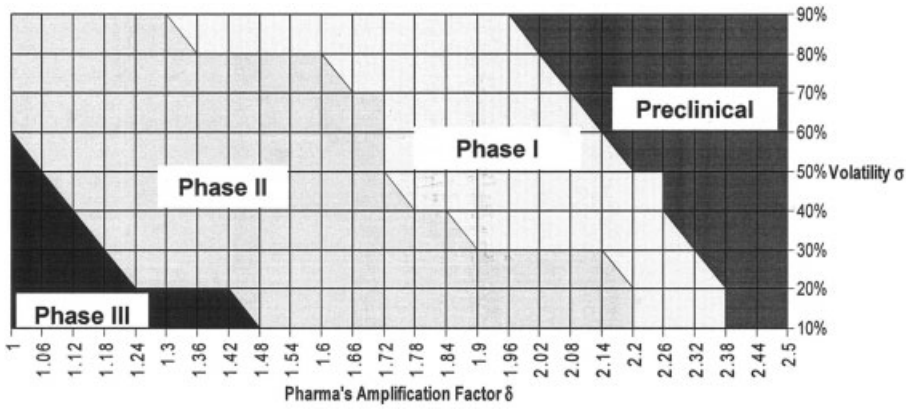

Figure 4. Optimal time to license as a function of market volatility and amplification factor for a moderate investment policy.

nology company is indifferent to the timing of the deal because the large pharmaceutical company has the dominant position. However, only about one third of all alliances between pharmaceutical companies and biotechnology companies are formed in preclinical and phase I development.[2] Although this is certainly attributed in part to biotechnology companies having some market power in influencing the deal terms, the general trend of delaying the alliances is ascribed to many pharmaceutical companies' risk aversion in committing capital to highly uncertain developmental projects. The results of the optimal time to license analysis reinforce the findings of Kalamas et al.,[16] which suggested that early licensing agreements are worth consideration to generate maximum value in the pharmaceutical company's portfolio of licensed projects. This insight directly follows from the ability to shape the risk profile of an R&D project using a stagewise decision process.

Determination of the optimal investment policy

In this second example, we move beyond an equal distribution of licensing payments to explore the case where the pharmaceutical company can select investment policies having different risk profiles. The same framework used in the first example can be used to compare investment policies under changing volatilities and amplification factors. For a preclinical licensing agreement signed at $t = 0$, we have the choice of a "moderate" investment policy, a "hedging" investment policy, and an "aggressive" investment policy, as described by alliance choices 1–3 in Table 1. Note that a moderate preclinical deal includes a 5% royalty ($\alpha^{j=1} = 95\%$). The hedging investment policy consists of smaller up-front payments and larger milestone payments in later stages of development. However, the smaller up-front investment deal includes a 15% royalty ($\alpha^{j=2} = 85\%$) in return for having 75% of the risk-adjusted payments made after the start of phase II testing at $t = 4$. The aggressive investment policy captures complete ownership of the drug at commercial launch ($\alpha^{j=3} = 100\%$), but consists of larger up-front payments and smaller late-stage milestone payments.

Figure 5 shows how the optimal investment policy for a preclinical deal changes as a function of market volatility and the pharmaceutical company's amplification factor. The optimal investment policy is characterized by a willingness to assume higher risk as the amplification factor and product volatility increase. In this case the cost to license the drug is low and the market potential is high, making it advantageous to license complete ownership of the drug at commercial launch. When market uncertainty is low and the cost to license is high, the hedging policy is preferred because it distributes the majority of the total licensing payment after the candidate drug has successfully completed two technical hurdles. Again, an analysis of the optimal investment policy for phase I, phase II, and late-stage deals reveals a similar behavior. Having the flexibility to choose an investment policy is critical as phar-

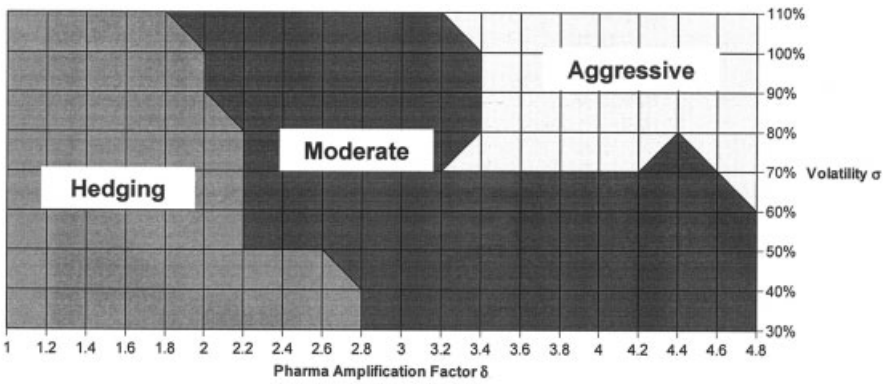

Figure 5. Optimal investment policies for licensing preclinical candidate drugs.

Table 2. Candidate Product Parameters

	V_0	σ (%)	$\phi_{s=1}$	$\phi_{s=2}$	$\phi_{s=3}$	$\phi_{s=4}$	$\phi_{s=5}$
P1	\$500M	80	0.7	0.5	0.5	0.9	0.9
P2	\$300M	50	0.5	0.8	0.6	0.8	0.9
P3	\$600M	40	0.4	0.6	0.5	0.8	0.85

maceutical companies structure licensing deals. In particular, consideration of different investment policies has important implications in balancing risk trade-offs and designing alliances within the limits of budgetary constraints.

Portfolio Optimization of Licensed Projects

This study extends the analysis of individual deals to include the selection and design of a portfolio of alliance deals subject to resource limitations such as available capital. Consider a pharmaceutical company that is interested in licensing one or more developmental compounds to fill a gap in its R&D pipeline for a particular therapeutic area. Given its marketing expertise in this therapeutic area, the pharmaceutical company believes it can double the value of each drug candidate, which corresponds to an expected amplification factor of $\delta = 2$. Constrained by an in-licensing R&D budget, the pharmaceutical company must decide, at the present time, which candidate products to license, when to license them ($t = 0$, 2, 4, or 6), and how best to structure these investments (hedging, moderate, or aggressive). Three developmental compounds, all in preclinical testing, are identified as possible licensing opportunities, and we assume no licensing competition from other pharmaceutical companies. Product launch is estimated to be 10 years away for each of these projects, and a discretization time interval of 6 months is used resulting in 21 commercial value-scenarios for each candidate drug. Required model parameters include the current value of the drug, probabilities of technical success for each stage of development, and the estimated annual volatility in the candidate drug's value. Representative values, based on historical studies of the pharmaceutical industry,[24-26] are chosen for the data used in this example as summarized in Table 2. The distribution of risk-adjusted licensing payments negotiated with the biotechnology companies for any alliance j is given by Eq. 10 using the terms summarized in Table 1.

The expected in-licensing budgetary allocation for $t = 0$ is varied with the other expected budgetary limits expressed in terms of the parameter $B_{t=0}$ as follows: $B_{t=2} = 2 \times B_{t=0}$, $B_{t=4} = 2.5 \times B_{t=0}$, $B_{t=6} = 3 \times B_{t=0}$, and $B_{t=8} = 4 \times B_{t=0}$. Here, the expected available budget for alliances in this therapeutic area increases with each stage of development to reflect the rising costs associated with late-stage clinical development and the pharmaceutical company's greater willingness to support licensed compounds that are closer to market launch.[22] Alternatively, the problem could be analyzed using nonlinear budgetary policies where the firm chooses to shift capital allocation to earlier years to gain immediate access to promising compounds while limiting its in-licensing capacity in later years. Although not explored specifically in this work, the model provides the necessary framework to analyze this interesting problem extension. Thus, the inclusion of resource constraints leads to a more complex planning setting. The resulting mathematical model of the case study includes 1620 binary variables and 15,589 continuous variables and solves to optimality in 3312 CPU s using an IBM RS/6000-270 workstation.

The results for this portfolio selection example are presented in Table 3 for the case where only the moderate investment policy is available and the case where the moderate, hedging, and aggressive policies are offered. When only limited capital is available to license drugs initially, the optimal alliance choices consist of later-stage phase II and phase III licensing deals because of the expectation that capital will be available to license in the future. As the R&D budget increases, the decision model selects earlier licensing deals to capture the upside of acquiring a large percentage of a potential blockbuster product. This is particularly true for candidate P1, which has the largest market volatility and thus the broadest distribution of market value. When all three investment policies are available, the optimal portfolio of alliances balances aggressive investment in P1 with hedging investments in P2 and P3, which have lower market potential, to comply with the budgetary limitations. Note that at $B_{t=0} = \$40$M, the decision model chooses to delay licensing each product by one stage when all investment policies are offered relative to when only the moderate investment policy is available. However, each of these delayed alliances is pursued aggressively to license an increased percentage of ownership. This suggests that risk-averse pharmaceutical companies should consider the risk management strategy of delaying licensing agreements until early technical hurdles are cleared, but then offering deals containing larger up-front payments to negotiate a large percentage of product ownership.

To further elucidate the flexibility offered by multiple investment policies, Figure 6 illustrates how the total alliance ROV is affected by the availability of investment policies under different R&D resource limitations. The option value of having multiple investment policies, defined as the difference between the ROVs of these two cases, is largest when the available budget is the smallest. This is a consequence of the OptFolio model affording more flexibility in distributing licensing payments, at different times and amounts, to satisfy the resource constraints. By considering additional investment policies to the three included in the model, a pharmaceutical company could creatively allocate its resources to maximize the revenue potential of its alliances. Similarly, the difference

Table 3. Optimal Portfolio of Alliances under Changing Resource Constraints

Budget at $t = 0$ (\$Mil)	Moderate Investment Only			All Investment Policies		
	P1	P2	P3	P1	P2	P3
3	Phase III	Phase II	Phase III	Phase III Hedging	Phase III Hedging	Phase III Hedging
5	Phase I	Phase III	Phase III	Phase II Aggressive	Phase III Hedging	Phase III Hedging
10	Phase I	Phase III	Phase III	Phase I Aggressive	Phase III Hedging	Phase III Hedging
15	Phase I	Phase II	Phase III	Phase I Aggressive	Phase I Aggressive	Phase III Hedging
40	Preclinical	Phase I	Phase I	Phase I Aggressive	Phase II Aggressive	Phase II Aggressive

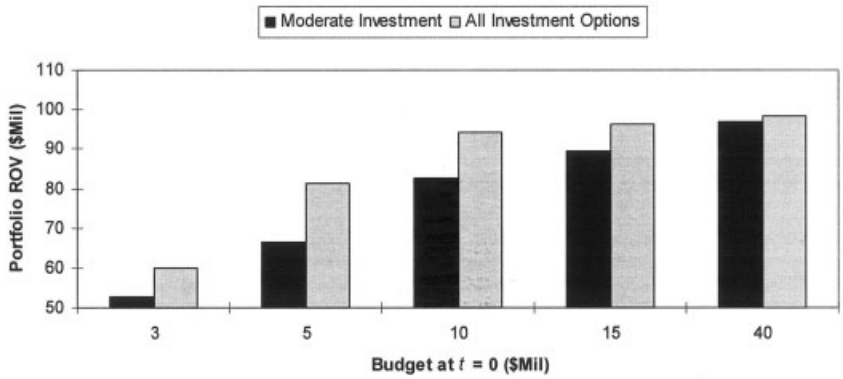

Figure 6. Comparison of optimal portfolio ROV for different investment options with respect to R&D budget at $t = 0$.

between the NPV and the ROV for each candidate project in the absence of resource constraints gives the value of the abandonment option, as shown in Figure 7. Because of the indifference condition, the pharmaceutical company's NPV of licensing each candidate product is independent of alliance timing or investment policy. However, the flexibility to select the time and structure of the alliance is a source of considerable value. Overall, the NPV metric undervalues the portfolio of alliances by about 15% because of its inability to capture managerial flexibility. This supports the application of the real options framework to recognize project volatility and the flexibility to manage this uncertainty.

Concluding Remarks

The goal of this article was to model licensing deals to acquire developmental biotechnology drugs as real options represented by decision trees that capture the market and technical uncertainty of each candidate drug. The OptFolio model of R&D portfolio selection was extended to assess resource-constrained partnership opportunities as real options and establish the optimal timing and payment structure (allocation of up-front payments, milestones, and royalties) for proposed alliances. The indifference condition that risk-adjusts the licensing payments was introduced to explore how the optimal time for the pharmaceutical company to license and the R&D investment policy change as a function of the market volatility and the value added to the alliance by the pharmaceutical company. The results suggested that pharmaceutical companies should consider the benefits of early licensing agreements and aggressive R&D investment to generate maximum value in their portfolio of licensed projects because of their ability to terminate these alliances in the event of disappointing market circumstances and/or budgetary restrictions.

The analysis of licensing deals can be extended from just evaluating hypothetical deals to actually using the OptFolio model to assist in the negotiation of real deals. In the OptFolio model, the licensing payments were risk-adjusted to keep the NPV of the biotechnology company constant under the assumption that it is indifferent to when licensing occurs, which is not always true. The exact deal structure must be negotiated and explicitly defined in the licensing contract. The model formulation thus allows for the values of various deal permutations regarding the distribution of up-front payments, milestones, royalties, and equity to be quantified. In addition, the OptFolio model framework supports a Monte Carlo simulation technique to perform a sensitivity analysis of input parameters and to balance risk vs. reward trade-offs.[27] The model introduced herein examined the flexibility provided by the abandonment option. Clearly, this is not the *only* option that is available for shaping uncertainty in licensing deals. A number of other strategic options can be envisioned and embedded in various stages of the development process. For example, a licensing agreement may grant the pharmaceutical company exclusive marketing rights in North America but reserve own-

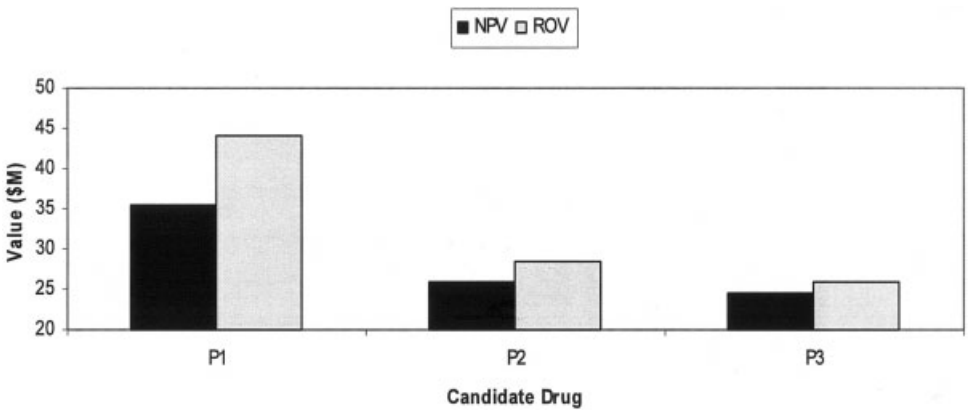

Figure 7. NPV and optimal ROV for each candidate product.

ership of the product in other markets for the biotechnology company. Using the decision model, the fair value of exercising the option to purchase global marketing rights can be calculated to guide the pharmaceutical company in negotiating the contract. As possible deal terms are identified, the OptFolio model can be modified to account for each of these deal options, which will lead to a comprehensive decision-making tool that can help direct licensing design. Ultimately, this framework provides a blueprint for contrasting new licensing strategies against historical data and rank-ordering them depending on risk preferences and resource availability.

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