A CASE STUDY ON THE DESIGN OF PHARMACEUTICAL R&D LICENSING DEALS

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Abstract

In today's intensely competitive business environment, pharmaceutical companies are augmenting their product pipelines by in-licensing proprietary compounds or drug discovery-related technologies from external sources. In a sample case study, the OptFolio model of pharmaceutical R&D portfolio management is used to evaluate the optimal stage to license developmental drugs in three distinct therapeutic categories in the face of technological and market uncertainties. Partnership deals are modeled within a decision tree as a series of continuation/abandonment options for the licensing pharmaceutical company, and Monte Carlo simulation is utilized to perform a sensitivity analysis of key managerial assumptions regarding market value and technical success probabilities. Using a proposed preclinical alliance deal as an example, the decision model determines the fair value of the abandonment option to guide the licensee in the negotiation of specific deal terms. The managerial implication of this analysis is that a real options approach to designing a licensing agreement enhances the deal's expected value because of the ability to control downside risk via the abandonment option.

Keywords

Pharmaceutical portfolio planning, real options valuation, drug licensing, stochastic programming

Introduction

To achieve their annual revenue objectives, 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.

The option nature of pharmaceutical licensing deals is derived from the fact that developmental projects have tremendous upside potential with downside risk limited to the amount invested at each stage of R&D. Following an initial up-front payment to license a candidate drug, the licensing 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 licensee may reserve the right to terminate the alliance due to unfavorable market conditions and/or internal budgetary priorities.

Many researchers in the management science community have applied real options valuation (ROV) to R&D investment decisions, but not within complex resource-constrained instances encountered in realistic situations (Ding and Eliashberg, 2002; Huchzermeier and Loch, 2001). In view of this, Rogers et al. (2002) introduced a stochastic optimization model (OptFolio) to make resource constrained portfolio selection decisions using real options valuation. The OptFolio model was later extended to evaluate R&D licensing opportunities as real options and determine the optimal timing and payment structure (allocation of upfront payments, milestones/sponsored research, and royalties) for proposed alliances in the face of technological and

market uncertainty (Rogers et al., 2004). To provide managerial insight into the optimal time to license a developmental project, the licensing payments were risk-adjusted to equalize the net present value of the deal for the licensor under all deal permutations. This indifference condition was used to generate a contour map depicting how the timing of the optimal deal changes as a function of the project's estimated market volatility and the value-enhancing synergy the licensee brings to the alliance.

This paper presents a case study analyzing the optimal time to license candidate projects within three distinct therapeutic areas: cardiovascular, genitourinary (pertaining to the urinary system), and hormonal. With the indifference condition relaxed, Monte Carlo simulation is used within the OptFolio decision framework to evaluate realistic alliance deals based on the historical probabilities of technical success and the average licensing deal terms. Using a preclinical genitourinary deal as an example, the fair value of the abandonment option is calculated to aid in the negotiation of exact licensing stipulations.

Model Formulation

The OptFolio stochastic optimization model of pharmaceutical R&D portfolio management, described in detail in Rogers et al. (2004), is as follows:

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

subject to

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

$$0 \le z^{j}_{ik_sk_{s+1}} \le M^{j\_upper}_{i,s+1,k_{s+1}} \cdot y^{j}_{isk_s} \quad (2)$$

$$M^{j}_{i,s+1,k_{s+1}} - M^{j\_upper}_{i,s+1,k_{s+1}} \cdot (1 - y^{j}_{isk_s}) \le z^{j}_{ik_sk_{s+1}} \quad (3)$$

$$z^{j}_{ik_sk_{s+1}} \le M^{j}_{i,s+1,k_{s+1}} + M^{j\_upper}_{i,s+1,k_{s+1}} \cdot (1 - y^{j}_{isk_s}) \quad (4)$$

$$M^{j}_{i,s=5,k_{s=5}} = u_i^{k_{s=5}} d_i^{N_{i,s=5}-k_{s=5}} \alpha^{j} V_{o_i} \quad (5)$$

$$u_i = e^{\sigma_i \sqrt{\Delta T}};\ d_i = 1/u_i;\ q_i = \frac{e^{r_f \Delta T} - d_i}{u_i - d_i} \quad (6)-(8)$$

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

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

$$k_s \le k_{s+1} \le k_s + \frac{T_{is}}{\Delta T} \quad (9)$$

$$\sum_j y^{j}_{i,s=1,k_{s=1}} \le 1 \quad \forall\ i \in P,\ s \in S,$$

$$j \in J, k_s = 1, \ldots, \quad N_{is} \quad (10)$$

$$y^{j}_{isk_s} \le y^{j}_{i,s=1,k_{s=1}} \quad \forall\ i \in P,\ s \in S,$$

$$j \in J, k_s = 1, \ldots, \quad N_{is} \quad (11)$$

$$y^{j}_{i,s+1,k_{s+1}} \le \sum_{k_s} y^{j}_{isk_s} \quad \forall\ i \in P,\ s \in S,$$

$$j \in J, k_s = 1, \ldots, \quad N_{is} \quad (12)$$

$$y^{j}_{i,s,k_s-1} \le y^{j}_{isk_s} \quad \forall\ i \in P,\ s \in S,$$

$$j \in J, k_s = 1, \ldots, \quad N_{is} \quad (13)$$

$$\sum_{i,s,j} \sum_{k_s}^{N_{is}} p_{ik_{s-1}k_s} I^{j}_{is} y^{j}_{isk_s} \le B_t \quad \forall\ t \quad (14)$$

$$M^{j}_{isk_s} \ge 0 \quad (15)$$

$$y^{j}_{isk_s} \in \{0,1\} \quad (16)$$

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 Eqn. (5). Eqn. (6) – (9) characterize the binomial value movements, the risk-neutral probability of an upward movement, and the market transition probabilities. $M^{j}_{isk_s}$ 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 Eqn. (1) defines the value-maximizing decision subject to the appropriate resource limitations. Eqn. (2) – (4) recast as equivalent linear expressions the continuous-binary products $M^{j}_{i,s+1,k_{s+1}} \cdot y^{j}_{isk_s}$ 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 $M^{j}_{i,s+1,k_{s+1}}$. The binary variables $y^{j}_{isk_s}$ control continuation/abandonment decisions, the stochastic probabilities of market uncertainty and technical uncertainty are given by $p_{ik_sk_{s+1}}$ and ϕ_{is}, respectively, and I^{j}_{is} is the cost of continuing alliance choice j in developmental stage s. Eqn. (10) – (13) describe drug precedence and value monotonicity constraints while Eqn. (14) represents budgetary constraints limiting R&D investment.

R&D Licensing Case Study

Looking forward from the present time, the pharmaceutical company has the opportunity to license at the following points in the developmental pipeline: (i) preclinical development, (ii) phase I development, (iii) phase II, and (iv) phase III clinical trials. Each one of these developmental periods is assumed to require two years to complete with another two years spent in production scale-up while awaiting FDA approval. A discrete time step of $\Delta T = 1/2$ is used to represent a six-month time interval for value upward/downward changes. Required OptFolio model parameters include the current estimated value of the drug V_{o_i}, probabilities of technical success for each stage of development ϕ_{is}, the estimated annual volatility in the candidate drug's market value σ_i, the milestone/sponsored research costs for continuing alliance j for each stage I_{is}^{j}, and the percentage of product ownership acquired by the licensee α^{j}. Table 1 and Table 2 summarize the data used in this example, which are based on historical pharmaceutical performance and licensing trends (DiMasi, 1995; Recombinant Capital, 2004; PharmaProjects, 2004). Note that the market potentials and deal terms of all three therapeutic areas are treated here the same because therapy-specific data could not be found.

In the first part of the case study, the OptFolio model addresses the risk versus reward tradeoffs of licensing early to realize a larger percentage of the rewards if the product is commercialized while simultaneously facing a larger risk of development failure. To facilitate Monte Carlo simulation, the technical success probabilities were modeled as triangular distributions (minimum, most likely, maximum) within a range +/- 10% of the values indicated in Table 1, V_o was modeled as the triangular distribution ($250, $375, $500), and σ was simulated as the triangular distribution (35%, 50%, 65%). Figure 1 shows the normalized average ROVs (mean real options values of all alliance choices divided by the largest mean ROV) within the three therapeutic areas based on Monte Carlo simulation using 10,000 iterations. The mathematical model of the case study includes 540 binary variables and 5,197 continuous variables and solves to optimality in 1.0 CPU s for each iteration using an IBM RS/6000-270 workstation. Note that the model allows the licensing pharmaceutical company to terminate the alliance at the start/end of a stage of development at no cost.

The OptFolio model chose to license the genitourinary compound in preclinical development in nearly 100% of the simulations because its high expected probability of technical success (23%) reduced the risk of having a large sunken investment cost due to developmental failure. In this case, the model suggests that a licensee should consider an early stage alliance to capture a large percentage of product ownership for a relatively low cost. In contrast, the model chose to license the cardiovascular compound at Phase I in 39% of the simulations, at Phase II in 54% of the simulations, and at Phase III in 7% of the simulations because of its low expected probability of technical success (4%).

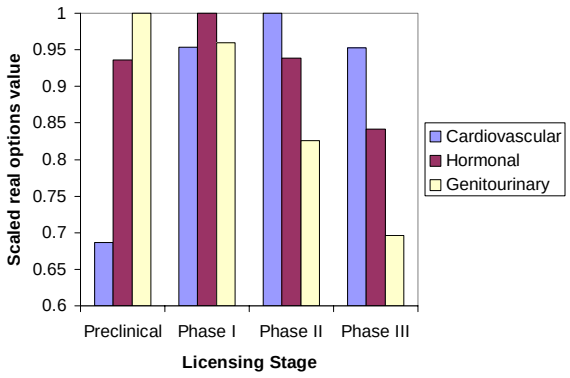

Figure 1. Scaled real options values for licensing deals at each stage of development

Here, the analysis reveals that it may be optimal to delay licensing until the compound demonstrates efficacy in preclinical and Phase I development because the lower product ownership/higher licensing cost are more than offset by waiting for technical uncertainty resolution before committing to the alliance. For the hormonal compound (expected probability of technical success equal to 8%), the model results recommend that a prospective licensee should wait until after preclinical development is completed before pursuing a Phase I alliance (89% of the simulations), which balances favorable ownership rights with lower costs.

In the second part of the case study, the OptFolio model determines the fair value of the abandonment option to guide negotiations for a preclinical licensing deal involving a genitourinary compound having estimated probabilities of technical success as summarized in Table 1. Suppose that competition for this particular genitourinary compound is high, and the licensor demands the following deal terms: $I_1 = \$5M$, $I_2 = \$15M$, $I_3 = \$30M$, $I_4 = \$50M$, $I_5 = \$100M$, and $\alpha = 90\%$ (10% royalty rate for licensor). Discounted cash flow analysis reveals that the estimated V_o has the triangular distribution of ($200, $300, $600) and the estimated σ has the triangular distribution of (30%, 60%, 100%) depending on the set of market assumptions used.

The value of the abandonment option is defined as the difference between the project's real options value

and expected net present value (no abandonment). Figure 2 depicts the Monte Carlo simulation derived values of the abandonment option. The mean value of the abandonment option was found to be \$14.8*M* if no exit costs are included. During negotiation, the licensor requests an additional \$5*M* upfront payment (I_1 = \$10*M*)

Table 1. Candidate Product Parameters .

Therapy	V_0	σ	$\phi_{s=1}$	$\phi_{s=2}$	$\phi_{s=3}$	$\phi_{s=4}$	$\phi_{s=5}$
Cardio.	\$ 375 M	50%	33%	68%	47%	42%	95%
Genitour.	\$ 375 M	50%	56%	84%	74%	69%	95%
Hormonal	\$ 375 M	50%	44%	67%	54%	53%	95%

Table 2. Alliance Terms Based on Stage of Licensing.

Alliance *j*	Stage	$I^j_{s=1}$	$I^j_{s=2}$	$I^j_{s=3}$	$I^j_{s=4}$	$I^j_{s=5}$	α^j
1	Preclinical	\$5M	\$ 6M	\$ 9M	\$ 12M	\$ 18M	92%
2	Phase I	0	\$ 10M	\$ 11M	\$ 20M	\$ 24M	90%
3	Phase II	0	0	\$ 15M	\$ 28M	\$ 42M	80%
4	Phase III	0	0	0	\$ 38M	\$ 72M	70%

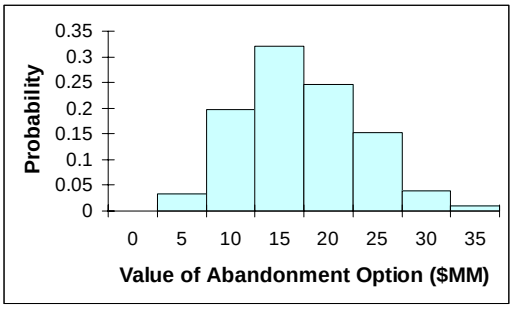

Figure 2. Probability Distribution of Abandonment Option Value

and a termination fee equal to 20% of the scheduled milestone/sponsored research payments in order for a termination clause to be stipulated in the licensing agreement. Monte Carlo simulation results revealed that the mean value of the abandonment option was \$8.8*M* under this proposed clause, thus indicating that the fair value of the abandonment option exceeded the cost of its inclusion in the licensing contract. Furthermore, the simulation derived real options values with abandonment were between \$2.3*M* and \$91.3*M* while the simulation derived net present values were between -15.4*M* and \$70.5*M*. This is a result of using the abandonment option to maximize upside potential while reducing downside risk in disappointing market conditions.

Conclusions

In this paper, a modified version of the OptFolio model was presented to allow for the values of various deal permutations to be compared. In a sample case study, the model identified the optimal stage to license three different classes of therapeutic compounds by quantifying the risk versus reward tradeoffs of licensing early within the context of the flexibility afforded by the abandonment option. Using the decision model, the fair value of exercising the abandonment option in a proposed licensing deal was calculated to guide the licensee in negotiating the contract. As possible deal terms are identified, the set of available options can be extended and valued, which leads to a comprehensive decision making tool to guide licensing design.

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