RISK MANAGEMENT IN REAL OPTIONS BASED PHARMACEUTICAL PORTFOLIO PLANNING

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Abstract

Recent research efforts in options pricing have shown that real options approaches are more appropriate for R&D project valuation because they account for the value of managerial flexibility to react to arising contingencies during R&D development. This technique allows for strategic decision-making in the context of hedging opportunities present in the financial markets by tracking the uncertainty in the value of a project in development through market-traded securities. In this work, we incorporate a Monte Carlo simulation procedure to a stochastic optimization model (***OptFolio***) of pharmaceutical R&D portfolio selection. This framework provides for a sensitivity analysis of candidate drug valuations and a risk management analysis for balancing risk versus reward tradeoffs. The resulting valuation method is applied to a case study involving the selection of optimal product portfolios, those that minimize risk for a specified level of return, to begin Phase I clinical testing from a set of candidate drugs.

Keywords

Real options, portfolio selection, pharmaceutical pipeline planning, stochastic programming

Introduction

In the pharmaceutical industry, the optimal management of the new product pipeline has emerged at the forefront of all strategic planning initiatives. Once a "seller's market," pharmaceutical companies are now under increasing market pressure from managed healthcare organizations, the entrance of branded competitor drugs, and competition from expired-patent generic drugs. In addition, the technical uncertainties of pharmaceutical R&D are significant in light of tightening regulatory restrictions and unforeseen scientific results. As pharmaceutical companies strive to satisfy their investors' growth expectations, the emphasis is on identifying blockbuster products and avoiding the high late-stage developmental costs of marginal projects.

Existing work on new product development in the process systems engineering community has focused on the technical outcome of R&D stages. Papageorgiou et al. (2001) and Gatica et al. (2001) applied stochastic optimization to the problem of pharmaceutical planning and capacity management. Blau et al. (2000) developed a probabilistic simulation model of a pharmaceutical product development pipeline to prioritize candidate drugs based on their reward/risk ratios. Subramanian et al. (2000) formulated a simulation-optimization framework that combined mathematical programming with discrete event simulation to make planning and scheduling decisions under uncertainty. In all of these methods, the traditional net present value (NPV) metric was used as the financial basis for decision-making, which assumes that all future cash flows are static, ignoring the managerial flexibility to gather more information about a project's potential and change the course of action to enhance the upside while limiting the downside. Myers (1984) classified R&D investment opportunities as *real options* best captured with the options analysis framework developed by Black and Scholes (1973) in finance literature.

The basis of real options valuation (*ROV*) is that a company can use a hedging portfolio consisting of cash and market-traded securities whose volatility is correlated with the market value of the R&D project in question to value the uncertainty present in the development process. In this context, Rogers et al. (2002) introduced a stochastic

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optimization model (***OptFolio***) of pharmaceutical R&D portfolio management, which viewed 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. This paper constitutes an extension of the ***OptFolio*** model by using Monte Carlo simulation to calculate the reward versus risk profile of each candidate drug. Inclusion of the portfolio selection technique of Graves et al. (2000) allows for the mitigation of portfolio risk during R&D development. We demonstrate this approach through a case study whereby we construct an efficient frontier of optimal portfolios that minimize risk for a desired level of return and compare the results to those given by the ***OptFolio*** model without Monte Carlo simulation.

Augmented Model Formulation

The ***OptFolio*** stochastic optimization model of pharmaceutical R&D portfolio management is as follows:

$$\max ROV = \sum_{i} M_{i,s=1,k_{s=1}}$$

subject to

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

$$0 \le z_{ik_sk_{s+1}} \le M^{upper}_{i,s+1,k_{s+1}} \cdot y_{isk_s} \quad (2)$$

$$M_{i,s+1,k_{s+1}} - M^{upper}_{i,s+1,k_{s+1}} \cdot (1 - y_{isk_s}) \le z_{ik_sk_{s+1}} \quad (3)$$

$$z_{ik_sk_{s+1}} \le M_{i,s+1,k_{s+1}} + M^{upper}_{i,s+1,k_{s+1}} \cdot (1 - y_{isk_s}) \quad (4)$$

$$y_{isk_s} \le y_{i,s=1,k_{s=1}} \quad \forall\ i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is} \quad (5)$$

$$y_{i,s+1,k_{s+1}} \le \sum_{k_s} y_{isk_s} \quad \forall\ i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is} \quad (6)$$

$$y_{i,s,k_s-1} \le y_{isk_s} \quad \forall\ i \in P,\ s \in S,\ k_s = 1, \ldots, N_{is} \quad (7)$$

$$\sum_{i,s} \sum_{k_s}^{N_{is}} p_{ik_{s-1}k_s} I_{is} y_{isk_s} w_{ist} \le B_t \quad \forall\ t \quad (8)$$

$$M_{isk_s} \ge 0 \quad (9)$$

$$y_{isk_s} \in \{0,1\} \quad (10)$$

Equation (1) characterizes a stochastic dynamic program 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. The binary variables y_{isk_s} control continuation/abandonment decisions for these market scenarios, the stochastic probabilities of market uncertainty and technical uncertainty are given by $p_{ik_sk_{s+1}}$ and ϕ_{is}, respectively, and I_{is} is the investment cost of developmental stage *s*. Equations (2) – (4) linearize the the continuous-binary products $M_{i,s+1,k_{s+1}} \cdot y_{isk_s}$ using continuous variables $z_{ik_sk_{s+1}}$ where $M^{upper}_{i,s+1,k_{s+1}}$ are upper bounds on the scenario values of $M_{i,s+1,k_{s+1}}$. Equations (5) – (7) describe drug precedence and value monotonicity constraints while Eq. (8) represents budgetary constraints limiting R&D investment.

Figure 1 illustrates the nature of the portfolio selection decisions under market and technical uncertainty for candidate drugs under consideration to begin Phase I clinical testing, assuming commercial launch is six years away.

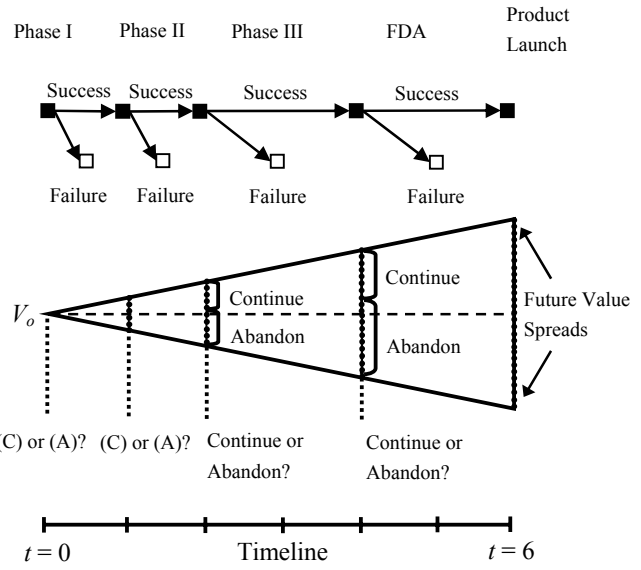

Figure 1. Schematic of product selection decisions under technical and market uncertainty

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. Consequently, the *ROV* is always non-negative and an *ROV* = 0 occurs when a candidate drug is not chosen to begin Phase I testing. Using fixed parameters ϕ_{is} for the probabilities of technical success instead of incorporating 0 (failure) – 1 (success) binomial probabilities does not account for sunken investment costs that occur when a project is terminated during development because of clinical failure. A realistic distribution of developmental outcomes should include both R&D losses and the financial rewards of successful commercial launch (Blau et al., 2000).

To facilitate a sensitivity analysis that incorporates R&D losses, the ***Optfolio*** model is modified to include the possibility of sunken investment costs through binomial technical success probabilities. Monte Carlo simulation is used to generate the probability distribution of portfolio returns. If in a simulated R&D outcome a candidate drug is a technical failure, then the R&D investment to that point is lost. In the event of technical success in all three clinical trials and FDA approval, the *ROV* of the candidate drug at $t = 0$ is computed using the continuation or abandonment option to limit downward market conditions and increase upside potential.

A flaw of many portfolio selection devices is that they evaluate projects in isolation, which can result in a distorted view of the project's effect on the overall product portfolio. Graves et al. (2000) suggested a risk management technique to choose R&D portfolios based on minimizing risk for a given level of return. They used the gini coefficient, defined as twice the covariance of an individual project's return and the cumulative probability distribution of the portfolio's return, to measure the risk of each project. The augmented model formulation (***MinRisk***) incorporating this risk management technique into the ***Optfolio*** model is given as follows:

$$\min Risk = \sum_i x_i G_i \qquad \text{subject to}$$

$$\sum_i x_i \overline{ROV_i} \geq R_{\min} \tag{11}$$

$$\sum_i x_i \leq B \tag{12}$$

$$x_i \in \{0,1\} \tag{13}$$

where $\overline{ROV_i}$ is the mean real options valuation and G_i is the gini coefficient of drug i determined by the ***Optfolio*** model using Monte Carlo simulation. Equation (11) ensures that the chosen portfolio meets a specified minimum level of *ROV* return, Eq. (12) limits the number of candidate drugs that can be included in the product portfolio, and x_i is the binary selection variable for drug i. Incrementally varying the specified level of portfolio return, ***MinRisk*** is solved repeatedly to construct an efficient frontier of optimal drug portfolios (minimum total risk) for the specified level of return.

Pharmaceutical Portfolio Case Study

As an illustrative example of the ***OptFolio*** and ***MinRisk*** models, we consider a pharmaceutical company that has nine candidate drugs ready to begin Phase I clinical testing. The duration of each phase of clinical development is postulated as follows:

Phase I – one year
Phase II – one year
Phase III – two years
FDA approval – two years

Following a successful FDA approval phase, the product can be immediately commercialized under the assumption that capacity investments and production preparations were made during the two years spent awaiting FDA approval. In general, candidate products with high probabilities of technical success and high current value to future investment ratios are preferable. However, real options valuation may show that a riskier project (higher market volatility σ_i) can be more valuable because it has a larger upside while still maintaining a fixed, staged level of potential loss. Restricted by resource constraints, the pharmaceutical company must decide which candidate projects to fund for further development during the upcoming year.

Required ***OptFolio*** model parameters include the current value of the drug V_o, probabilities of technical success for each stage of development ϕ_{is}, the investment costs for each stage of development I_{is}, and the estimated annual volatility in the candidate drug's market value σ_i. Table 1 summarizes the data used in this example.

Figure 2 shows the simulated portfolio *ROV* containing the nine candidate drugs described in Table 1 based from Monte Carlo simulation using 10,000 iterations.

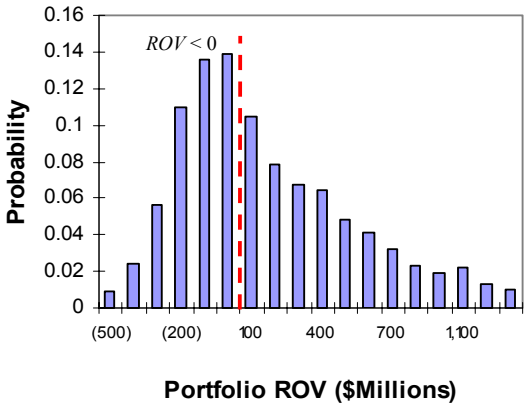

Figure 2. Portfolio ROV probability distribution derived from Monte Carlo simulation

The technical success probabilities were simulated as binomial random parameters and V_o, I_{is}, and σ_i were simulated as uniform random parameters within a range +/- 20% of the values indicated in Table 1. The probability distribution was approximately log-normal, which reflected the fact that most candidate drugs fail during R&D and experience fixed investment losses, but the few surviving drugs may have high valuations. Approximately 47% of the simulations resulted in a negative net *ROV* as candidate drugs failed during clinical testing, but the upside from successful commercial launchs raised the average portfolio *ROV* to over $100 M.

The Monte Carlo simulation allowed for input parameters to be regressed against resulting *ROV* values,

Table 1. Candidate Drug Parameters

	V_o	σ	$\phi_{s=1}$	$\phi_{s=2}$	$\phi_{s=3}$	$\phi_{s=4}$	$I_{s=1}$	$I_{s=2}$	$I_{s=3}$	$I_{s=4}$
P1	\$400 M	60%	0.4	0.5	0.6	0.8	\$15 M	\$15 M	\$50 M	\$100 M
P2	\$250 M	70%	0.5	0.7	0.8	0.9	\$10 M	\$20 M	\$70 M	\$80 M
P3	\$650 M	60%	0.5	0.6	0.8	0.8	\$30 M	\$40 M	\$70 M	\$150 M
P4	\$600 M	80%	0.5	0.5	0.6	0.75	\$20 M	\$30 M	\$75 M	\$150 M
P5	\$300 M	45%	0.7	0.35	0.7	0.85	\$10 M	\$25 M	\$35 M	\$80 M
P6	\$1000 M	100%	0.5	0.5	0.5	0.8	\$20 M	\$50 M	\$75 M	\$200 M
P7	\$100 M	20%	0.9	0.75	0.8	0.9	\$5 M	\$15 M	\$25 M	\$45 M
P8	\$120 M	75%	0.7	0.8	0.8	0.9	\$5 M	\$10 M	\$25 M	\$45 M
P9	\$240 M	15%	0.8	0.7	0.8	0.9	\$20 M	\$40 M	\$50 M	\$50 M

leading to a measurement of the sensitivity of *ROV* to different model parameters. In this example, the mean simulation-derived *ROV* was most sensitive to Phase III and FDA success probabilities because they contained the risk of large sunken investment costs if these late-stage trials failed.

Modifying Eq. (8) to allow for the selection of a maximum of six candidate products, the ***OptFolio*** model selected P2, P3, P4, P6, P8, P9 and had a total *ROV* of \$119 M. Figure 3 shows the efficient frontier generated by solving the ***MinRisk*** model iteratively, increasing the required portfolio return R_{min} after each run. Every point shown in Figure 3 is "efficient," meaning that it represents the optimal R&D portfolio that minimizes risk (as given by the gini coefficient) for a desired level of portfolio *ROV*. The ***MinRisk*** result matched the ***OptFolio*** selection only when the required portfolio return was allowed to exceed \$110 M.

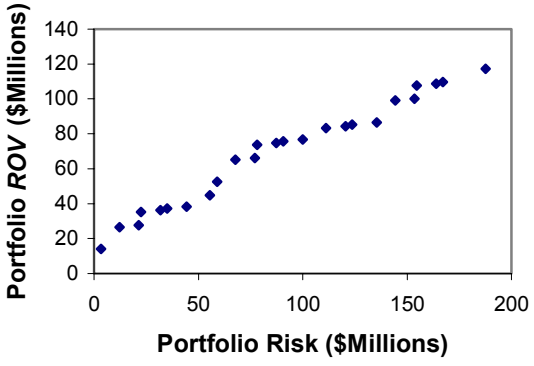

Figure 3. Efficient frontier of optimal portfolios that minimize risk for a given level of return

Conclusions

In this paper we described how to incorporate a probabilistic simulation of model parameters into the ***OptFolio*** model of pharmaceutical R&D. The integration of the risk management strategy of Graves et al. (2000) improved the decision model by capturing "project interactions so as to minimize portfolio risk for any given return." The applicability of this approach was demonstrated by a portfolio selection case study, which illustrated the risk versus reward tradeoffs of new product development in the pharmaceutical industry. The results of the sensitivity analysis revealed that simulation-based *ROV*s were largely impacted by Phase III and FDA success probabilities, consistent with the desire of pharmaceutical companies to avoid the high late-stage investment costs of risky, marginally profitable products.

Acknowledgments

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