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**PARTNERSHIP CONDITIONS FOR NEW DRUG DEVELOPEMNT
BASED ON A REAL OPTION**

A Thesis in

Industrial Engineering

by

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Abstract

The partnership between a big pharmaceutical company which has capital and marketing resources and a biochemical company which possesses intellectual property of a candidate drug has become a trend in new drug development projects. While preoccupation of market share is important for big pharmaceutical companies, such positioning is beyond a small biotechnology company's capabilities to deal with a project which requires substantial time and huge investment to commercialize the product. To realize a mutually beneficial partnership, conditions and timing should satisfy the both parties. This paper suggests a real option methodology by which managerial decisions have their basis in the value of the option premium to determine the optimal timing and conditions accompanying the partnership. Various factors such as contractual finances, ownership ratio, project value, and money policy are considered to determine the optimal timing. This study can provide the interests of both pharmaceutical and biomedical companies with a blueprint for partnership.

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Chapter 1

Introduction

Research and development (R&D) projects for a new product imply that scientific and technical knowledge regarding a particular product apply to their creation and improvement. As the complexity of scientific and technological development increases, the uncertainty of a R&D project increases, and consequently, the cost of the R&D projects increase astronomically. The pharmaceutical industry has become a research-oriented sector in which R&D is quite important. Compared to R&D as a percent of sales for other US industries, the pharmaceutical industry estimates 17% percent of sales applied to R & D in 2000. This amount is significantly large because other high-technology industries that are regarded as research-oriented fields (e.g. electrical & electronics, 8.4%; telecommunications, 5.3%; automotive, 3.9%) (PhRMA, 2002). According to trade association Pharmaceutical Research and Manufacturers of America (Washington, DC), from 1995 to 2005, the pharmaceutical industry reported that R&D expenses increased from \$23 billion to \$59 billion in real terms: an increase of 160% (Kessel and Frank, 2007). Synergistic effects

Although R&D spending by the pharmaceutical industry has increased steadily over the past decade, the industry's productivity has fallen. The implication is that the productivity of R&D investments has been declining, over the same period as proven by the number of submissions for regulatory approval of novel drug candidates. The US Food and Drug Administration (FDA) reported that the number of new drugs submitted to the FDA declined from 88 in 1995 to just 49 in 2004. Although the likelihood is that a new drug will successfully progress through the stages of clinical testing and receive regulatory approval as new technology

tools increases, the number of new candidate treatments continues to decline. The diseases that remain without satisfactory treatments are much more complex than those already the beneficiaries of cures because the underlying mechanisms of newly recognized sicknesses are currently not completely understood. The result is that finding new treatments is difficult without new and innovative knowledge.

To cope with the high level of difficulties in discovering new candidate drugs and enormous R&D expense, the number of partnerships among companies who may complement each other has rapidly increased since the 1990s. According to J. Hagedorn (2001), high-tech industries involving such interests as information and medical technology lead the trend toward R&D partnerships by representing 80% of this domain.

A partnership is the relationship existing between two or more persons or companies to expect enhancement effects that cannot be obtained with only one side's efforts. Specifically, Savvy and Sholters (2006) defines the effects of these synergies through partnership as follows: risk sharing and flexibility. Developing new drug to launch in the market embeds the countless risks such as technical risk of phase failures, long lead time until revenue occurs and market risk after launch-out. Licensing agreements between pharmaceutical company and biomedical company enable to share its risk as well as responsibilities and required capital and lead to reduce the amount of the risk each has to cover. The companies to agree in the partnership can have flexibilities to intensify positive aspects by taking the other's core competencies and by supplementing the lack points each other in uncertain circumstances.

Viewing partnerships in the medical industries in specific, newly established pharmaceutical biomedical alliances are the main partnership-structure for completing new drug

development projects. Partnerships between a big pharmaceutical company, which has capital and marketing resources, and a biotechnology company, which possesses intellectual property of a candidate drug, have become a trend in new drug development projects. While preoccupation of market share is important for big pharmaceutical companies, such positioning is beyond a small biotechnology company's capabilities to deal with the substantial time and huge investment required to commercialize a product.

To realize a mutually beneficial partnership, conditions and timing should satisfy the both parties. For instance, pharmaceutical companies, who are licensors, do not achieve a partnership when the value of the project is less than the total licensing payment. Biotechnology companies also would agree to a partnership when the value of the transferred project is larger than the alliance payment. Moreover, since the value of the project varies as factors surrounding the market and the project change, the decision regarding optimal conditions and timing of an alliance are crucial and need careful examination.

The overall trends and factors impacting partnerships between pharmaceutical companies and biotechnology companies have had significant examination. Cohen et al. (2005), Smith (2006), and Arnold et al. (2002) all studied the advantages and disadvantages of partnerships in medical fields and elaborated the synergistic effects throughout a partnership by providing case studies.

This paper proposes the real option analysis to evaluate partnership opportunity as a call option for pharmaceutical company and as a put option for biomedical company. The characteristics of the partnership agreements include high uncertainty associated with project cash flows, unavailability of immediate payoffs and existence of multiple technical uncertainties at different R&D phases. Licensing agreements of new drug development requires sequential

decision points companies made at every stages. A series of sequential nature of the agreement and high uncertainties of the new drug development project make decision makers fascinate to choose real options. Decision makers for the agreement want to get specific guidelines from the evaluation methodology so the binomial pricing approaches which is easy and efficient to calculate and which can provide transparent answers with closed solutions are selected.

Several authors have addressed partnerships on the basis of a “real options approach.” Roger et al. (2005) evaluates the R&D licensing opportunities from the perspectives of pharmaceutical companies based on the real option to determine the best license-timing, and Merck applied real options with respect to valuation of biotechnology investment (Nichols, 1994). However, studies that analyze licensing in a view of biotechnology companies are rare because most studies of licensing alliances in the medical field focused only on pharmaceutical companies.

Also, little work has been done to understand the effect of real options in light of synergies created by licensing and the optimal timing and subsequent terms that both types of companies can satisfy, and simultaneously obtain maximum gains. Among numerous decisions in finalizing the new drug development project or licensing, real option analysis offers valuable information for go/no-go decisions based on evaluation of the project. Contractors may bring about a licensing agreement by expecting the positive effects as well as negative ones after the agreements. On the other, they may also decide not to reach an unsatisfactory agreement by letting time flow until the uncertainties are resolved. Real option analysis enables contractors to think over multi-sided views for licensing deals. The aim of this study is to fill this gap by presenting a framework that explains the interrelationship between two types of companies, when licensing a product, based on the real option methodology.

The goal of this research is to provide a concept for optimal timing for a contractual agreement which establishes an R&D project partnership, and the best policy, including optimal timing and licensing expenses, that satisfies both pharmaceutical and biotechnology companies, based on the real option approach.

In the following chapter, this study discusses the background of new drug development, partnerships, and real option application to R&D project evaluation. Chapter 3, drawing on the real option approach as well as conditions and methodologies to achieve successful partnership, elaborates new drug development project policies. Chapter 4 analyzes numerical examples related to the partnership. Finally, concluding remarks appear in Chapter 5.

Chapter 2

Background

2.1. Partnership trend in the medical industry

Traditionally, partnerships in the medical sector more or less accomplished before 1990 contained initiatives only for large pharmaceutical companies because they tended to offer capital and clinical development capabilities, which are the driving forces for commercializing products (Kessel & Frank, 2007), and such positioning is beyond a small biotechnology company's capabilities to deal with the substantial time and huge investment required to commercialize a product. Therefore, the pharmaceutical companies are only interested in less risky, candidate drugs in the later stages of development. Licensing deals are rarely achieved before the final clinical test stage (Phase III clinical trial).

However, drastic changes across almost all the industries in the 1990s also had a significant influence in the medical sectors (Hagedorn, 2001). Interests focusing on health improvement are rising, and biomedical knowledge has increased as well. Owing to this favorable atmosphere, pharmaceutical companies delivered double-digit growth rates, on average. The intrinsic assets for the companies are the candidate drugs in pipelines, so these companies continuously invest in R&D projects with the potential for increased profits. To sustain this path, at least four new drug launches per year are required for every one of the large pharmaceutical companies (Bolten and Degregorio, 2002), but only one new drug is actually launched, on average. This decline in productivity leads to the crisis in the management of pharmaceutical companies.

Tracking the productivity crisis reveals that the most significant reason for the decline in pharmaceutical introduction is fortified regulations on overhauls. Regulatory authorities stress safety and stability requirements in response to observed risks from already commercialized products, as well as anticipated risks not yet realized. Also, development of a new medicine for a previously uncured disease requires considerable effort and investment. Some diseases without the previous definite treatment are recognized as too complex to understand, so a cure may be obtained only by integrating emerging knowledge, such as genome information, into the R&D process (Hu et al., 2007). However, most revolutionary but risky approaches are conducted by a biotechnology company who is inclined toward greater technological challenges (Schwartz, 2000). And this adventurous propensity increases the probability of a break-through via a very limited way to discover a new remedy. To overcome the risk, pharmaceutical companies depend significantly on strategic alliances with biotechnology companies because the innovation gap results from a lack of a promising product in the drug pipeline (Pavlou and Belsey, 2005).

Comparing the partnership trends in the medical industry before 1990 and after 1990, the initiative power of biotechnology companies relatively increased as the need for promising new drugs in the pipeline to pharmaceutical companies rapidly increased (Kessel & Frank, 2007). The popularity of new candidate drugs that biotechnology companies developed have ridden a rising curve, and the rate of competition among compelling new products increases. The change in the medical industry provides stronger positions for biotechnology companies for selecting partners on more favorable terms. The somewhat balanced relationship of a partnership stresses the need to carefully evaluate an association. The critical component in an alliance is determining the financial value of the project throughout the partnership, as affected by market and technical

uncertainties. As a result of these factors, this study examines the project evaluation process to obtain perspectives for appropriate partnerships.

2.2. New drug development process

The pharmaceutical R&D process consists of a number of well-defined phases that must be processed in a fixed, sequential order. If no barrier arises to interrupt this implementation, many procedures occur until a drug enters the commercial market. All the newly launched drugs in the market typically pass through the following stages (Marcus and Hassan, 2006; Kennedy et al., 2006):

- **Discovery**

This stage is a preparation step occurring from synthesis of new molecular entities.

Actually, this stage requires a significant amount of effort to create and prove its candidacy as a cure, because most new chemical compounds are eventually abandoned.

- **Pre-clinical**

In order to register the chemical compound as a potential candidate drug, the company must first submit safety data to prove that the drug is safe enough based on small-scale clinical trials. New chemical components are screened to check pharmacological effects and toxicology in vitro, in vivo, and then through animal testing. Tests on drug absorption and metabolism, as well as the speed with which the drug and its metabolites are excreted from the body are executed. If the drug appears to be a promising candidate for further development, the company will report the preclinical result to the Food and Drug Administration (FDA), Investigational New Drug Application Division (IND). If

IND allows this candidate drug component to be tested in humans, the next stage are the clinical trials.

- **Phase I clinical trials**

Phase I Clinical Trials include the initial testing of a new drug in humans. These tests are conducted on a very small number of healthy volunteers to obtain information on toxicity, safe dosing range through observation of side effects associated with increased/decreased doses in humans.

- **Phase II clinical trials**

This test involves a larger number of selected patients who could gain benefit from the candidate drug. This data provides assurances of safety and efficacy to the intended objectives.

- **Phase III clinical trials**

This trial is the last testing step to obtain additional evidence of efficacy and safety.

These tests involve the largest number of patients who suffer from the disease that the candidate drug is to treat. In some sense, this final test is a kind of simulation before commercialization because the test setting is almost the same as real-time application to patients would be after approval for marketing.

- **FDA filing and review**

If all manner of tests are completed and the resulting data are organized according to FDA regulations, the company will submit a New Drug Application (NDA) to the FDA for review. Approval from the FDA allows the company to begin to commercialize drug officially.

2.3. Real option application for R&D project evaluation

The development of a new drug is risky. Of the virtually infinite number of molecular compounds that may have pharmacological effects, drug companies must choose carefully the compounds in which to invest the millions of dollars required to cover development costs prior to launching a new product in the market. According to the Katin et al. (2006) the average cost involved in the development of a single successful drug is estimated to be \$1.2 billion, representing a significant hurdle. The extremely expensive clinical and preclinical studies required to demonstrate safety and efficacy take an average of about 15 years. Together, these represent a huge investment without reaping any profit prior to commercialization. Adding to the high level of uncertainties, Kessel & Frank (2007) asserted that the rate of products arriving at launch-phase in the market is very low. They suggested that from every 10,000 compounds initially identified, only one, on average, will ultimately be approved. Even among the most promising groups of drug candidates that show sufficient potential to warrant human clinical trials, only one in five will ever be approved.

Given the high level of uncertainties associated with cash flow, unavailability of immediate payoff, and high technological failure rate, R&D projects involving new drug development is difficult to evaluate. At every point of the investment decision process, the project manager determines the direction to follow depending on the project's value. An appropriate valuation of R&D expenditures is a critical issue (instrument) for deciding whether or not to invest in a new drug's application.

Investigating the background of project-value studies identifies discounted cash flow (DCF) as a common measurement (Brandao, Dyer and Hahn, 2005). Through the DCF approach,

the net present value (NPV) of a project is calculated by discounting the future expected cash flow at a discounted rate. The net present value of a project gives the project manager an indication for guiding investment decisions. However, despite wide use, the DCF approach has limitations because the DCF fails to account for the value of managerial maximization of the expected returns. Thus the outcome of the project will be unaffected by the firm's future decisions unless managerial flexibilities are considered (Schwartz, 2000).

Discounted cash flow analysis, a traditional valuation model, fails to fully capture the value created by pharmaceutical companies because they do not correctly model the nature of the drug developing process and cannot capture the flexibilities. R&D Project value can be variable by numerous decisions that project managers have made until the project finalized. The R&D project is surrounded over the market uncertainties and technical uncertainties. These uncertainties make project managers consider whether the project will be continued as planned or planned course of actions will be altered in the future given then-available information. Real option analysis was developed to improve the DCF approach which is taking the fixed path for investment decision by considering these uncertainties (Loch, 2001).

A real option analysis is a relatively new and insightful way to consider corporate investment decisions. The basis for this technique is the premise that any decision, either to invest or divest real assets, can be viewed as an option. This type of option is similar to a financial call option in that it gives the holder not an obligation but a right to undertake an investment. Viewed in this way, the use of real options could allow project managers to make decisions with managerial flexibility. Managerial flexibility is quite important in an uncertain, changing economic environment. It enables the project manager, when making an investment

decision, to maintain an open option and wait until the market condition is favorable before final commitment.

Numerous studies have emphasized the importance of real options analysis for corporate managerial decision-making, including McDonald and Siegel (1986), Brennan and Schwartz (1985), Dixit (1989), and Grenadier and Weiss (1997). Dixit and Pindyck (1994) mentioned that irreversible investment can be explained as a perpetual financial option, and the real option theory can provide more accurate valuation of a project. The model suggested by Dixit and Pindyck (1994) showed that an investment can be exercised when a project's value is larger than or equal to the total cost, and its optimal timing to invest can be determined when the option premium has the largest positive value. Clark and Rousseau (2002) provided a study of an optimal timing problem for an option to abandon. Herath and Park (2002) illustrated the value of managerial flexibility to delay a project.

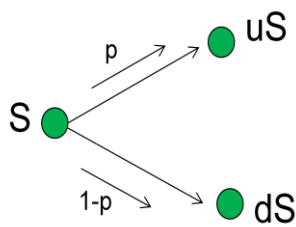
A multi-stage investment such as a new drug development project is an especially good candidate for evaluation using real options because of the project's intrinsic characteristics: high uncertainty associated with project cash flows, unavailability of immediate payoff and multiple sources of uncertainty at every project phase. Application of real options pricing has been proposed for determining value in R&D projects in the literature of Nichols (1994), Herath and Park (1999), Rogers et al. (2005). For instance, Mitchell and Hamilton (1988) applied real options to drug valuation with the price of a call option on the future commercialization of the project. Roger et al. (2002) solved the portfolio selection decision using real option valuation from the perspectives of pharmaceutical companies.

Option premium is identified by the uncertainty of the value of the underlying asset (S), the striking price (X) and the time to expiration (T). To calculate the option premium, the

uncertainty of the value of the project, over time, is modeled as a stochastic process. The optimal value for this is obtained by a partial differential equation of Bellman's Equation with boundary conditions (Mun, 2006; Herath, 2002). This continuous approach is so complex that the closed form might not exist. Also, this approach, based on continuous time, is not well suited to value the asset by multi-stage investment because later staged decisions are contingent upon those that occur earlier.

Discrete approximation is suggested as a simple approach. Also assumed is that underlying asset (S) follows a multiplicative binomial process, one of the stochastic processes. The binomial pricing approach developed by Cox et al. (1979) is known as not only transparent and computationally efficient (Brandao et al., 2005; Dimasi et al., 2003), but also suggests a closed form solution for the real-life problem. It implies that investors obtain the specific guideline if they track all the procedures step-by-step. For this reasons, this study primarily uses this discrete real option approach.

As a method to express the uncertainty of a new drug development project, the value of the project follows a multiplicative binomial process as shown in Figure 2.1. The binomial tree approximates a geometric motion approximation of the uncertainty in the value of the project without options over time and incorporate options in this tree. The value of underlying asset value (S) can be uS with probability, p , and dS , with probability $(1-p)$ at one discrete time.



- S : Value of underlying asset
- u = Up step size
- d = Down step size
- p = Risk-neutral probability
(probability of an upward move to uS)

Figure 2.1 Binomial pricing approach

A binomial pricing approach can be viewed as tree methodology with binary chance branches. The initial underlying asset (S) will become either uS ($u > 1$) with probability, p , (risk neutral rate) or dS ($d < 1$) with probability $1 - p$.

Examining the relationship between u , d , and p , allows creating a replication portfolio that has the same cash flow as the individual project (S). Its portfolio is made by purchasing the underlying asset with borrowed money. For a simpler approach, one period model is observed. The main assumption is that the stock price follows a multiplicative binomial process as shown in Figure 2.2. Risk-free rate (r_f) is defined as a profit rate corresponding to risk-free security. The portfolio is composed of purchasing shares, A , of the underlying security with a current price, S , per share and lending, B , at the risk-free rate. Currently the portfolio's value (V) equals $AS - B$. The value of the portfolio at the end of one period can be expressed as V_u and V_d as follows.

$$V = AS - B$$

$$V_u = A(uS) - B(1 + r_f)$$

$$V_d = A(dS) - B(1 + r_f)$$

These equations are solved for A and B .

$$A = (V_u - V_d) / (uS - dS)$$

$$B = (uV_d - dV_u) / (u - d)(1 + r_f)$$

And Figure 2.2 summarizes the flow of replicating the portfolio.

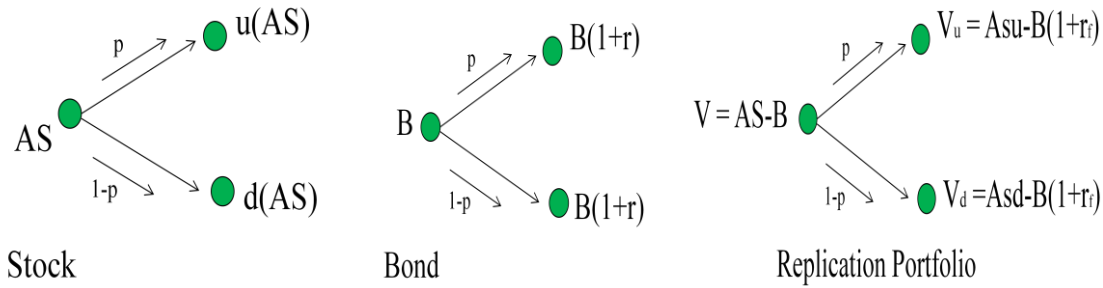


Figure 2.2 Replicating the portfolio

The relevance with real option concept shows that the portfolio payoff is exactly same as the profit from applying the call-option as in Figure 2.3.

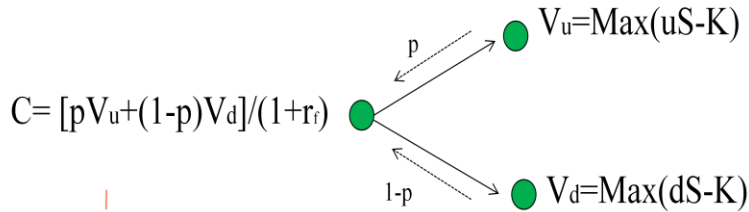


Figure 2.3 Calculation by using a risk-neutral probability in one step

Therefore,

$$V = AS - B$$

$$= pV_u + (1 - p)V_d ,$$

where,

$$p = \frac{(1+r_f-d)}{(u-d)} \text{ is the risk neutral possibility.}$$

The value of the portfolio, C , at the starting point is found by discounting the value of the expected output (V_u and V_d) with respect to the risk-neutral probability, p , to time zero.

Because the replicating portfolio's payoff is exactly same as that of the call option, its current value must equal the value of the call option. Thus, the value of the call option is obtained by discounting the expected value of the option with respect to the risk-neutral probability (p) and using risk free rate (r_f). If the call option, C , is larger than zero, it is exercised by paying the strike price, B , and receiving the underlying asset, AS . The central idea of option pricing can be applied to the value of a real asset.

Chapter 3

Implementation

3.1. Model of a single company based on the real option

New drug development is a sequential process. At least in the process pharmaceutical companies use to review the status of the drug's testing the decisions of whether or not to continue with its development or abandon the project. The decisions depend on factors such as potential therapeutic benefits, expected frequency and severity of adverse reactions, projected additional development, marketing and estimates of the future revenue stream (Dimasi et al., 1991).

Once the new chemical component is found, it must traverse a well-defined pipeline prior to its launching in the market. If the cost for preclinical testing is invested and the results are successful, the company has the option to conduct three more clinical tests and complete FDA filing to commercialize the drug, or to abandon the project.

The decision procedure to develop the new drug is the same as the one to exercise a call option. Companies with a new drug project have the right to continue or abandon it because of market and technological uncertainties, just as a financial option could be exercised or nullified due to the existence of an unstable financial index. Plus, the profit of the project could be obtained after finalizing all staged investments and achieving all staged technological successes, as Figure.3.1 shows. This sequential nature of investments for new drug development projects could be regarded as purchasing a coupon for exercising a call option on the expiration date of a financial option. These analogies allow pharmaceutical companies to evaluate the project on a

call option basis. The ways to calculate the option premium by considering continue/ abandonment cases throughout the 5-staged decision continuum are seen as Figure 3.1.

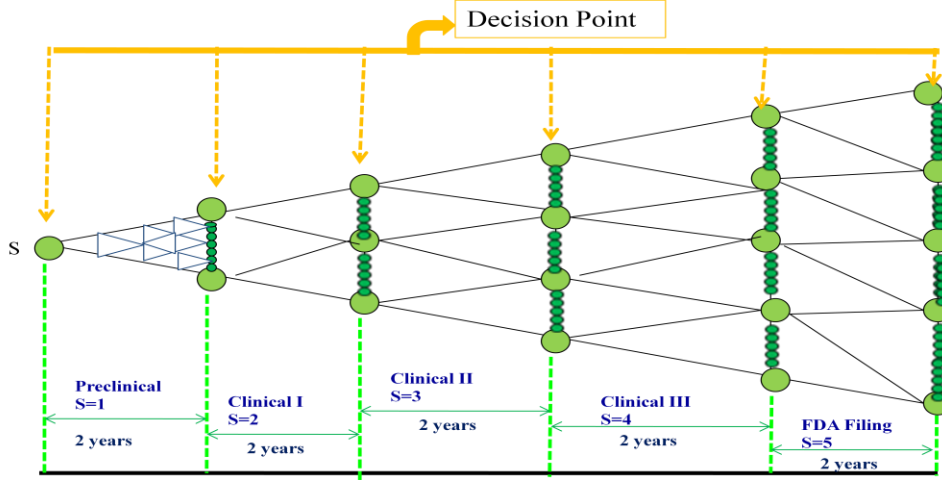


Figure 3.1 Decision tree for new drug development

The key parameters for the proposed formulation are identified and defined as:

S = stage of drug development ($S = 1, 2 \dots N$)

V_0 = current value of drug at $t = 0$

V_t = value of drug at time (t)

u = upward movement in value

d = downward movement in value

p = risk-neutral probability of upward movement

r_f = risk free rate

Z_s = probability of technical success at stage s

T_s = length in years of stage s ($T_s = 2$ for this case)

K_s = investment cost of development at stage S

T = length of stage from the current stage to the expiration date

N_s = number of scenarios of available at the beginning of the current stage

vol = volatility in the market uncertainty

V_o = current value of original drug project

L = time when the alliance is attained

The first step is to create a lattice which considers the upward effect and downward effect at every discrete time as presented in Figure 3.2. The parameter V_0 represent the estimated value of a drug based on the net present value of all cash flow that results if the drug is commercialized at time, $t=0$, of the planning horizon. The market volatility (vol) is the estimated annual standard deviation of the rates of return of a product. If the estimated starting value of a project without flexibility is V_0 , its multiplication of up and down movements (u & d) is driven by market uncertainty.

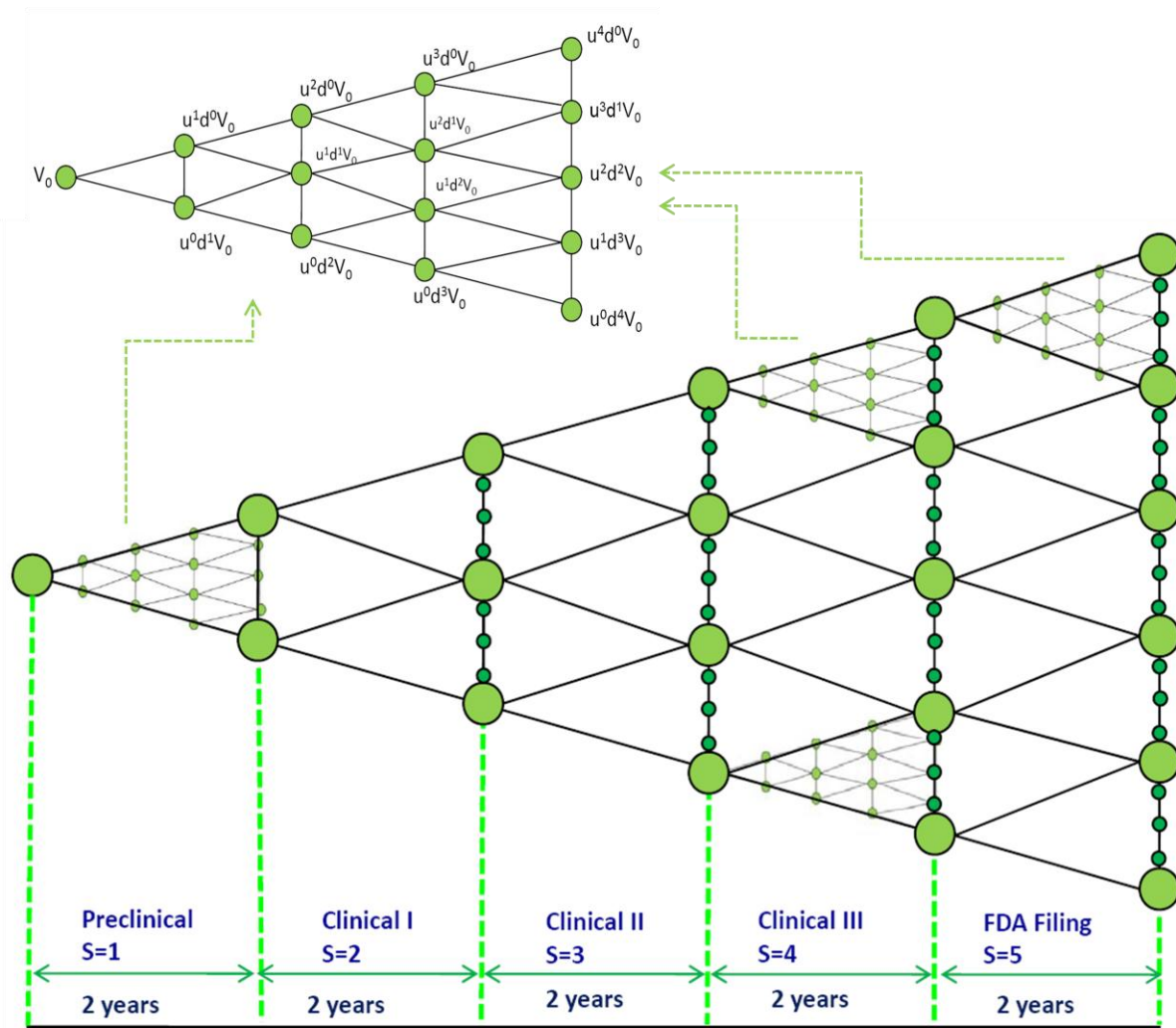


Figure 3.2 Binomial pricing tree (showing possible value scenarios for a product at the end of preclinical testing $N = 4$)

If a project begins at preclinical testing at $t=0$, the value of the project available at the end of preclinical testing ($t=2$) can be obtained by:

$$V_{t=2} = V_0 u^{N-i} d^i \quad (i = 0, 1, 2 \dots N) .$$

Figure 6 explains the binomial tree when the number of available scenarios for a project at the end of preclinical testing is 4. The maximum value a project can reach is $u^{20} d^0 V_0 a$, and the minimum value is $u^0 d^{20} V_0$ at the end of the 5th stage. The project value at the end of Clinical Phase I testing ($t=4$), Phase II testing ($t=6$), Phase III testing ($t=8$) and FDA approvals ($t=10$) can be calculated by:

$$V_{t=2} = V_0 u^{N-i} d^i \quad (i = 0, 1, 2 \dots N)$$

$$V_{t=4} = V_0 u^{2N-i} d^i \quad (i = 0, 1, 2 \dots 2N)$$

$$V_{t=6} = V_0 u^{3N-i} d^i \quad (i = 0, 1, 2 \dots 3N)$$

$$V_{t=8} = V_0 u^{4N-i} d^i \quad (i = 0, 1, 2 \dots 4N)$$

$$V_{t=10} = V_0 u^{5N-i} d^i \quad (i = 0, 1, 2 \dots 5N)$$

Equation 3.1 Terminal node valuation ($t=10, S=5$)

The next step is to evaluate a real option based on a binomial lattice that is made by 1st step. A binomial lattice contains every possible scenario that a new drug development project can have with the maximum value of the project, $u^{20} d^0 V_0$, and the minimum value, $u^0 d^{20} V_0$.

To describe this step simply: The starting terminal nodes move backward to the 1st node throughout the intermittent nodes by backward induction. The upward market movement, u , occurs with risk-neutral probability (p) where the downward movement occurs with probability ($1-p$). And risk-neutral probabilities are used so that future revenue can be

discounted using the risk-free rate (r_f) of return. In detail, terminal nodes are calculated by maximization between executing the option and letting the option expire as worthless if the cost exceeds the benefits of execution as seen Equation 3.1. If the benefits of execution exceed the loss, the option will be exercised. Otherwise, the option will be abandoned. And its calculation is expressed by Equation 3.2.

$$C_{t=10}^{i_5} = \max(0, V_5 Z_5 - K_5, 0)$$

Equation 3. 2 Terminal node valuation ($t=10, S=5$)

What makes this option valuation worthwhile is the assumption of no technical failure as an obstacle. Unless the project arrives at technical success before completion, the project must be abandoned which implies a lack of reimbursement for a technically failed project. Therefore, the probability of technical success must be considered at every decision point. The value of the terminal node, that is the 1st decision point, is calculated as in Equation 3.2.

The next concern in valuation is the calculation of intermediate nodes. This is well described in Figure 3.3. Intermediate nodes are calculated using a risk-neutral probability analysis until reaching decision points where the exercise or abandon decision is made. Calculation of the decision points are obtained the same the one for the terminal node case as in Equation 3.3:

$$C_{t=8}^{i_4=m} = \max(0, \sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=10}^{i_5=j} Z_4 - K_4, 0) \quad (m = 0, 1, 2 \dots 4N)$$

$$C_{t=6}^{i_3=m} = \max(0, \sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=8}^{i_4=j} Z_3 - K_3, 0) \quad (m = 0, 1, 2 \dots 3N)$$

$$C_{t=4}^{i_2=m} = \max(0, \sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=6}^{i_3=j} Z_2 - K_2, 0) \quad (m = 0, 1, 2 \dots 2N)$$

$$C_{t=2}^{i_1=m} = \max(\sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=4}^{i_2=j} Z_1 - K_1, 0) \quad (m = 0, 1, 2 \dots N)$$

Equation 3.3 Intermediate nodes valuation

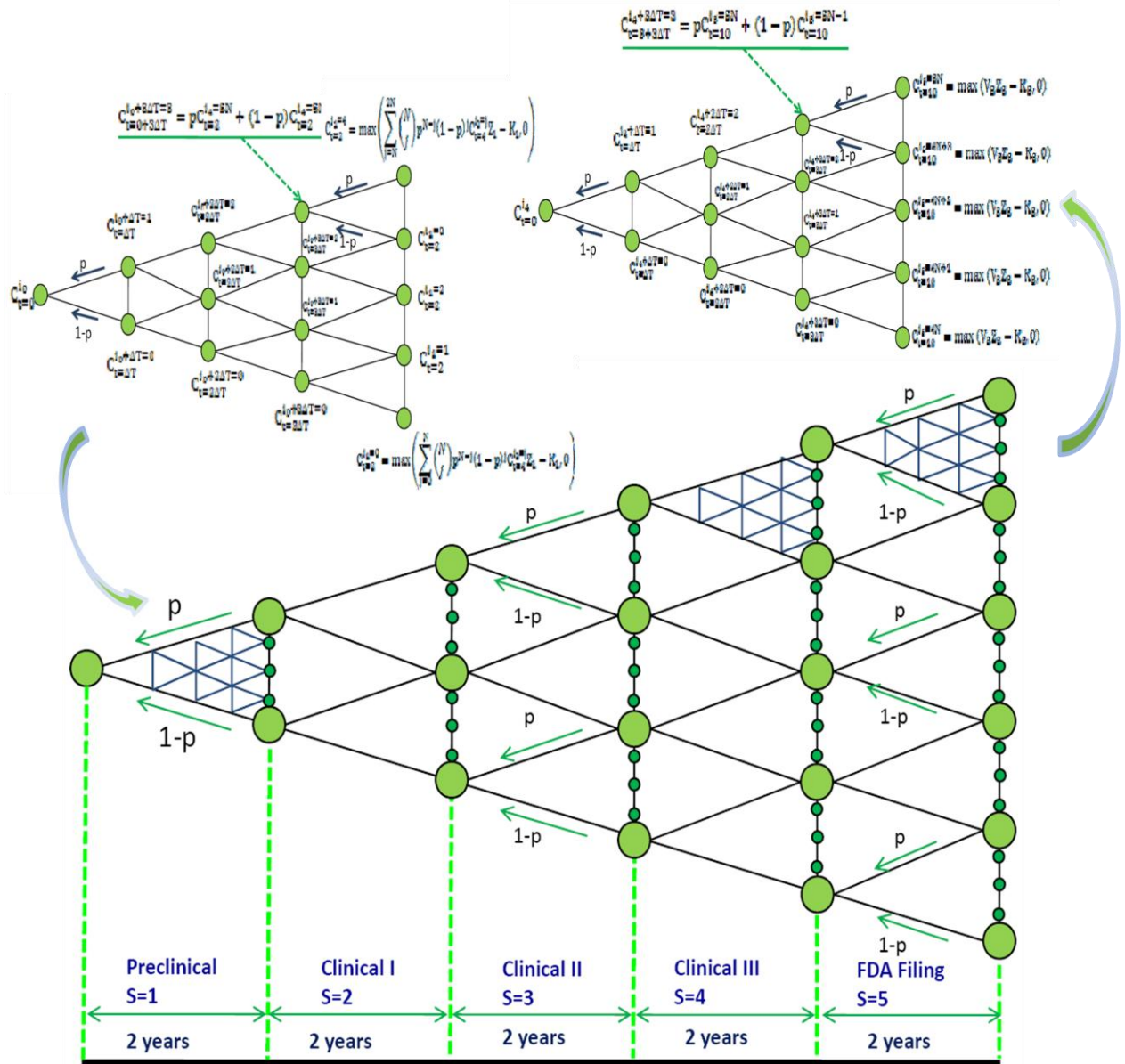


Figure 3.3 Valuation lattice

Finally the option premium is obtained when the option pricing arrives at the point when initial investment begins at $t=0$ as shown in Equation 3.4. The final value (option premium)

implies the direction for investment decision. If the option premium is positive, investment in the destined drug project deserves consideration. Otherwise, abandoning the project is the better choice.

$$C_{t=0}^{i_0} = \sum_{j=0}^N \binom{N}{j} p^{N-j} (1-p)^j C_{t=2}^{i_1=j}$$

Equation 3.4 Option premium (initial nodes) valuation

3.2. Model for partnership

In many real options studies of general R&D projects, the optimal timing decision gives a project manager a threshold for either investing or delaying the project at every stage. This idea can be simply applied to licensing between pharmaceutical and biotechnology companies. Investing timing for pharmaceutical companies and the timing for selling intellectual property for biotechnology companies can be derived based on the optimal stopping problem. As shown in Figure 3.4, the partnership divides into the two viewpoints: that of pharmaceutical companies and that of biotechnology companies. The consensus in a contract could be regarded as exercising a call option for pharmaceutical companies because the partnerships provide the opportunity to invest or not. Achieving the contract could be regarded as exercising a put option for biotechnology companies because licensing implies selling ownership of intellectual property in return for: licensing payment that bears all cost for further clinical and regulatory development, upfront payment, and milestone payments at the end of each successful stage in the development pipeline

3.2.1. Considerations for a licensing agreement

A licensing agreement can be made only when both sides have their own needs satisfied. Since they have different expectations for the partnership, disagreements may arise in achieving an alliance. By reflecting on their opinions in a partnership, several contractual terms must be considered, such as: ownership ratio (a), synergy effect (b) and payment options that reflect allocation of up-front payments and milestone payments at every successful stage.

Exploring these considerations based on the real option approach, the consensus in the contract could be regarded as the exercise of the call option for pharmaceutical companies because a partnership for them implies investment in a new drug development project whose value is proportional to the ownership ratio. Achieving a contract could be regarded as the exercise of the put option for the biotechnology company because it could sell the ownership of the patent for a price that bears all cost for further clinical and regulatory development, marketing costs, and milestone payments at the end of each successful stage of the development. This approach anticipates an overlapping zone fulfilling both sides' needs because the direction of exercising the partnership option pursued is totally opposite for each as shown in Figure.3.4. This overlapping region can finally provide contract timing and other conditions that are the most important considerations for the contract.

Furthermore, this real option approach could provide the optimal timing strategies for the partnership. In specific, these are the steps required to determine the optimal timing and conditions policies as explored in the current study. First, the search for the optimal timing range that satisfies both companies is followed by determining out the optimal timing to reach the maximum value throughout the partnership on the base of the sum of the option premium for the

More parameters require consideration in a partnership based on the proposed option pricing methodology:

a = ownership ratio ($0 < a < 1$)

b = synergy effect ($b \geq 1$)

Y_s = fractions of the total contractual payment at every stage s

C = total cost in alliance deal (upfront payment + milestone payment)

K_s = cost for all the testing and FDA registration corresponding to stage s

V_o = current value of original drug project

L = time when the alliance is attained

$C_{t=0}^{i_0}$ = call option premium

$P_{t=0}^{i_0}$ = put option premium

3.2.1.1. Ownership ratio (a)

When choosing to license with a pharmaceutical company, a biotechnology company transfers a particular percentage of ownership (a) of the new drug to the pharmaceutical company, receiving in return payments for costs of further testing, and up-front and milestone remuneration. The value of the new drug that a biotechnology company owns is multiplied by $(1 - a)$ at the original value without considering the partnership. Alternatively, the value of the new drug that a pharmaceutical company achieves is multiplied by a at an original value.

3.2.1.2. Synergy Effect (b)

Pharmaceutical companies with advanced marketing resources and stable economic conditions may at the very least generate more income than the value of a licensed product than smaller biotechnology companies can. The synergy effect (b) is a parameter defined as the value-added contribution, from the pharmaceutical company to the value of the project. When the alliance forms, the project can have an expected value of bV_o at time, $t=0$.

3.2.1.3. Payment options

Pharmaceutical companies and biotechnology companies have opposite preferences for license payment options. The payment options should consider ownership ratio when establishing the optimal timing of an alliance. Pharmaceutical companies originally take responsibility for the testing expenses as well as an upfront payments and milestone payments. Upfront payments could be regarded as the first milestone payment because payment occurs when the alliance is attained for convenience. When considering upfront payment as one of the milestone payments, the fraction (Y_S) of the total licensing payments at the developmental stage, S , made to a biotechnology company, is a parameter that reflects strategies that each company pursues. For instance, a pharmaceutical company wants a smaller upfront payment and larger milestone payments in later stages because they try to avoid taking risks during the new drug's development process. Biotechnology companies, however, prefer to obtain a license agreement with larger upfront payments and smaller milestone payments in later stages because they desire more income because of the risk that the project may fail during development. Within these constraints, payment policies can be largely classified as:

1) Increasing ratio payment policy: The payment ratio (Y_S) increases over time. It is the payment option that the large pharmaceutical companies seek.

- 2) Constant ratio payment policy: The payment ratio is always the same. The expected uncertainties are almost equally distributed.
- 3) Decreasing ratio payment policy: The payment ratio decreases over time. Biotechnology companies who chase rewards as early as possible prefer this payment option.

Table 3.1 Tradeoff between money policy and optimal timing versus ownership

Contract Timing	Payment Option	Stage1	Stage2	Stage3	Stage4	Stage5	Ownership(a)
Stage 1. <i>(Preclinical)</i>	Increasing ratio	0.3	0.25	0.2	0.15	0.1	0.95
	Constant ratio	0.2	0.2	0.2	0.2	0.2	0.915
	Decreasing ratio	0.1	0.15	0.2	0.25	0.3	0.880
Stage 2. <i>(Clinical-I)</i>	Increasing ratio	0	0.4	0.3	0.2	0.1	0.880
	Constant ratio	0	0.25	0.25	0.25	0.25	0.845
	Decreasing ratio	0	0.1	0.2	0.3	0.4	0.810
Stage 3. <i>(Clinical-II)</i>	Increasing ratio	0	0	0.44	0.34	0.22	0.810
	Constant ratio	0	0	0.33	0.34	0.33	0.775
	Decreasing ratio	0	0	0.22	0.34	0.44	0.740
Stage 4. <i>(Clinical-III)</i>	Increasing ratio	0	0	0	0.4	0.6	0.740
	Constant ratio	0	0	0	0.5	0.5	0.705
	Decreasing ratio	0	0	0	0.6	0.4	0.670
FDA Filing	Constant ratio	0	0	0	0	1	0.670

In detail, pharmaceutical companies want to obtain more ownership by later partnerships and increasing ratio payment options. And biotechnology companies want to assign less

ownership to pharmaceutical companies but embrace earlier partnership and decreasing payment ratio options. These conflicting aspirations may reveal some link among ownership ratio (a), contract timing (M) and payment options. Table 3.1 explains that a greater ownership stake requires earlier partnership and a decreasing ratio money policy. Conversely, a later partnership implies smaller ownership stake and an increasing ratio payment option.

3.2.2. Viewpoint for the partnership

Pharmaceutical companies having capital strength and marketing experience are interested in the alliance extending their market presence because they not only know the power of preoccupancy in drug markets, but also know the necessity of new promising pipelines to keep balanced finances. On the other hand, biotechnology companies usually have financial and managerial difficulties to commercialize new drugs because of cash-flow shortages required to complete the whole drug-pipeline sequence which require persistent investments for extended periods despite holding patents. By seeking partnerships, both companies require conditions that both of companies pursue by totally different avenues. Discord in forming an alliance is normal.

This section investigates viewpoints that each company has and presents procedures that will arrive at the points by which both of company can consolidate their interest in a partnership based on the real option methodology.

3.2.2.1. Biomedical company's aspect.

Biotechnology companies fear the effects of technical and market risks for a new drug development project because staged failure comes from abandoning a project without receipt of any intermittent profit. Licensing can be a smart decision because it can help reduce fear of losses by guaranteeing secure money ($C \cdot Y_S$) received from a pharmaceutical company at the end

of each staged success in return for a portion of project ownership ($a \cdot V_{t=L}$) after forming an alliance at time, $t=L$. Specifically, licensing for biotechnology companies indicates a decision to sell a project ($V_{t=L}$) with staged testing cost (I_s), licensing payment ($C \cdot Y_s$) at every stage (s), and $a \cdot b \cdot V_{t=10-L}$ when the product is commercialized.

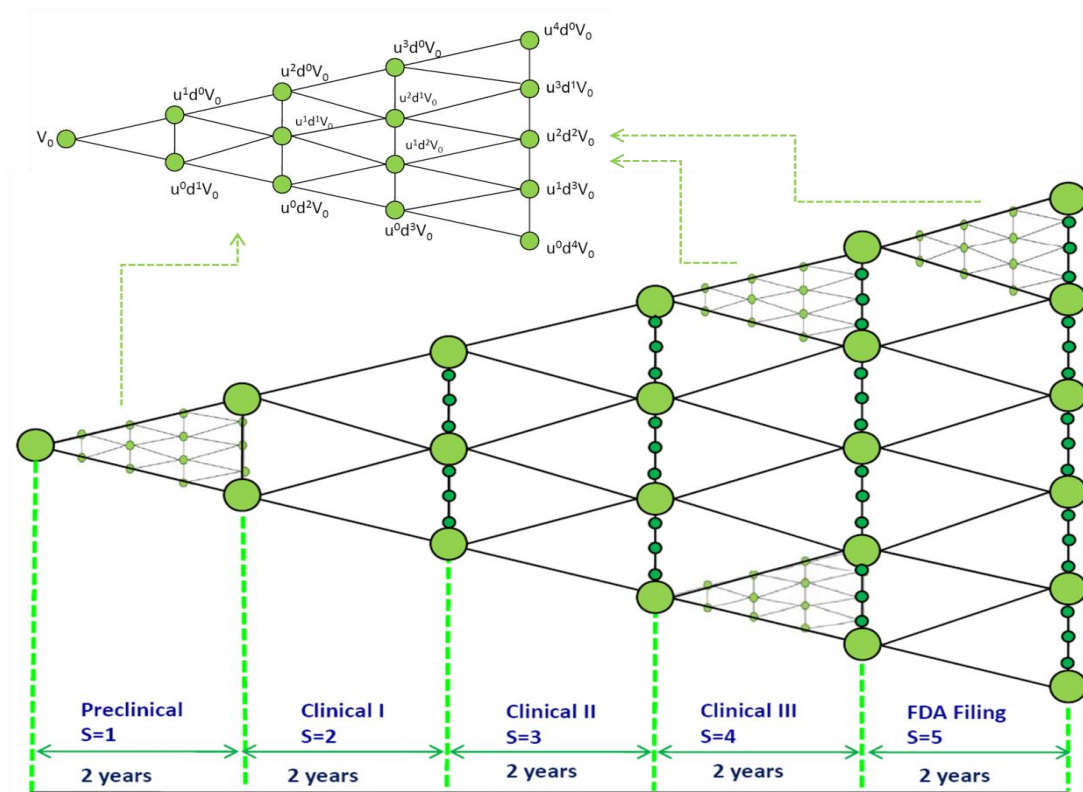


Figure 3.5 Binomial pricing tree of possible value scenarios for a product at the end of preclinical testing ($N = 4$)

Viewing this idea as a real option methodology, a contract for biotechnology companies can be regarded as exercising a put option. A partnership can result only when a put option premium is positive, and optimal timing is obtained by maximizing a put option premium. When

a project enters the phase of preclinical testing at $t = 0$ ($L=0$), the value of a project available at the end of preclinical testing ($t = 2$) could be:

- Project value at the end of preclinical: $V_{t=2} = V_o u^{N-i} d^i \quad (i = 0, 1, 2 \dots N)$

Figure 3.5 illustrates the binomial tree when N (number of available scenarios) is 4 at the beginning of the current stage. The lattice steps are: $i = \{0, 1, 2 \dots N, N+1, N+2 \dots 5N\}$ which are shorthand as: $i = \{0, 1, 2, 5N\}$. The project values at the end of Phase I Clinical Testing ($t = 4$), Phase II testing ($t = 6$), Phase III testing ($t = 8$) and FDA approvals ($t = 10$) can be calculated:

- Project value at the end of Clinical I: $V_{t=4} = V_o u^{2N-i} d^i \quad (i = 0, 1, 2 \dots 2N)$
- Project value at the end of Clinical II: $V_{t=6} = V_o u^{3N-i} d^i \quad (i = 0, 1, 2 \dots 3N)$
- Project value at the end of Clinical III: $V_{t=8} = V_o u^{4N-i} d^i \quad (i = 0, 1, 2 \dots 4N)$
- Project value at the end of FDA approval: $V_{t=10} = V_o u^{5N-i} d^i \quad (i = 0, 1, 2 \dots 5N)$

Having enumerated the value for all possible scenarios in an overall partnership framework, option value can be calculated: Beginning with terminal nodes, the nodes move backward to the first node throughout the intermittent nodes by backward induction. Basic considerations for calculating gains from exercising a put option are all total amounts in an alliance arrangement (*upfront payment + milestone payments*), C , cost for all testing and FDA registration to Stage s , I_s and probability of technical success in its stage S , Z_s . In detail, the terminal nodes are calculated through the maximization between executing the option and allowing the option to expire making it worthless. If benefits of execution exceed costs, a put option will be exercised. Otherwise, the project will be abandoned. Terminal node:

$$P_{t=10}^{i5} = \max[CY_5 + I_5 + (1 - a)bV_0 u^{5N-m} d^m Z_5 - V_0 u^{5N-m} d^m Z_5, 0]$$

$$= \max\{E[CY_5 + I_5 + (b - ab - 1)bV_0u^{5N-m}d^m)Z_5, 0].$$

An additional aspect requires consideration when a put option is exercised: technical risk. An assumption necessary for rendering a put option evaluation valid is that the absence of an obstructive technical failure. Even one technical failure in a project before a commercialization stage renders a project unviable. This implies that put option pricing for a project having a barrier of a technical failure renders the pricing meaningless because the value of the project may ultimately be zero.

The next concern in valuation is the calculation of intermediate nodes. Intermediate nodes are calculated using a risk-neutral probability analysis until they meet the decision point at which the decision as to whether or not to exercise or abandon the option occurs. Calculation of the decision point occurs similarly to that of the terminal node:

- Intermediate decision point:

$$P_{t=8}^{i_4=m} = \max\{E[CY_4 + I_4 - \sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j P_{t=8}^{i_4=j} Z_3, 0) \quad (m = 0, 1, 2 \dots 4N)$$

$$P_{t=6}^{i_3=m} = \max\{E[CY_3 + I_3 - \sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j P_{t=8}^{i_4=j} Z_3, 0) \quad (m = 0, 1, 2 \dots 3N)$$

$$P_{t=4}^{i_2=m} = \max\{E[CY_2 + I_2 - \sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j P_{t=6}^{i_3=j} Z_2, 0) \quad (m = 0, 1, 2 \dots 2N)$$

$$P_{t=2}^{i_1=m} = \max\{E[CY_1 + I_1 - \sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j P_{t=4}^{i_2=j} Z_1, 0) \quad (m = 0, 1, 2 \dots N)$$

- Put option Premium : $P_{t=0}^{i_0} = \sum_{j=0}^N \binom{N}{j} p^{N-j} (1-p)^j P_{t=2}^{i_1=j}$

3.2.2.2. Pharmaceutical Company's Aspect.

Pharmaceutical companies, before making a decision about partnerships with biotechnology companies, will compare returns expected by acquiring a new drug development project and the licensing payment. Based on a real option framework, a licensing agreement can be regarded as exercising a call option. The initial value of the asset (V_o) is determined as the value of a project when a product is commercialized ($V_{t=10}$), multiplied by ownership ratio (a), and multiplied by the synergy effect (b). And the strike price is determined as all the expenses for the remaining testing (I_S), an upfront payment, and milestone payments ($C \cdot Y_S$). Throughout a binomial pricing approach, used by a put option of biotechnology companies, the call option premium is calculated, and its investment can be accomplished only when a call option premium is positive. The optimal investment rule for pharmaceutical companies can be obtained when the value of a call option premium is maximized.

The following is a case in which a partnership is attained at the Preclinical Testing Stage. The representation is the processes that results in a call option premium. The first step is to create a lattice considering the upward effect and downward effect at every discrete point in time.

$$V_{t=0} = abV_o ;$$

$$V_{t=2} = abV_o u^{N-i} d^i \quad (i = 0, 1, 2 \dots N);$$

$$V_{t=4} = abV_o u^{2N-i} d^i \quad (i = 0, 1, 2 \dots 2N);$$

$$V_{t=6} = abV_o u^{3N-i} d^i \quad (i = 0, 1, 2 \dots 3N);$$

$$V_{t=8} = abV_o u^{4N-i} d^i \quad (i = 0, 1, 2 \dots 4N), \text{ and}$$

$$V_{t=10} = abV_o u^{5N-i} d^i \quad (i = 0, 1, 2 \dots 5N).$$

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- Terminal node:

$$\begin{aligned} C_{t=10}^{i_5} &= \max(abV_5 Z_5 - K_5, 0) \\ &= \max(abV_0 u^{5N-m} d^m Z_5 - K_5, 0) \quad (m = 0, 1, 2 \dots 5N). \end{aligned}$$

- Intermediate decision point:

$$C_{t=8}^{i_4=m} = \max\left(\sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=10}^{i_5=j} Z_4 - K_4, 0\right) \quad (m = 0, 1, 2 \dots 4N);$$

$$C_{t=6}^{i_3=m} = \max\left(\sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=8}^{i_4=j} Z_3 - K_3, 0\right) \quad (m = 0, 1, 2 \dots 3N);$$

$$C_{t=4}^{i_2=m} = \max\left(\sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=6}^{i_3=j} Z_2 - K_2, 0\right) \quad (m = 0, 1, 2 \dots 2N), \text{ and}$$

$$C_{t=2}^{i_1=m} = \max\left(\sum_{j=m}^{N+m} \binom{N}{j} p^{N-j} (1-p)^j C_{t=4}^{i_2=j} Z_1 - K_1, 0\right) \quad (m = 0, 1, 2 \dots N).$$

- Call option premium:

$$C_{t=0}^{i_0} = \sum_{j=0}^N \binom{N}{j} p^{N-j} (1-p)^j C_{t=2}^{i_1=j}.$$

Once the call option premium is calculated, pharmaceutical companies can decide how to react to a licensing problem. If a call option is positive, the company may be willing to propel this licensing agreement forward. Otherwise, the company will seek other alternatives because this licensing agreement will be financially disadvantageous to the pharmaceutical company.

Chapter 4

Numerical Example (Case Study)

Chapter 3 explains the project evaluation and partnership conditions based on real options. Following the methodology with all assumed parameters will suggest optimal partnership timing as well as subsequent conditions in a successful partnership. These consecutive conditions embrace the ownership ratio, money policy and amount of milestone payment at every stage. These are consequently determined when the partnership is achieved in an optimal environment. As a numerical example, the parameters have the fixed values as shown in Table 4.1.

Table 4.1 Numerical Example Setting

S (initial underlying asset)	180
X (Test expense)	30 /70 /80 /150 /40
Z (Technical success ratio)	0.25 /0.45 /0.60 /0.80 /0.95
r (risk-free interest rate)	0.05
T (staged period)	2
vol (volatility)	0.25
M (Total stage to consider)	5
N (Denominator for the discrete time interval)	24
b (synergy effect ratio)	1.5

Applying these values to Equation 3.1 through Equation 3.4 suggested in the previous chapter, allows evaluation of a project's value in the case of achieving alliance or developing a new drug project without any independent help. Finally, the best timing for doing partnership

and its subsequent conditions such as money policy and contract cost are determined as shown in Table 4.2

Table 4.2 Result of the Numerical Example

Ownership ratio transferred from the Bio. To Pharmaceutical company (<i>a</i>)	0.44
Contract Cost (<i>c</i>)	191
Optimal Partnership Time (<i>M</i>)	4 (<i>Clinical III</i>)
Project value after partnership (Call option premium of pharmaceutical companies + put option premium of biomedical companies)	6.3031
Money policy to payment (<i>Money</i>)	1

In some sense, attaining partnership conditions and timing with pre-suggested parameters is not realistic. Pragmatically, many parameters are very sensitive to a fluctuating market and unpredictable technical factors. Setting these parameters as fixed numbers in a practical view is very difficult. Thus, more realistic and better approaches are required to determine the effects of parameters. Sensitivity analysis is a plausible approach to identify the power of parameters' influence by creating a set of scenarios within specific boundaries. This study observes important parameters, such as synergy effects ratio, technical success ratio, market volatility, and remaining R&D expenses. Sensitivity analysis with these parameters and studying their influence on a real partnership allows real project managers to obtain a blueprint for optimal partnership strategies.

4.1 Influence of Synergy Effect (b)

Looking at the change of optimal partnership timing for the increase in a synergy effect will be likely occur for the partnership at a later stage, such as Clinical (III) Stage (number of stage = 5). An optimal timing for an alliance shows that the contract will be delayed when the parameter (b) is large. Figure 4.1 shows a preferred alliance timing at Clinical (III) Stage, when a synergy factor is larger than 2.

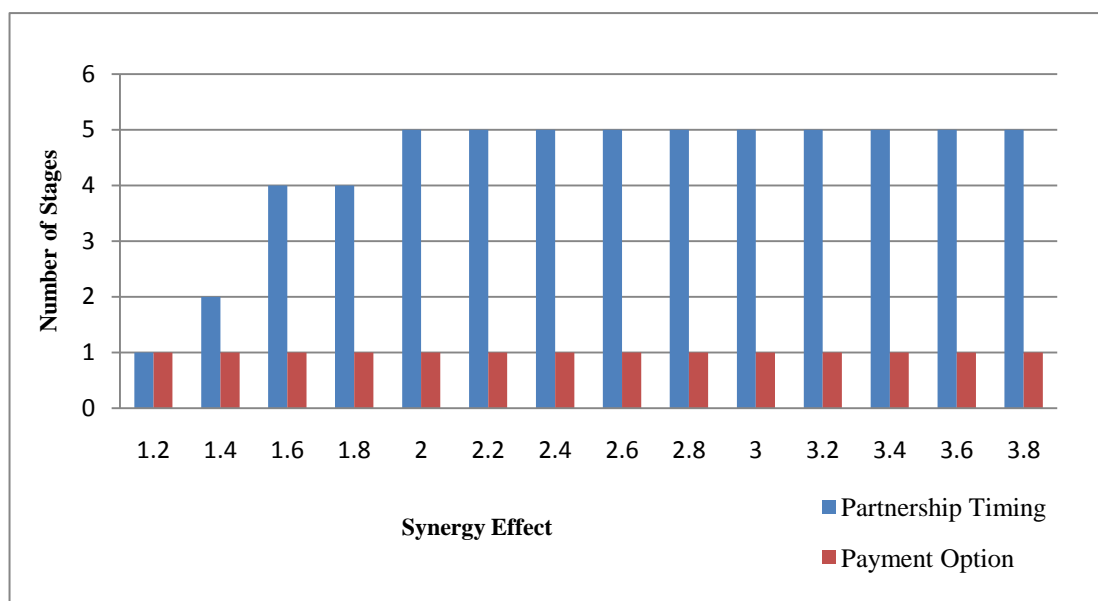


Figure 4.1 Partnership timing/payment option vs. synergy effect

This phenomena can be traced as the fact that synergy effects throughout a partnership is typically created by pharmaceutical companies who have powerful making skills, sophisticated management skills, high market occupancy power and stable monetary structure. It implies that the synergy effects come from power that pharmaceutical companies have. Its larger synergy effects allow pharmaceutical companies to a wait-and-see attitude toward circumstances surrounding the partnership until the resolution of more or less of the uncertainties.

Also, payment options that reflect a partnership strategy are a constant 1 (increasing payment policy). This implies that the payment option does not occupy a significant role in change-of-synergy effect factors.

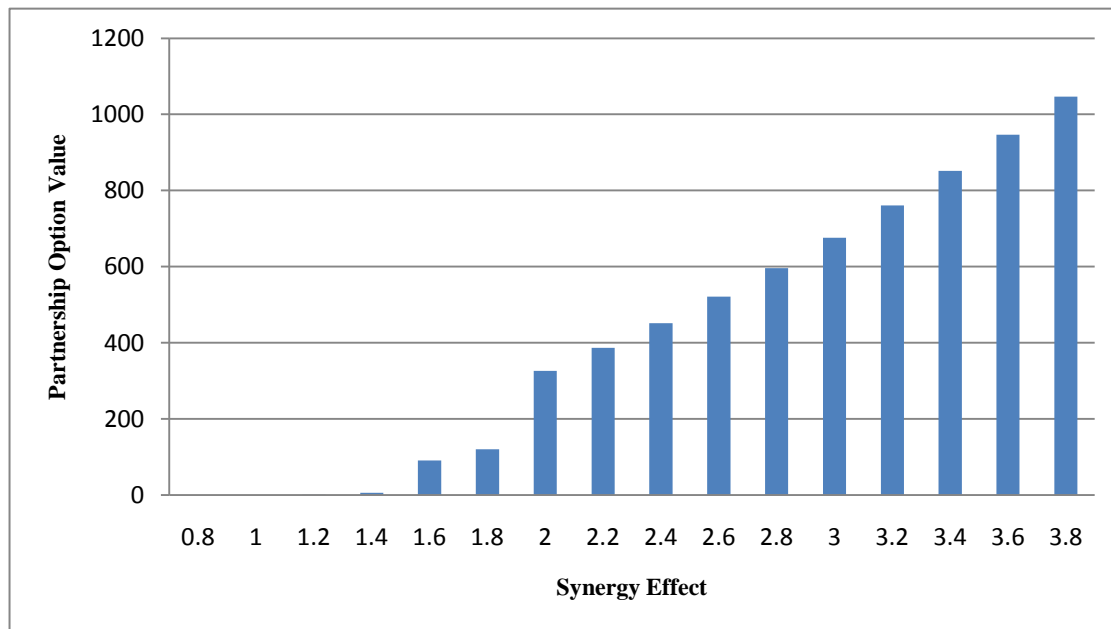


Figure 4.2 Partnership option value vs. synergy effect

Intuitively, the estimate of the value of the project after partnership increases as the incremental value of synergy's effect because the parameter (b) gives positive effects on the worth of the project. The partnership option premium, the main criterion in determining partnership timing, implies the value of the project upon conception of an alliance. The partnership option value, obtained by summing a call option premium of a pharmaceutical company and a put option premium of a biomedical company increases according to the rise of the synergy factor, as Figure 4.2 shows.

4.2 Effect of Volatility (*vol*)

Volatility is an uncertainty factor in a market. Typically, uncertainty is considered negative factor for the valuation of traditional cash flow. In contrast, uncertainty increases the value of real options. So, in today's uncertain environment, the value of options actually increases. In a thread of connection, high volatility enhances the value of the option of a partnership. If the environment is volatile, the chance that the value of the project has in the future will exceed the investment. As an example of two investments: One has a wide range of possible outcomes; the other has a relatively narrow range. In the former, during a more volatile scenario, a good chance exists for producing a project with a positive NPV in the future. Hence, a real option under this set of outcomes would have value. The latter, more stable scenario has no chance of producing a project with a positive NPV. An option using the latter set of outcomes would have no value.

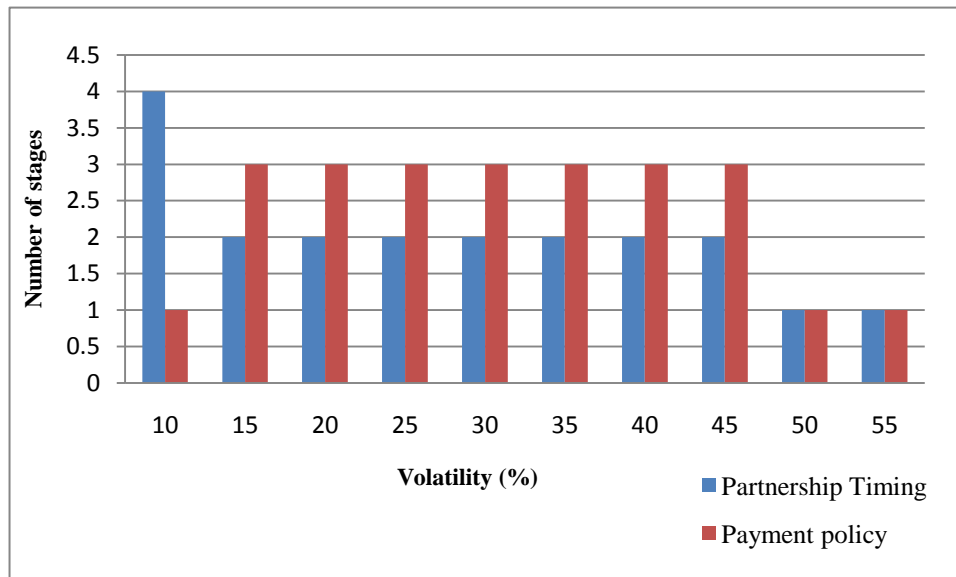


Figure 4.3 Partnership timing/payment option vs. volatility

This analysis of high uncertainty based on real option can easily estimate the responses in partnership for the change in the volatility. The value of the project will increase as the parameter incrementally increases. The projects increased value will have a positive effect on the power of the partnership, so the alliance will be attained as soon as possible. And the expectations are realized throughout volatility sensitivity analysis as Figure 4.5 and Figure 4.6 show.

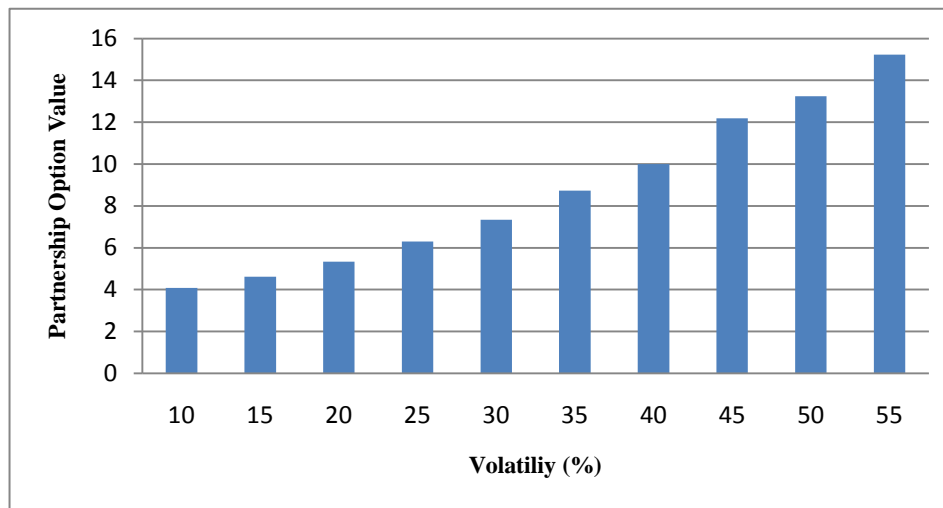


Figure 4.4 Partnership option value vs. volatility

4.3 Effect of Technological Success Rate (Z_i)

Tracking the influence of the estimated technical success rates for every stage allows anticipating that composition of the lower technical success ratios can permit alliance later because pharmaceutical companies do not want to invest in a project with lower success-rate possibilities. If the technical uncertainties are not resolved and the project comes to failure in the middle of development, the project must be abandoned because its value becomes zero.

If the project is guaranteed to be technically successful, the new drug development project will finally arrive at the market after a long journey of the staged pipeline. The pharmaceutical companies who necessitate promising new drugs take aggressive actions to attain a partnership, and undertaking a partnership as an early stage is proper.

Table 4.3 Scenarios for Technical Success Ratio

	Preclinical	Clinical (I)	Clinical (II)	Clinical (III)	FDA Filing
Scenario 1	0.1000	0.2000	0.3	0.45	0.7
Scenario 2	0.2500	0.4500	0.6	0.8	0.9
Scenario 3	0.4500	0.5500	0.65	0.7	0.95

The expectation for technological success rate can have confirmation by the three scenarios appearing in Table 4.3. Composing these scenarios, the later staged success ratio must be larger than earlier one because the previous staged success adds affirmative possibilities to next stage. The technical success ratio in a last stage has the greatest value but it must be less than 1. Three scenarios reflect different, increasing ratios for every stage. The first scenario implies unfavorable technical success ratios, and the third scenario consists of a favorable technical

success ratio. Therefore, staged success ratios in every scenario have different values but the third scenario's staged success ratio must be larger than anything else at the same stage.

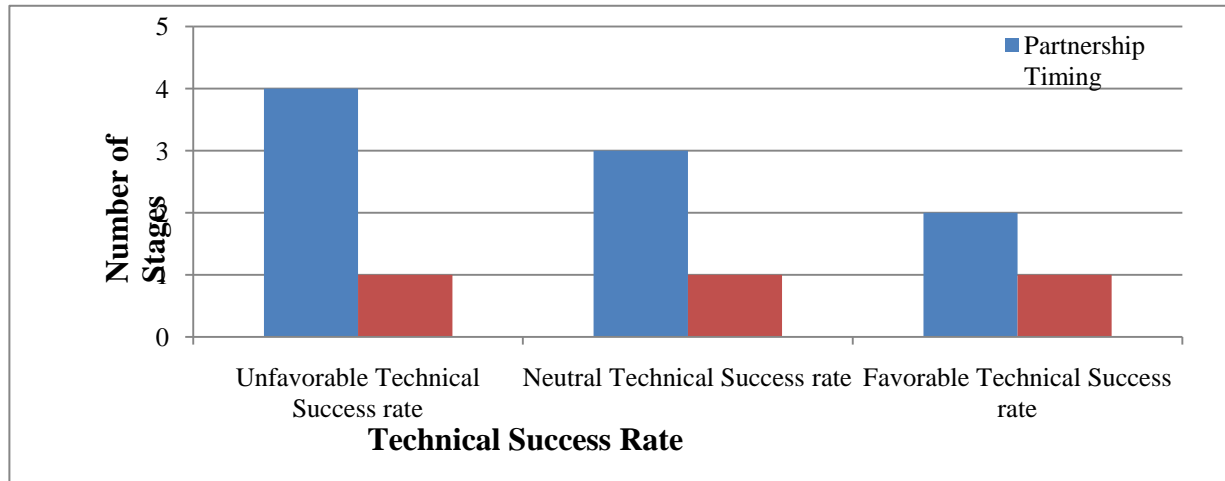


Figure 4.5 Partnership timing/payment option vs. technical success scenario

The transition in partnership timing for the three scenarios is apparent as Figure 4.5 presents. The scenario's organized; higher technical success rates lead to the alliances as soon as possible. On the other hand, the first scenario with lower technical success rates makes a contract possible at a later stage. Payment option is not changed due to the shift in technical success rate.

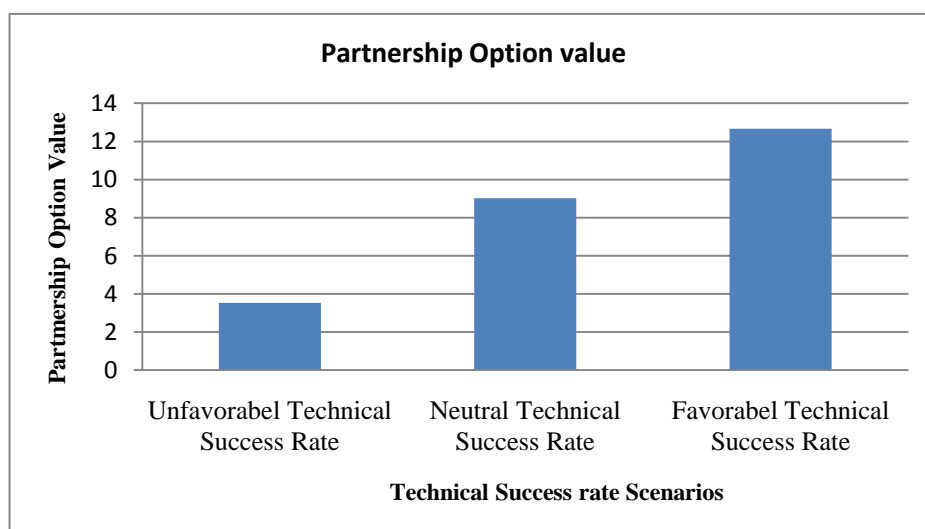


Figure 4.6 Partnership option value vs. technical success scenarios

Also, the high likelihood of reaching at a commercial market in terms of technical success gives a hint of the power confidence accruing to investors. The favorable conditions result in an earlier alliance as shown in Figure 4.5 and Figure 4.6.

Chapter 5

Discussion

5.1 Summary and conclusion

The paper suggests a methodology for determining the optimal timing and partnership terms in a real options approach that provides managerial flexibility. In this model, the decision to invest in a new drug development as an aspect of a pharmaceutical company's consideration is represented as exercising a call option. A decision to sell ownership of a new drug is considered as a biotechnology company's exercising a put option. Based on this structure, a model to determine the optimal timing is proposed by considering ownership ratio, synergy effect, and payment options.

The real options framework can be useful for project valuation, especially in an R&D project because previous methodologies such as NPV or DCF tend to undervalue investments made during uncertain situations. Economic and business conditions are volatile; outcomes are extremely uncertain; investments are high, and the risk of losing everything is real. Yet the upside potential can be huge. Under these unstable environments, real options recognize these characteristics of business trends and give investors the guidelines for choices for pursuing further investments, later, if conditions appear favorable or for abandoning a project if the environment has deteriorated.

Unlike general R&D projects, new drug R&D projects have to pass through five well-defined steps. R&D projects in medical fields incur substantial R&D expenses and take significant amounts of time to complete all developmental stages. Failure halfway along could

return nothing to the investor, thus consideration for decisions at every point in time is essential. This study introduces a project evaluation methodology based on a real option analysis.

As one way to cope with the high level of difficulties in discovering new candidate drugs and enormous R&D expense, a number of partnerships among companies who may complement each other are achieved. Viewing partnerships in the medical industries in specific, newly established pharmaceutical biomedical alliances are the main partnership structure to complete new drug development projects. The partnership between a large pharmaceutical company which has capital and marketing resources and a biotechnology company which possesses intellectual property for a candidate drug has become a trend in new drug development projects. The partnership consideration is regarded as extending choices in new drug development project. Real option analysis can be a good approach to obtain optimal timing for creating a contract for a R&D project partnership, and an optimal policy, such as optimal timing and licensing expense timeline that satisfies both pharmaceutical and biotechnology companies

The partnerships' main assets arise from the value of the project. A partnerships' contract is regarded as a call option for a pharmaceutical company because the partnership means buying part ownership from the biotechnology company. In the instance of a biotechnology company, the contract means exercising a put option to sell ownership. Throughout this real option base, the search is for the optimal timing range that could satisfy both companies. Having determined that range, the next task is determining the optimal timing to reach maximum value throughout the partnership on the basis of the sum of the option premiums for the two firms.

If all assumed parameters are provided, this methodology will suggest optimal partnership timing as well as subsequent conditions in a successful partnership. These

consecutive conditions embrace the ownership ratio, money policy, and amount of milestone payments at every stage. That can be consequently determined when the partnership is achieved in optimal environment.

Under the real option framework, partnership conditions and timing can be easily calculated if all the parameters are determined. However, these parameters are very sensitive to fluctuating market environments and unpredictable technical factors in real life. These parameters may not be expressed as fixed values. To cope with this limitation, sensitivity analysis that recognizes weights of individual parameters in a whole model by creating a set of scenarios within specific boundaries is suggested. This study regards important parameters as synergy effects ratio, technical success ratio, and market volatility. This research considers sensitivity analysis with these parameters.

Examining the influence of synergy effect throughout the partnership, the project value is enlarged, and the partnership is attained at a later stage, as the synergy effect increase. The low technical success rate impacts the timing of a partnership, delaying it as late as possible. All manner of staged, costs such as testing expense and FDA registration fees, are also significant factors for a partnership. The composition of the high cost influences delays the partnership because pharmaceutical companies must bear all these expenses after the partnership. Looking at the change in the volatility could verify the fact that as volatility increases, so does the value of the real option. And the higher value of the project encourages conclusion of an earlier alliance timing and larger contract payment. Its comparative approach may help project managers involved a partnership alliance to determine how changes in each volatile variable will impact timing as well as the subsequent conditions when a partnership is made.

Arriving at an accurate valuation is somewhat complicated and time consuming. But real options ultimately can provide an extremely useful method of unlocking the value embedded in investments that many practitioners recognize but are unable to quantify. Ultimately, the real option approach within this framework provides a blueprint for examining optimal timing strategies for partnerships.

5.2 Future studies

The model discussed in this article takes into account the option to abandon the project, uncertainty in the cost to complete the project, market uncertainty, and the possibilities of technical failure that could put an end to the effort before it is completed. It also allows for the possibility of abandoning the project when costs become larger than expected or when estimated cash flow becomes smaller than expected. This abandonment option represents a very substantial part of the project value when the project is marginal or when uncertainty is great.

Considering the option to delay investments or the option to restart a project that has been previously stopped is possible. It can be considered as an unreasonable framework when the drug to be produced in the future is protected by a patent during a specified time. If the period protected by law is determined by the registration time of new chemical components, the product might return with profit after the protected period. It implies situations in which the duration of the cash flow depends on the duration of the investment.

If the period of the cash flow and time to development are independent, considering an option to delay is valuable because delaying investment does not shorten the duration of cash

flow. Also a favorable environment could restart a stopped project from a previous time. The framework developed in this thesis has value for future studies.

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Appendix

Matlab Simulation Code for Project Evaluation based on Real Option

```
S=180;
X=[10; 30; 40; 50; 30]; %Staged cost(Test expense)
Z = [0.70 0.80 0.85 0.90 0.95];%%<= Technological success ratio
r = 0.05;
T= 2;
vol = 0.25
M = 5;
N =24;
b = 1.5;

function [Val,Vala,Valc,Valmoneypolicy,ValM] = Optimaltime11(S,X,Z,r,T,vol,N,b)
%%this is the total stage to consider is 5. If you want to change the
%%number of stage, you just change into M = 1:#.

C = 30:1:S*1.5;
[mm,nn] = size(C);
mn= 5*3*nn; % 5 is coming from the total stage to consider to find out the optimal contract time,
3 is coming from the 3 kinds of moneypolicy & nn is coming from the events that C could get.
tempa = zeros(1,mn);
tempc = zeros(1,mn);
tempval = zeros(1,mn);
tempmoneypolicy = zeros(1,mn);
tempM = zeros(1,mn);
Val = 0;
Vala = 0;
Valc = 0;
Valmoneypolicy = 0;
ValM = 0;
j = 1;
for M = 1:5
    for Moneypolicy = 1:3
        for C = 30:1:S*1.5
            [a,Y,TT] = optimaltimecond(M,Moneypolicy,S,Z);
            c=C;
            % if a*b*S*TT >= C*exp(-0.05*M) & (1-a)*b*TT*S+C*exp(-0.05*M) >= S*TT
            % c = C;
            % else
            % c = 0;
            % end
            [Biotechnology companieschem, Pharmaceutical companies,Without] =
Partner(S,X,Y,Z,r,T,vol,N,M,a,b,c);
            if Biotechnology companieschem >= Without & Pharmaceutical companies >= 0
```

```

tempval(j) = Pharmaceutical companies + Biotechnology companieschem;
tempa(j) = a;
tempc(j) = c;
tempmoneypolicy(j) = Moneypolicy;
tempM(j) = M;

if Val < tempval(j)
    Val = tempval(j);
    Vala = tempa(j);
    Valc = tempc(j);
    Valmoneypolicy = tempmoneypolicy(j);
    ValM = tempM(j);

end
    j = j+1;
end
end
end
end
end

```

```

function [a,Y,TT] = optimaltimecond(M,Moneypolicy,S,Z)

```

```

A = 0.90:-0.05:0.50; %Ownership trasferring to the Pharmaceutical companiesaceutical
company(rely on the stage and money policy

```

```

%5 Stage
P5 = [0.30 0.25 0.20 0.15 0.10;
      0.20 0.20 0.20 0.20 0.20;
      0.1 0.15 0.20 0.25 0.30];
%4 Stage
P4 = [0 0.4 0.3 0.2 0.1;
      0 0.25 0.25 0.25 0.25;
      0 0.1 0.2 0.3 0.4];
%3 Stage
P3 =[0 0 0.44 0.34 0.22;
      0 0 0.33 0.34 0.33;
      0 0 0.22 0.34 0.44];

%2 Stage
P2 =[0 0 0 0.4 0.6;
      0 0 0 0.5 0.5;
      0 0 0 0.6 0.4];

```

```

%1 Stage
P1 =[0 0 0 0 1];

%Money Policy
%5 Stage
if M == 5
    if Moneypolicy == 1
        a = A(1);
        Y = P5(1,:);
    else if Moneypolicy == 2
        a = A(2);
        Y = P5(2,:);
    else Moneypolicy == 3
        a = A(3);
        Y = P5(3,:);
    end
end
end
%4 Stage
if M == 4
    if Moneypolicy == 1
        a = A(3);
        Y = P4(1,:);
    else if Moneypolicy == 2
        a = A(4);
        Y = P4(2,:);
    else Moneypolicy == 3
        a = A(5);
        Y = P4(3,:);
    end
end
end
%3 Stage
if M == 3
    if Moneypolicy == 1
        a = A(5);
        Y = P3(1,:);
    else if Moneypolicy == 2
        a = A(6);
        Y = P3(2,:);
    else Moneypolicy == 3
        a = A(7);
        Y = P3(3,:);
    end
end
end

```



```

end
%2 Stage
if M == 2
    if Moneypolicy == 1
        a = A(7);
        Y = P2(1,:);
    else if Moneypolicy == 2
        a = A(8);
        Y = P2(2,:);
    else Moneypolicy == 3
        a = A(9);
        Y = P2(3,:);
    end
end
end
%1 Stage
if M ==1
    a = A(9);
    Y = P1(1,:);
end

%Total Tehcnological success(TT)
TT = 1;
for i = 1:5
    TT = Z(i)* TT;    %Z is technological success for every stage
end

function [Biotechnology companiescehm, Pharmaceutical companiesaceutical company,Without]
= Partner(S,X,Y,Z,r,T,vol,N,M,a,b,C)
Biotechnology companiescehm = Partnershipbiotechnology
companies(S,X,Y,Z,r,T,vol,N,M,a,b,C);
Pharmaceutical companiesaceutical company = PartnershipPharmaceutical companiesaceutical
company(S,X,Y,Z,r,T,vol,N,M,a,b,C);
Without = Stagedcall(S,X,Z,r,T,vol,N,M);

function [price, f_tree] = Partnershipbiotechnology companies(S,X,Y,Z,r,T,vol,N,M,a,b,C)

%Defining Parameters
dt = T/N;
u = exp(vol*sqrt(dt));
d = 1/u;
p = (exp((r)*dt)-d)/(u-d);

%%j = column(time node)
%%i= row(Level of price)

```

```

S_tree = zeros(M*N+1,M*N+1);
for j = M*N+1:-1:1
    for i = 1:j
        S_tree(i,j) = S*u^(j-i) *d^(i-1);
    end
end

%Calculating the option payoff (at expiration day)
f_tree = zeros(M*N+1,M*N+1);

%Partnership put option case
% % if
f_tree(:,M*N+1) = max((1-a)*b*(Z(M)*S_tree(:,end)-X(M))+C*Y(M),0);

%Caluculating the every node by reverting the direction
for k =M:-1:1
    for j = k*N:-1:(k-1)*N+2
        for i = 1:j
            f_tree(i,j) = exp(-r*dt)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1));
        end
    end
    if k ~=1,
        j = (k-1)*N+1;
        for i = 1:j
            if Z(k-1)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1))-X(k-1) > 0
                P = (1-a)*b*(Z(k-1)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1))-X(k-1))+C*Y(k);
            else
                P = 0;
            end
            f_tree(i,j) = max(0,-(1-a)*b*(Z(k-1)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1))+X(k-1))+C*Y(k));
        end
    else
        j = 1;
        i = 1;
        f_tree(i,j) = max(0, exp(-r*dt)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1)));
    end
end

%Final option value
price = f_tree(1,1);

function [price, ff_tree] = PartnershipPharmaceutical companiesaceutical
company(S,X,Y,Z,r,T,vol,N,M,a,b,C)
%
% S=50;

```

```

% X=[2; 10; 20; 30]; % Staged cost(Test expense)
% Y=[0.25; 0.25; 0.25; 0.25]; % Paymnet ratio for every stage<=Put option
% Z = [0.6 ; 0.7; 0.8; 0.95]; % %<= Technological success ratio
% r = 0.05;
% T= 1;
% vol = 0.8;
% N = 12;
% M= 4; %Number of Stage to consider
% a = 0.8 ; %ratio of ownership.
% b = 2.5 ; %Enhancement effect by partnership.
% C = 80 ; %Total amount for the project.

%Defining Parameters
S = a*b*S ;
X = C*Y;
dt = T/N;
u = exp(vol*sqrt(dt));
d = 1/u;
p = (exp((r)*dt)-d)/(u-d);

%%j = column(time node)
%%i= row(Level of price)
S_tree = zeros(M*N+1,M*N+1);
for j = M*N+1:-1:1
    for i = 1:j
        S_tree(i,j) = S*u^(j-i) *d^(i-1);
    end
end

%Calculating the option payoff (at expiration day)
f_tree = zeros(M*N+1,M*N+1);
f_tree(:,M*N+1) = max(0, Z(M)*(S_tree(:,end)-X(M)));

%Caluculating the every node by reverting the direction
for k =M:-1:1
    for j = k*N:-1:(k-1)*N+2
        for i = 1:j
            f_tree(i,j) = exp(-r*dt)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1));
        end
    end
    if k ~=1,
        j = (k-1)*N+1;
        for i = 1:j
            f_tree(i,j) = max(0, exp(-r*dt)*(Z(k-1)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1))-X(k-1)));
        end
    else

```

```

        j = 1;
        i = 1;
        f_tree(i,j) = max(0, exp(-r*dt)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1)));
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

SS_tree = zeros(M*N+1,M*N+1);
SS = S*a*b;
for j = M*N+1:-1:1
    for i = 1:j
        SS_tree(i,j) = SS*u^(j-i) *d^(i-1);
    end
end

%Calculating the option payoff (at expiration day)
ff_tree = zeros(M*N+1,M*N+1);
for i = M*N+1:-1:1
    if f_tree(i,M*N+1)>0
        ff_tree(:,M*N+1) = max(0, Z(M)*(SS_tree(:,end)-C*Y(M)));
    else
        ff_tree(:,M*N+1) = 0;
    end
end

%Caluculating the every node by reverting the direction
for k =M:-1:1
    for j = k*N:-1:(k-1)*N+2
        for i = 1:j
            ff_tree(i,j) = max(exp(-r*dt)*(p*ff_tree(i,j+1)+(1-p)*ff_tree(i+1,j+1)),0);
        end
    end
    if k ~=1,
        j = (k-1)*N+1;
        for i = 1:j
            if f_tree(i,j) >0
                ff_tree(i,j) = max(0, exp(-r*dt)*(Z(k-1)*(p*ff_tree(i,j+1)+(1-p)*ff_tree(i+1,j+1))-
C*Y(k-1)));
            else
                ff_tree(i,j) = 0;
            end
        end
    end
end

```

```

else
    j = 1;
    i = 1;
    ff_tree(i,j) = max(0, exp(-r*dt)*(p*ff_tree(i,j+1)+(1-p)*ff_tree(i+1,j+1)));
end
end
end

```

```

%Final option value
price = ff_tree(1,1);

```

```

function [price, f_tree] = Stagedcall(S,X,Z,r,T,vol,N,M)

```

```

%Defining Parameters

```

```

dt = T/N;
u = exp(vol*sqrt(dt));
d = 1/u;
p = (exp((r)*dt)-d)/(u-d);
% Put option
% z=-1;

```

```

%Call option

```

```

z= 1;

```

```

%Binomial Tree

```

```

%%j = column(time node)
%%i= row(Level of price)
S_tree = zeros(M*N+1,M*N+1);
for j = M*N+1:-1:1
    for i = 1:j
        S_tree(i,j) = S*u^(j-i) *d^(i-1);
    end
end
end

```

```

%Calculating the option payoff (at expiration day)

```

```

f_tree = zeros(M*N+1,M*N+1);
f_tree(:,M*N+1) = max(0, Z(M)*(z*(S_tree(:,end)-X(M))));

```

```

%Caluculating the every node by reverting the direction

```

```

for k =M:-1:1
    for j = k*N:-1:(k-1)*N+2
        for i = 1:j
            f_tree(i,j) = exp(-r*dt)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1));
        end
    end
end
if k ~=1,

```

```

j = (k-1)*N+1;
for i = 1:j
    f_tree(i,j) = max(0, exp(-r*dt)*(Z(k-1)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1))-X(k-1)));
end
else
j = 1;
i = 1;
f_tree(i,j) = max(0, exp(-r*dt)*(p*f_tree(i,j+1)+(1-p)*f_tree(i+1,j+1)));
end
end

%Final option value
price = f_tree(1,1);

```