

# EVALUATIONS OF DRUG DEVELOPMENT STATUS IN BIOPHARMACEUTICAL INDUSTRY

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**Abstract:** This study aims to investigate the evaluation methods of drug development status in biopharmaceutical industry by comparing the traditional NPV analysis, the risk-adjusted NPV (rNPV) method, and the real option evaluation approach. Theoretical models and simulations are represented and discussed in the paper. The paper also gives an empirical case study. We demonstrate that the risk-adjusted approach and the strict option-based method have better performance in the valuation of the biopharmaceutical R&D projects. The empirical results of our study may provide empirical evidence of the reliable valuation models.

## INTRODUCTION

Valuation of biopharmaceutical R&D project is quite difficult to managers and investors in making the investment decision because of the great technological and market uncertainties in this industry. It believes that the traditional NPV analysis is not the appropriate tool to evaluate an early-stage R&D project as it ignores the managerial flexibility in the stage of an investment. Therefore, the major aim of our study is to investigate the better method for R&D evaluation in which can be applied to investment decisions, collaboration or M&A in biotechnology companies, by comparing the traditional NPV analysis, the risk-adjusted NPV (rNPV) method, and the real option evaluation method. We demonstrate that the risk-adjusted approach and the strict option-based method have better performance in the valuation of the biopharmaceutical R&D projects.

Biotechnology industry is considered as “shining star” in the 21 century. Many countries invested abundant resources and tried to enhance the development of the biotech industry. However, with achievement of Human Genome Project in 2000, the total financing in biotechnology industry in USA had come to \$38 billion but decreased significantly in 2001 (\$15.1 billion) (Eramian *et al.*, 2005). The one of the most possible reasons is because of the low successful rate in the R&D process of product, especially in drug discovery and development projects. Investors often tend to invest biopharmaceutical companies that do not have products on the market. Valuations of biopharmaceutical R&D projects are hard tasks in investment decision. In general, developing a new drug may take 12-15 years to pass through several stages, including discovery, pre-clinical development, clinical phase 1 to 3, new drug application review and launch (PhRMA, 2001). The traditional capital theory – net present value (NPV) analysis is not adequate for valuations of biopharmaceutical R&D projects because of the discounted cash flow (DCF) technique ignores risk factor and the value of flexibility in the R&D process. In NPV calculations, managers or investors get used to take higher discount rates for the valuation of drug R&D projects and obtain a lower NPV (Perlitz, Peske, and Schrank, 1999; Remer, Ang, and Baden-Fuller, 2001).

The concept of real options approach was brought up by Myers (1977) who suggested many business investment decisions can be considered as a financial call option. At various stages in the further, managers will be able to response to the preliminary result from the project and adjust their strategy to continue or abandon it accordingly. Real option theory has been applied to many kinds of R&D projects analysis and investment decision making (Dixit and Pindyck, 1995; Trigeorgis, 1996; Newton, Paxson, and Widdicks, 2004). Kester (1984) first indicated that option-based valuation models are more appropriate to capture the value of flexibility inherent in the stage of R&D projects than DCF methods. Some experts have also suggested that biotechnology R&D projects can be dealt with using the real option valuation methods (Ottoo, 1998; Remer, Benninga, and Tolkowsky, 2002; Villiger and Bogdan, 2005). Jäggle (1999) demonstrated that binomial option tree has more sound theoretical framework to produce different valuations and acquire different decisions than a simple DCF tree approach in a pharmaceutical R&D project. Furthermore, Kellogg and Charnes (2000) used the decision-tree and binomial-lattice methods to value a biotechnology company which was sum of the values of its drug-development projects and then compared actual market values at selected time points. However, the outcomes of the calculated values deviated farther from the actual stock price because of different assumptions between investors and authors.

In our paper, we explain real option and risk-adjusted net present value (rNPV) methods, and use the methods to compute the value of a biological component in which was invented by a biopharmaceutical company in Taiwan. Then, we compare our computed results with actual value – the licensing fee when the component was licensed to a big pharmaceutical company. The empirical results of our study may provide empirical evidence of the reliable valuation models. Briefly, the plan of the paper is as follows. An

introduction of the literature study will be presented in section 1. Section 2 presents the evaluation models, including the NPV, rNPV, and Real option method. Section 3 gives a case of empirical study. Concluding remarks are shown in section 4.

## EVALUATION MODELS

### rNPV method

The risk-adjusted NPV (rNPV) method is particularly considered as a convenient and useful valuation method in biopharmaceutical R&D projects (Stewart, Allison, and Johnson, 2001). It combined the clinical-trial success rates with traditional DCF methodology to produce a risk-adjusted NPV. The rNPV equation is shown as equation (1).

$$rNPV = \sum_{j=1}^m \frac{P_j R_0}{(1+r)^{n+j}} - \sum_{i=0}^n \frac{C_i R_0 / R_i}{(1+r)^i} \quad (1)$$

where  $i$  is an index of the stages from discovery, clinical phase to post-approve.  $j$  is an index of the stages after product launch.  $P_j$  is expected commercialization payoff at time  $j$ .  $R_0$  is current risk; the likelihood that a biological component reach the market.  $R_i$  is conditional risk; the probability at time  $i$  to market successful.  $C_i$  is the expenditures at time  $i$ .  $r$  is the discount rate according to capital asset pricing model. The rNPV model is represented graphically as Figure 1 below:

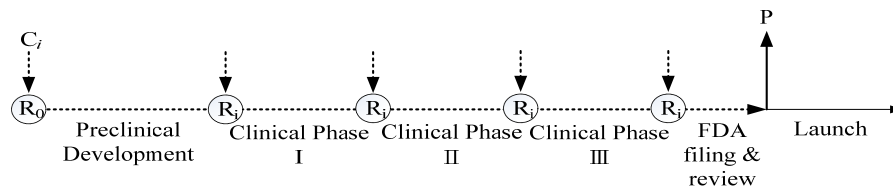


Figure 1. rNPV valuation for a biopharmaceutical R&D project

The discount rate  $r$  reflects the opportunity cost of capital or the requisite return from an investment of similar risk in which means the capital market risk by investors (Brealey, Myers, and Allen, 2003). In the company perspective, the discount rate is the cost of capital with activities are funded and the capital asset pricing model (CAPM) is commonly used to present an appropriate return. The capital asset pricing model (CAPM) is depicted as equation (2).

$$r_e = r_f + \beta(r_m - r_f) \quad (2)$$

where  $r_e$  is the expected return on equity,  $r_f$  is the risk-free rate,  $\beta$  is the covariance of a company's equity with the market and the term,  $(r_m - r_f)$ , is the market risk premium. If a company not only issue equity but also debt, it should be concerned the return requirement for debt. The weighted average cost of capital (WACC) would be the suitable equation to gain the discount rate. In the biotechnology industrial standards, the discount rates used for big pharmaceutical companies are about 10%, public biotechnology companies are around 20%, and for private biotechnology companies are reaching to 30% (Bode-Greuel and Greuel, 2005).

### Real option method

The key insight behind the real option valuation is that each stage in biopharmaceutical R&D projects can be considered as a call option on the next stage in R&D process. Each stage of the R&D process has its own technical risk and value. It could exercise the options at any stages according to the investment and commercialization of the product, if the future payoff exceeds the necessary investment. Alternatively, if the cost of each stage more than the possible value, then it could abandon the option. In the option pricing theory, the most commonly used valuation model for determining the value of a financial call option is Black-Scholes formula. However, it's not quiet suitable for applying the Black-Scholes model on evaluating biopharmaceutical R&D projects because of the basic assumptions of the model cannot deal with the investment in which include several stages of the investment duration. So we conduct the other real option method, binominal model brought up by Cox, Ross, and Rubinstein (1979) based on the risk-neutral valuation, for our analysis.

The crucial parameters for valuation in a binomial tree are the current value of the project ( $S$ ), volatility of the project ( $\sigma$ ), risk-free rate ( $r$ ), time scales of the individual stages ( $dt$ ), exercise price ( $K$ ), and the probabilities of a development project proceeds the next stage ( $P$ ). Figure 2 represents one-period binominal tree. The current value  $S$  at the beginning of the period is found by discounting the expected commercialization cash flows. At the end of period,  $S$  can either move up to a new level  $Su$  or down to  $Sd$ , while  $q$  is the risk-neutral probability.

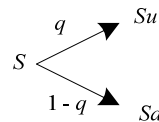


Figure 2. One-period binomial tree.

The step size  $u$ ,  $d$  and the probability  $q$  depend on the market uncertainty (the volatility) and can be calculated as the following:

$$u = e^{\sigma\sqrt{\delta t}}; d = e^{-\sigma\sqrt{\delta t}} \quad (3)$$

$$q = \frac{e^{r\delta t} - d}{u - d} \quad (4)$$

The value of the R&D project is constructed along a path of the binomial tree. For instance, if the tree is designed all possible combinations of up and down movements of the project value for each stage until the end stage in which has end-node values  $A_i$ ,  $i = 1, \dots, 6$ . At the end stage, it can decide whether the management would launch the product or not by compare with the  $K_6$  which is the expense in the stage. The value of the project at the launch stage becomes as equation (5) and is called option value ( $f$ ).

$$f_i = \max [A_i - K_6, 0] \quad (5)$$

The  $f$  values are then rolled back to previous one stage by taking the expectation of the up and down scenario with the risk-neutral probabilities,  $q$ , and risk-free rate,  $r$ . In the meanwhile, the probability of the success and the expense of development at the stage are concerned in the calculation of option values. The roll-back option values ( $V_{n,m}$ ) are:

$$V_{n,m} = \max \{ [V_{n+1,m} q + V_{n+1,m+1} (1-q)] e^{-r\delta t} - P_n - K_n, 0 \} \quad (6)$$

## AN EMPIRICAL CASE STUDY

AbGenomics Corporation is a star-up company in Taiwan which focuses on the discovery and development of biological compounds. In June 2005, AbGenomics signed an out-licensing agreement with a German pharmaceutical company, Boehringer Ingelheim. Boehringer Ingelheim acquired the worldwide exclusive rights to develop, manufacture and market the drug – Antibody-168 which is an antibody discovered by AbGenomics. Simultaneously, AbGenomics received licensing fee during the development stage from licensee. Antibody-168 is a well candidate for the development of drugs for the treatment of psoriasis, a kind of autoimmune disease. Antibody-168 has completed pre-clinical testing and is ready to enter clinical trials after 1 to 2 years as finish the manufacturing and scale-up. Before the valuation of Antibody-168 R&D project, the assumptions on future costs, revenues and risk must be assessed charily. Sales forecast are more credibly as the more information about the candidate in comparison to competitors is obtained. We use the bottom-up method to estimate the product sales according to epidemiology-based forecasts on treatment population, identification of the patients' eligible for treatment for market penetration, and relative information about product price.

Table 1 shows the each development stage, duration years, probability estimates for each stage and total cost. After Antibody-168 launch successfully, the company is rewarded about 60% of gross sales for manufacturing and marketing annually.

Table 1. Total cost, likelihood of success and durations of each stage

Stage	Likelihood of eventual success	Years in stage	Total cost (thousands in \$US)
Clinical Phase I	25%	1	\$1,100
Clinical Phase II	35%	2	3,640
Clinical Phase III	72%	3	16,500
FDA filing & review	81%	1	1,000

Table 2 illustrates the cash flows for Antibody-168 including the development stages and launch. Net cash flows were discounted by AbGenomics Corporation's cost of capital in which was calculated by CAPM model of 11.82%. Expiry of market exclusivity is determined to the end of 2022 and the net cash flows of product decrease by 40% in the following year because of generic competition after the expiration of patent protection. The NPV of the Antibody-168 R&D project is about \$3 billion. Furthermore, when thinking over the effect of probability of success in each R&D stage, the risk-adjusted NPV is showed as \$779 million. In real option valuation, the current value of Antibody-168 is obtained by discounting the value of the expected commercialization cash flow to time zero is about \$3 billion. Volatility of the underlying asset is a measurement of the fluctuant level in the underlying asset's value. Here, we use the company's market value as underlying asset to calculate the standard deviation of returns for stocks. A volatility of 0.29 was used

in the real option valuation of Antibody-168 R&D project. The risk-free rate is the 10-year Central Government Bond rate in Taiwan, which was 2.53% in 2004.

Compared with the licensing fee (\$89.7 – 134.6 million) received by AbGenomics, our calculated results by rNPV and real option methods are both exceeding the actual value. So we adjust the assumption about discount rate which is determined by CAPM model originally to expect the valuations given by the models would be more reliable. Bode-Greuel and Greuel (2005) have pointed out the typical discount rate for a private biotechnology company is about 30%. In our case study, AbGenomics Corporation was founded in 2000 and had no operating income from products before the license deal in 2005. To reflect the required return on investment under high risk, we adjust the assumption of discount rate to 30%. Table 3 indicates the multiple outcomes in Antibody-168 R&D project valuation under different assumptions and valuation models. After discount rate adjusting, the simulation results from rNPV and real option methods are both close to actual value while option value is less than rNPV slightly (\$94.8 million v.s. \$125.7 million).

Table 3. Results of Antibody-168 R&D project using rNPV and real option method

Discount rate	Actual licensing fee	Traditional NPV method	rNPV method	Real option method
	\$89.7 – 134.6 million			
11.82%		\$3.1 billion	\$779.8 million	\$762 million
30%		\$513.1 million	\$125.7 million	\$94.8 million

## CONCLUDING REMARKS

It is shown in the paper that both rNPV and real option approaches are properly applied to evaluate biopharmaceutical R&D projects. However, the rNPV approach is widely accepted for the evaluation of R&D process in biopharmaceutical industry because of several reasons. For instance, it could reflect probabilities of success in each R&D stage and the traditional financial model doesn't; additionally, it could form an expected net present value. In literature, academic researchers believe that the real option evaluation model can be applied in evaluating biopharmaceutical R&D projects based on the restrained theoretical framework. The only one limitation of real option models is calculating processes are more complex than that of the rNPV method.

We believe that besides choosing a useful evaluative model, it should take the assumptions into account carefully when evaluate an R&D project. With more information available the uncertainty of estimation could decrease, and sometimes it is important to consider experiences from the analyzer. Our empirical study illustrates that the assumption of discount rate was adjusted by industrial benchmark to use truthfully in evaluative processes. In the perspective of industrial application, using the rNPV approach with accurate assumptions could be a powerful toolbox in evaluating the biopharmaceutical R&D procedures.

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Table 2 Cash flows of Antibody-168 R&amp;D project

(Thousands in US dollars)

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
stage	Clinical Phase I	Clinical Phase II	Clinical Phase II	Clinical Phase III	Clinical Phase III	Clinical Phase III	FDA review	Launch	Launch
<b>Revenue</b>									
Product sales								270,068.63	838,977.67
<b>Cost &amp; Expense</b>									
Clinical trial cost	600	1,320	1,320	5,000	5,000	5,000			
Supporting animal studies	500	500	500	500	500	500			
FDA filing & review							1,000		
Manufacture & marketing								162,041.18	503,386.60
<b>Net cash flows (CF)</b>	(1,100.00)	(1,820.00)	(1,820.00)	(5,500.00)	(5,500.00)	(5,500.00)	(1,000.00)	108,027.45	335,591.07
Discounted cash flows	(1,100.000)	(1,627.616)	(1,455.568)	(3,933.727)	(3,517.910)	(3,146.047)	(511.544)	49,419.428	137,294.927
<b>NPV</b>	3,132,426.627								
<b>Risk-adjusted</b>									
$R_0 / R_i$	1.0000	0.7143	0.7143	0.3472	0.3472	0.3472	0.3086	0.2500	0.2500
$CF * R_0 / R_i$	(1,100.00)	(1,300.00)	(1,300.00)	(1,909.72)	(1,909.72)	(1,909.72)	(308.64)	27,006.86	83,897.77
Risk-adjusted discounted cash flows	(1,100.000)	(1,162.583)	(1,039.691)	(1,365.877)	(1,221.497)	(1,092.378)	(157.884)	12,354.857	34,323.732
<b>rNPV</b>	779,789.850								

Note: Discount rate = 11.82%. Terminal value assumption: net cash flows are decreased by 40% after 2022.

Table 2 Cash flows of Antibody-168 R&amp;D project. (cont.)

(Thousands in US dollars)

Year	2016	2017	2018	2019	2020	2021	2022	Terminal value
stage	Launch	Launch	Launch	Launch	Launch	Launch	Launch	
<b>Revenue</b>								
Product sales	1,729,959.95	3,211,082.87	3,387,575.59	3,560,261.07	3,763,043.95	3,931,086.05	4,102,226.14	
<b>Cost &amp; Expense</b>								
Clinical trial cost								
Supporting animal studies								
FDA filing & review								
Manufacture & marketing	1,037,975.97	1,926,649.72	2,032,545.35	2,136,156.64	2,257,826.37	2,358,651.63	2,461,335.69	
<b>Net cash flows (CF)</b>	691,983.98	1,284,433.15	1,355,030.24	1,424,104.43	1,505,217.58	1,572,434.42	1,640,890.46	3,166,519.60
Discounted cash flows	253,174.901	420,258.616	396,492.173	372,655.883	352,245.894	329,078.653	307,105.271	529,993.293
<b>NPV</b>								
<b>Risk-adjusted</b>								
$R_0 / R_i$	0.2500	0.2500	0.2500	0.2500	0.2500	0.2500	0.2500	
$CF * R_0 / R_i$	172,995.99	321,108.29	338,757.56	356,026.11	376,304.40	393,108.60	410,222.61	791,629.90
Risk-adjusted discounted cash flows	63,293.725	105,064.654	99,123.043	93,163.971	88,061.473	82,269.663	76,776.318	132,498.323
<b>rNPV</b>								

Note: Discount rate = 11.82%. Terminal value assumption: net cash flows are decreased by 40% after 2022.