Valuation of a Biotechnology Firm:

An application of real-options methodologies

David Kellogg
Sprint
7301 College Blvd.
Overland Park, KS 66210
Dave.Kellogg@mail.sprint.com

John M. Charnes
The University of Kansas
School of Business
Lawrence, KS 66045
jcharnes@ukans.edu

Riza Demirer
The University of Kansas
School of Business
Lawrence, KS 66045
riza@ukans.edu

Introduction

Much of the value contained in early stages of pharmaceutical projects is in the promise of developing a blockbuster drug. This is especially apparent for firms in the biotechnology industry. Many biotech firms have significant valuations, yet do not have profits from which to value the firm using traditional methods because their products are in early stages of development. In the past ten to fifteen years investors have bid up the stock prices of these firms, and their prices have remained high relative to their discounted cash flow valuations. This is surprising to many investors, because some authors e.g. Grabowski and Vernon (1994) suggest that pharmaceutical research has a net present value close to zero.

Real-options pricing techniques can help assess the value investors place on biotech firms. The valuation of the firm is derived from the expected profits of the firm's products and the potential for growth of the firm into one with many profitable drugs. The real-options valuation model will help us determine the worth of individual projects, but the question here is, can real-options valuation models be used to assess a portfolio of projects (i.e., the firm)?

In this paper we compute the value of a biotechnology firm, Agouron Pharmaceuticals, Inc., as the sum of the values of its current projects. Each project's value is found using the decision tree and binomial-lattice methods. An influence diagram method is also used and discussed. The decision tree and influence diagram methods yield identical results, but the influence diagram method has advantages as the decision trees become more complex. We compare our computed values of Agouron to actual market values at selected points in time during the development of Viracept®, a drug used to treat HIV-positive patients.

The approach and results are of interest to stock analysts because it provides a means to value biotechnology companies that have no current revenue. Financial analysts in pharmaceutical companies can use these methods to value projects and compare their relative worth for capital budgeting purposes. Executive management of pharmaceutical firms can use these methods to better understand the value of their projects and convey it to investors. Finally, for academic readers this is an interesting case study that provides empirical evidence of the usefulness of real-options valuation methodologies.

New Drug Development

The development of a new drug is risky business. Of the virtually infinite number of molecular compounds that may have pharmacological effect, drug companies must choose carefully the compounds in which to invest the millions of dollars in development costs required to launch a new product on the market. The development process progresses through several stages, during which the firm gathers evidence to convince government regulators that it can consistently manufacture a safe and efficacious form of the compound for the medical condition it is intended to treat. At the beginning of each stage, the firm uses the technological and market information revealed up to that point to decide whether to abandon or continue development.

Drugs that reach the market in the United States typically pass through the following stages:

1. Discovery. In this stage, a significant amount of effort is expended by chemists and biologists to develop concepts for synthesizing new molecular entities (NMEs). Many NMEs are abandoned at this stage.

2. Pre-clinical. The NME is screened for pharmacologic activity and toxicity *in vitro*, and then in animals. If the NME is a promising candidate for further development, the firm will file with the Food and Drug Administration (FDA) an Investigational New Drug Application (IND). An approved IND allows the firm to continue development by testing the drug on humans in clinical trials. Clinical trials are generally broken down into three phases.

3. Phase I clinical trials. Testing is conducted in a small number of (usually healthy) volunteers to obtain information on toxicity and safe dosing ranges in humans. Data are also collected on the drug's absorption and distribution within the body, the drug's metabolic effects, and the rate and manner in which the drug is eliminated from the body.

4. Phase II clinical trials. The drug is administered to a larger number of individuals selected from patients for whom the drug is intended to be of benefit. Successful Phase II trials provide significant evidence of efficacy, and additional data on safety.

5. Phase III clinical trials. This final pre-marketing clinical development phase involves large-scale trials on patients to obtain additional evidence of efficacy. Larger sample sizes increase the likelihood that actual benefits will be found statistically significant, and that adverse reactions occurring infrequently in patient populations will be observed. Phase III trials are designed to closely approximate the manner in which the drug will be utilized after marketing approval.

6. FDA filing and review. After the clinical development phases have been completed and the firm believes it has sufficient evidence for approval, it will submit a New Drug Application (NDA) to the FDA for review. Marketing for approved uses may begin upon notification from the FDA.

7. Post-approval. While the firm receives revenues from the sales of its new drug, it intensifies its efforts to conduct additional research that supports the marketing of the product, and to develop extensions of the product. These extensions include alternate formulations and dosages for subsets of patients such as children.

Brief History of Agouron Pharmaceuticals, Inc.

Agouron was founded in 1984 and became a publicly traded company in 1987. Until 1997 the company had no operating income from products and most of its efforts focused on the discovery of NMEs and clinical trials thereof. Agouron also formed partnerships with larger pharmaceutical companies to collaborate on the discovery, development and commercialization of drugs based on biotechnology.

Such partnerships are common in the pharmaceutical industry. For the biotech companies, the partnerships provide credibility, capital, additional technical expertise and vehicles to market their products in many areas of the world where the larger company has established operations. For the larger pharmaceutical companies, the biotech companies provide additional sources of innovative ideas and become an extension of their existing R&D group. In a typical partnership the larger company acquires equity in the biotech company, and provides payments to the biotech company upon the initiation of a specified phase of development or governmental approval. The companies then share the resulting cash flows of the approved drug.

At the starting point of this study (July 1994), Agouron was conducting research on anti-cancer and anti-HIV compounds. It had two anti-cancer NMEs in Phase I clinical trials, and one anti-HIV NME in pre-clinical development. During the next four-and-one-half years, Agouron made several major announcements about the progress of its research and development. We show below the results of applying real-options valuation techniques to the firm, and compare our computed values to the actual market values at the times of these announcements. On January 26, 1999, Agouron announced that it was being acquired by Warner Lambert Co. for stock valued at $US 2.1 billion.

Assumptions

Due to the political environment regarding health care costs, much has been written recently in regard to pharmaceutical R&D. For this study, we made assumptions about development costs, probabilities of success, and profitability of new drugs based on the work of Myers and Howe (1997), Office of Technology Assessment (1993), DiMasi, et al. (1991), and Grabowski and Vernon (1994). All costs and revenues are stated in 1994 constant dollars ($US).

Table 1 shows the assumed pre tax costs of development by stage, years in stage and probability of successful completion of that stage conditional on successful completion of the prior stages.

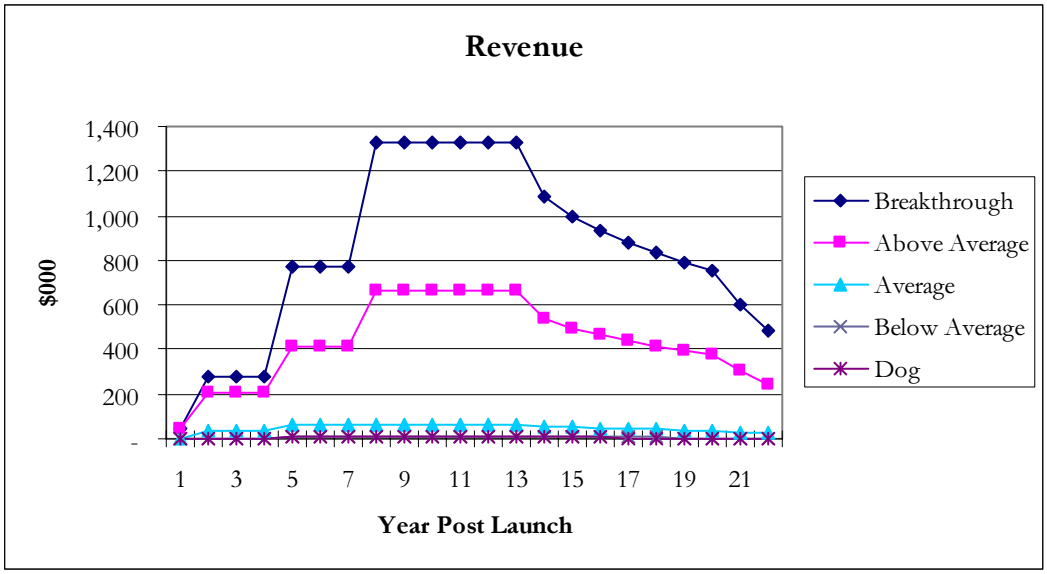
Table 1. Pre tax costs of development, durations and conditional probabilities of success for drug development stages

R&D Stage	Total Cost ($000s)	Years in Stage	Conditional P success
Discovery	$2,200	1	60%
Pre Clinical	13,800	3	90%
Phase I	2,800	1	75%
Phase II	6,400	2	50%
Phase III	18,100	3	85%
FDA Filing	3,300	3	75%
Post-Approval	$31,200	9	100%

Source: Myers and Howe (1997)

Furthermore it was assumed for R&D stages of duration greater than one year, that total was allocated evenly to each year. If a drug is approved, it was assumed that post approval clinical trials would be done. The purpose of these trials is to support the marketing effort for the drug. For example, the results of additional clinical trials are often cited in promotional literature that is shared when a sales representative calls on a doctor. Without new information, it is often difficult to get busy doctors to give sales representatives their attention. Only when sales are low (dog or below average) is it assumed that revenues are insufficient to warrant post approval development.

It was assumed that the revenue of the drug would fall into one of five quality categories 1) dog, 2) below average, 3) average, 4) above average or 5) breakthrough. The average drug has a 60% probability of occurring and all the others have a 10% probability of occurring. The results are highly skewed, with the peak revenue for dog and below average drugs being no more than $7.4 million per year and that of breakthrough drugs being over $1.3 billion per year. The revenue for each category by year after launch is shown in Figure 1. Peak annual revenue by category is shown in Table 2.



Source: Years 1-13 from Myers and Howe (1997), Years14-24 from OTA (1993).

Table 2: Peak annual revenue ($US 000's) by quality category

	Annual Revenue
Breakthrough	1,323,920
Above Average	661,960
Average	66,200
Below Average	7,440
Dog	6,620

Like most products, drugs are subject to a product life cycle. The peak of a drug's life cycle is just prior to patent expiration. Once patents expire, generic competition sets in and revenues drop. Myers and Howe (1997) did not include revenues past the peak year, as the post-patent expiration years were not relevant to their analysis. For this analysis the assumptions regarding post-patent years were obtained from the OTA (1993) report.

Table 3 details other cash flow assumptions.

Table 3. Other Assumptions

Item	Assumption	Source
Cost of Revenue	25.5% of revenue	OTA
Marketing Expense	100% of revenue in the first year after launch 50% of revenue in year 2 after launch 25% of revenue in years 3-4 after launch 20% of revenue in years 5-13 after launch	Myers
G&A	11.1% of revenue	OTA
Tax Rate	35% of profit	Myers
Working Capital	17% of Revenue	OTA

Valuation Methods

Three methods to value Agouron will be discussed: the decision tree method, the influence diagram method and, the binomial-lattice method.

Decision Tree Method

In the first method a model was constructed with the purpose of calculating the expected net present value (*ENPV*) of that drug without taking into account growth options. *ENPV* is calculated as follows:

$$ENPV = \sum_{i=1}^{7} \rho_i \sum_{t=1}^{T} \frac{DCF_{it}}{(1+r_d)^t} + \rho_7 \sum_{j=1}^{5} q_j \sum_{t=1}^{T} \frac{CCF_{jt}}{(1+r_c)^t}$$

where $i = 1,\ldots,7$ represents the seven stages from discovery through post approval described previously above, ρ_i is the probability that stage i is the end stage for the drug, T is the time at which all future cash flows become zero, DCF_{it} is the expected development stage cash flow at time t given that stage i is the end stage, r_d is the discount rate for development cash flows, $j = 1,\ldots,5$ is an index of quality for the drug (defined on page 4), q_j is the probability that the drug is of quality j, CCF_{jt} is the expected commercialization cash flow at time t for a drug of quality j and, r_c is the discount rate for commercialization cash flows. This is represented graphically in Figure 2.

Figure 2. Decision Tree for Pharmaceutical Development

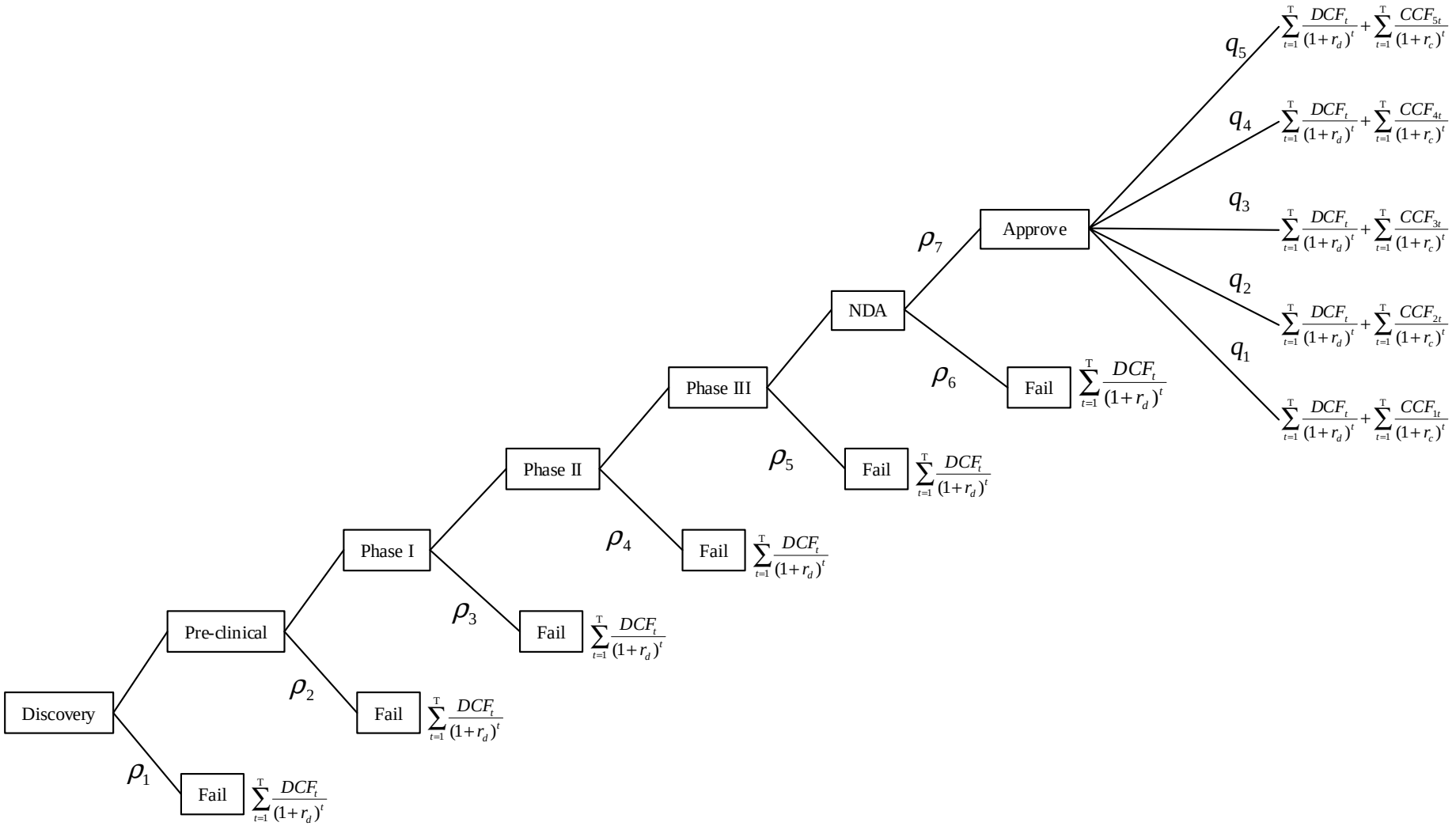


Table 4 shows the *ENPV* calculation of a discovery phase NME in spreadsheet form. This is made by determining the present value of all the possible end points and calculating the sum product of the present values and the probabilities of those end points.

Table 4. ENPV Calculation of a discovery phase NME ($US 000's)

End Phase		i	j	(1) ρ_i	(2) q_j	(3) $\sum_{t=1}^{T} \frac{DCF_t}{(1+r_d)^t}$	(4) $\sum_{t=1}^{T} \frac{CCF_{jt}}{(1+r_c)^t}$	((3)+(4)) × (1) × (2)
Discovery		1		40.0%		(2,004)		(802)
Pre-clinical		2		6.0%		(13,203)		(792)
Phase I		3		13.5%		(15,223)		(2,055)
Phase II		4		20.3%		(19,455)		(3,949)
Phase III		5		3.0%		(29,810)		(894)
NDA Submission		6		4.2%		(31,395)		(1,319)
Approval	Dog	7	1		10%	(31,395)	3,762	(356)
	Below Average	7	2		10%	(31,395)	4,230	(350)
	Average	7	3	12.9%	60%	(31,395)	33,011	125
	Above Average	7	4		10%	(31,395)	315,819	3,669
	Breakthrough	7	5		10%	(31,395)	615,013	7,529
							ENPV =	805

The values of each of the firm's project *ENPV*s are adjusted according to the sharing agreements with partners, and are then summed and divided by the shares and warrants outstanding to obtain a per share value for the firm.

This method has several advantages. First, it is easy to construct and calculate because for any NME there will be no more than eleven potential end points. Second it is easy to communicate using either tables or decision trees. Third, it incorporates the notion of an abandonment option as well as the potential of five scenarios of successful outcomes.

However, the decision-tree method is limited by the facts that continuous outcomes are discretized, and growth options are ignored.

Influence-Diagram Method

Recently, Lander and Shenoy (1999) proposed the use of influence diagrams (IDs) for modeling and valuing real options. An influence diagram is an alternative to a decision tree for representing and solving a decision problem. A primary advantage of IDs over decision trees is that the graphical representation of a decision problem with an ID grows linearly in the number of variables in the problem, whereas the representation of the problem with a decision tree grows exponentially. Therefore, decision problems that include many sequential stages can be represented in an intuitive and compact manner, which makes the ID an effective tool for communication, elicitation, and detailed representation of a decision maker's knowledge (Shenoy 1994).

In addition to representational compactness, IDs also have advantages for solution of the problem. One advantage stems from the decomposition of uncertainty and value into separate functional forms, followed by local solution of the problem (Shachter 1986). Decomposition and local solution lead to a great deal of computational efficiency when solving IDs. Further, the

automation of ID representation through the use of several software packages has made IDs one of the most popular tools for representing and solving decision problems.

An ID representation of the Agouron's new drug development decision problem is given in Figure 3. The seven rectangular nodes represent the decisions to continue with each stage of development or to abandon the project. The uncertainty in the problem is represented by the seven chance variables, which are depicted as elliptical nodes in the diagram. A solid-line arrow between two elliptical nodes indicates that a conditional probability distribution links the two chance variables. For example, the arrow from the node labeled "Dis" to the node labeled "PC" indicates that the outcome of the Pre-clinical stage is conditioned on the outcome of the Discovery stage. A dashed-line arrow from a chance node to a decision node indicates that the realization of the chance variable is known to the decision-maker when that decision is to be made. For example, the arrow from "P_2" to "D_5" indicates that the decision-maker knows the results of the Phase 2 clinical trials at the time of making the decision to continue with Phase 3 clinical trials. Finally, a solid-line arrow from a decision node to a chance node indicates that information on the outcome of the chance variable is available to the decision-maker only after the decision has been made. The node labeled "V" represents the *ENPV* of the project.

Figure 3. ID Representation of Stages in New Drug Development

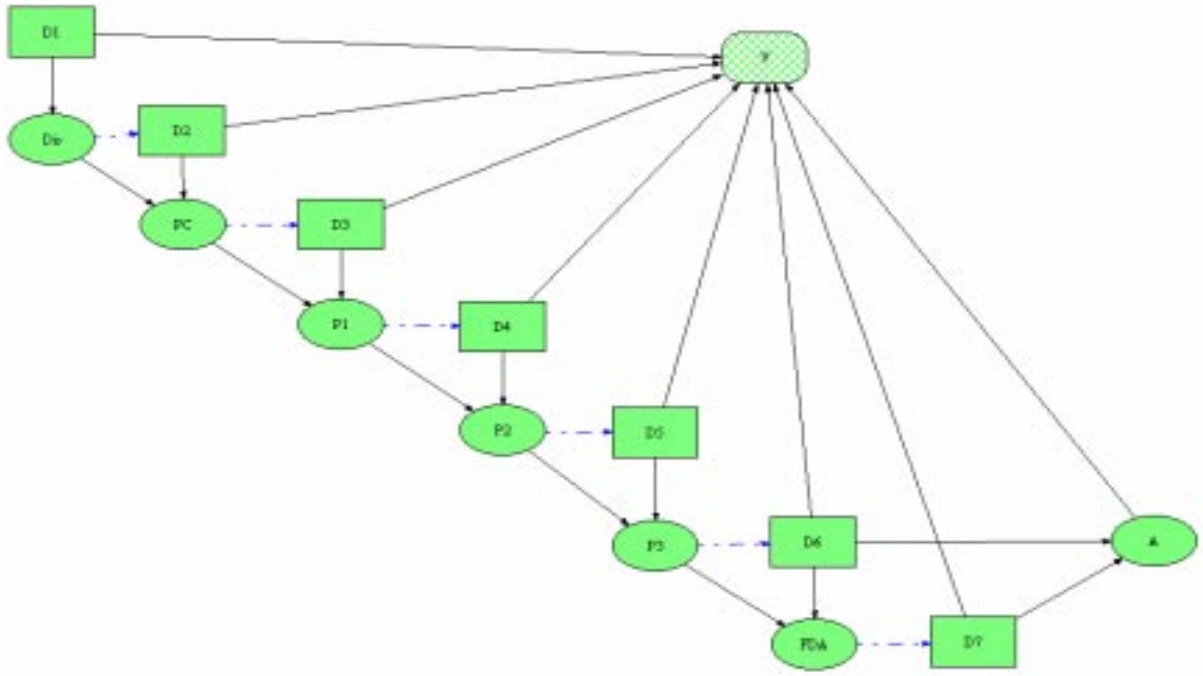


Figure 3 continued. Description of ID Nodes

Node	Description	Node Type	State Space
D_1	Discovery decision	Decision (D)	{continue (c),abandon (a)}
D_2	Pre-clinical Test decision	D	{ c, a }
D_3	Phase 1 decision	D	{ c, a }
D_4	Phase 2 decision	D	{ c, a }
D_5	Phase 3 decision	D	{ c, a }
D_6	FDA filing decision	D	{ c, a }
D_7	Post approval decision	D	{ c, a }
Dis	Discovery results	Chance (C)	{success(s), failure(f)}
PC	Pre-clinical Test results	C	{s , f }
P_1	Phase 1 results	C	{s , f }
P_2	Phase 2 results	C	{s , f }
P_3	Phase 3 results	C	{s , f }
FDA	FDA filing results	C	{s , f }
A	Post approval results	C	{dog (d),below average (ba), average (a), above average (aa), breakthrough (bt)

Binomial-Lattice Method

Values for Agouron were also found using a binomial lattice with the addition of a growth option. The growth option is a second binomial lattice for a research phase NME whose value at the time of launch of the first NME is added to the last branch of the first NME's binomial tree. This approach takes into account elements of Copeland's (1997) discussion of compound rainbow options, and Amram and Kulatilaka's (1998) description of periodic reevaluations of decisions using a binomial approach.

The key inputs to the binomial lattice are: 1) current value of asset, 2) standard deviation of the asset, 3) risk free rate, 4) amount and timing of the exercise prices and, 5) probability of proceeding to the next phase of development.

The value of Viracept® at 6/30/94 is used to illustrate the calculation. The current value of the asset, *A*, is found by discounting the value of the expected commercialization cash flows to time zero:

$$A = \sum_{j=1}^{5} q_j \sum_{t=1}^{T} \frac{CCF_{jt}}{(1+r_c)^t}$$

The standard deviation is found as $\sigma = \ln (h/A)^{1/l}$, where h is the maximum discounted commercialization cash flows at time of launch

$$h = \max_j \left\{ \sum_{t=1}^{T} \frac{CCF_{jt}}{(1+r_c)^t} (1+r_c)^l \right\}$$

and, l is the time until the year before launch. For Viracept, h = 2,875,675 and σ = 26%.

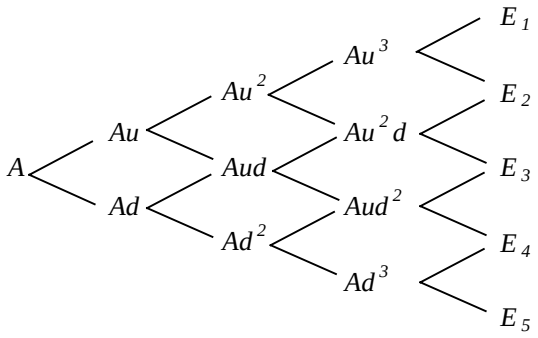
To construct the binomial lattice of asset values, the movements up or down per year starting at the asset value are calculated.

$$u = e^{\sigma\sqrt{\Delta t}} \qquad \text{and} \qquad d = \frac{1}{u}$$

Setting Δt=1 yields u = 1.300 and d = 0.769.

The binomial lattice of asset values is created by taking A and calculating two possible outcomes, one of Au and one of Ad. That process is then perpetuated (e.g. Au^2, Adu, Ad^2, Au^3, Au^2d, etc…) until launch of the NME, resulting in various end branch values denoted E_k. Figure 4 illustrates a binomial lattice that extends four periods.

Figure 4. Four-period Binomial Lattice



The next step is to add in the value of the growth option. The idea is that engaging in the development of an initial NME is similar to purchasing a call option on the value of a subsequent NME. By engaging in development of the initial NME, the firm earns the right but not the obligation to develop the subsequent NME. The assumptions for the growth option are identical to the first option. The value of the growth option at the time of the launch of the first NME is added to each of the E_k values of the first NME.

Once the binomial tree of asset values is completed, the next step is to calculate the possible payoffs and roll back the values using risk neutral probabilities. The possible payoffs are calculated using the following equation:

$$P_k = Max\left[E_k(\theta_t) - DCF_t, 0\right]$$

The value θ_t is the probability of continuation to the next year in year *t* (in this case, 75%) and DCF_t is the R&D payment that occurs in year *t* (in this case $1,619). Because the value at launch of an NME is large (even if it is a dog) relative to the last year's R&D payment (exercise price) the possible payoff is very rarely (if ever) going to be zero.

The P_k values are then rolled back by multiplying the adjacent values, such as P_1 and P_2 (denoted $V_{t+1,k}$ and $V_{t+1,k+1}$) times the respective risk neutral probabilities (*p* and 1-*p*), the probability of continuation to the next year and a discount factor resulting in $V_{t,k}$. The risk neutral probabilities are calculated using the following equation:

$$p = \frac{e^{r\Delta t} - d}{u - d}$$

The risk free rate, *r*, is the 10-year United States Treasury-bill rate, which was 7.09% in 1994. This results in $p = 0.573$. Table 5 shows all the possible payoff values.

Table 5. Calculation of the possible Payoff values ($US 000's)

DCF_t =	1,619
θ_t =	0.75
value of growth option =	2,085

k	E_k	P_k
1	2,877,759	2,156,699
2	1,704,795	1,276,976
3	1,010,273	756,085
4	599,041	447,661
5	355,548	265,041
6	211,373	156,910
7	126,006	92,885
8	75,460	54,975
9	45,531	32,528
10	27,810	19,238
11	17,317	11,368
12	11,104	6,708
13	7,425	3,949

As the option values are rolled back, they are also adjusted for the probability of success at that phase of development and for the cost of development in that year. The equation rolling back the option values is:

$$V_{t,k} = Max[(V_{t+1,k}\,p + V_{t+1,k+1}(1-p))e^{-r\sqrt{\Delta t}}\theta_t - DCF_t, 0]$$

When the stage of development has a duration of more than one year, θ_t is the probability of success for that stage in the final year of that stage and 1 for all other years. DCF_t can be regarded as an annual exercise price. For example, $V_{12,1}$ is calculated as follows:

(2,156,669 (.573) + 1,276,979 (1-.573)) .9316 (1) - 1,564 = 1,657,654 ($US 000's)

This process is then continued until $V_{1,1}$ is reached, which is the value of the option.

Results

Table 6 shows the values of Agouron Pharmaceuticals, Inc. we calculated for selected dates using the decision-tree analysis/influence method (DT/ID) and the Binomial method. The actual stock prices are also shown for comparison.

Table 6. Per Share Values

	6/30/94	10/20/94	6/30/95	6/30/96	12/23/96
DT/ID Method	$ 4.31	$ 5.70	$ 7.17	$ 10.26	$ 15.05
% difference from stock price	*(23.4%)*	*1.3%*	*(39.3%)*	*(47.4%)*	*(55.6%)*
Binomial Method	$ 4.51	$ 5.87	$ 8.51	$ 10.44	$ 15.45
% difference from stock price	*(19.8%)*	*4.3%*	*(27.9%)*	*(46.5%)*	*(54.4%)*
Stock Price	$ 5.63	$ 5.63	$ 11.81	$ 19.50	$ 33.88

The significance of the selected dates is,

1) June 1994, fiscal year end and Viracept® was undergoing preclincal trials;
2) October 20, 1994, an announcement was made that Viracept® would begin Phase I trials;
3) June 1995, fiscal year end;
4) June 1996, fiscal year end; and
5) December 23, 1996, an announcement was made that Agouron was filing a New Drug Application (NDA) for Viracept®.

During the period June 30, 1994 to December 23, 1996 Agouron had other projects in the Discovery, Pre-Clinical and Phase 1 clinical trial stages of development. However, Viracept® was the only NME to make it to Phase II, III and NDA submission during this period. The fiscal year end dates are helpful in assessing valuation because the 10-K reports filed with the Securities and Exchange Commission (SEC) indicate which projects were in the pipeline and at what stage. Rarely was abandonment of a project announced. This resulted in the potential of projects being included in the valuation when in fact they were not part of the product pipeline for valuations conducted on dates other than fiscal year end.

Table 6 indicates that the methods valued Agouron relatively well when all the projects were in Phase I or earlier, but the calculated values deviated further from the actual stock price as Viracept® worked its way through the development process. Thus it appeared that investors are making different assumptions regarding this NME than they would for the average NME specified in the model. If so, and if our model was adjusted for these assumptions, how close would the valuation of the model be to the actual stock price?

There are several reasons to believe that investors were making different assumptions. First, there was (and remains) tremendous political pressure for the FDA to approve drugs for HIV positive patients. Therefore, investors might have assumed that it would take less than eight years from beginning of Phase II till launch. It took slightly less than two years. Another key assumption is the probability distribution of the revenue stream. An assumption of our model is an 80% probability that revenue will be under $100 million per year at peak. In fact, sales of Viracept® were over $400 million during fiscal year 1998 (its first full year of sales) and are

expected to be between $430 and $440 in fiscal year 1999. Again, it is likely that the market was assuming a different probability distribution for revenue. Lastly it is likely the market assumed a probability of approval for VIRACEPT® greater than that for an average NME.

By adjusting the assumptions in the DT/ID model at 6/30/96 and 12/23/96 in the following way,

1. one year for Phase III and NDA each instead of three years each;
2. a revenue distribution from dog to breakthrough of 10%, 10%, 30%, 35% and 15% respectively instead of 10%, 10%, 60%, 10% and 10%; and
3. probabilities of success increased from 85% and 75% for Phase III and NDA to 90% and 90% respectively;

the resulting valuations were 19.1% higher and 15.9% lower than the stock price on the two dates in question. Changing these assumptions in the Binomial model yielded similar results.

One other observation is that the inclusion of the growth option into the value of the initial option did not significantly increase the value of the initial option. This is because the value of a research project (assumed as the growth option) is relatively low. This is then compounded when it gets discounted to an even lower level as a result of the discounting for probabilities of success on the initial option.

Conclusion

The real-options approach can be used to value a biotechnology firm. Usage of average assumptions works well when the projects in the pipeline are in Phase I or earlier and less is known about the drug. As projects move into Phase II and later, more specific assumptions regarding time to launch, market size and probability of success should be utilized to reflect the value of the firm more accurately.

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