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Investment decisions in pharmaceutical R&D projects

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In a recent interview, Fred Hassan warned that many of the good opportunities in pharmaceutical R&D have already been picked off and new opportunities are increasingly hard to find [1]. His statement parallels that of Charles Duell in 1899, the then commissioner of the U.S. Office of Patents; 'everything that can be invented has been invented'. Of course, the growth of science defied that prediction and we expect it to continue to do so in the future. On the one hand, Hassan's point is valid- pharmaceutical R&D is risky; each gamble could result in a billion-dollar product or become an empty promise. But on the other hand, not investing in research would lead to ever-decreasing returns in a genericized market and would leave potential opportunities unexplored. In substance, there are risks, but the pharmaceutical industry has to take those risks.

Pharmaceutical R&D risks arise from scientific uncertainty in the discovery process, continuing unpredictability of the safety profile until the late stages of product trials and, ultimately, from the market place (i.e. changing disease profiles and expected or unexpected competitors). Still, the evidence suggests that, over the years, investment decisions in pharmaceutical R&D projects have been successful. The American pharmaceutical industry grew at an average rate of >11% per annum between 1970 and 1999, the American economy managing an average growth rate of <3.5% per annum during the same period. Alongside this phenomenal growth, returns on investment for the pharmaceutical industry have remained better than the overall market average [2]. Pharma has, therefore, outperformed the economy considerably and continuously, churning out new chemical entities. Companies have undertaken negative NPV (net present value) projects consistently, citing strategic importance. These were not intrinsically 'bad' business decisions, but the valuation methodology produced negative figures. Correspondingly, however, some were uncomfortable with the purely subjective decisions taken in the face of negative valuations.

This sense of discomfort led to intensive research in pharmaceutical research project valuation, culminating in the application of working practices such as real-options-based evaluation of R&D projects, as implemented by Merck. However, real-options-based models proved too complicated for common sense and more troublesome were the assumptions that accompanied this methodology.

Between the two extremes of NPV and real options approaches, there lies the simple method of ENPV (expected NPV), which incorporates the virtues of decision-tree analysis and provides an excellent tool for investment decision-making in the pharmaceutical R&D context.

Here, we provide a comparative analysis of the three alternative methodologies, concluding that the ENPV method is the most appropriate for pharmaceutical R&D project evaluation.

Modeling pharmaceutical R&D for valuation

A pharmaceutical R&D project can be modeled as a series of sub-projects, where investment in each step is dependent on the results obtained from the previous step. Returns are not obtained until the last stage, that is, until the drug is marketed. The probability of success at each stage and in market performance can be assigned according to historical data, medical need and the pharmacological profile of the molecule, as demonstrated by Sedlacek, Sapienza and Eid [3].
A simplified, illustrative model used to explain the methodologies is shown in Table 1.

A comprehensive model would have nodes of discovery, pre-clinical, Phase I, II and III, FDA approval and market stages. The first six are decision nodes in which the outcome could be abandonment of the project. The last node is based on chance. In market, five end-states (maximum, optimistic, realistic, pessimistic, and minimum) can be envisaged. Thus, there are eleven possible end-states; the first six reflecting technical uncertainties, and the last five reflecting market uncertainties.

An option is a right, without obligation, to do something. In pharmaceutical R&D, one has a right to abandon a project at the end of any of the phases before marketing, if the results are unfavorable; thus, we have 'abandonment' options. Conversely, we have 'growth' options – the possibility of expanding or altering the

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Table 1. Illustrative model and NPV and ENPV calculations

Stage	Discovery	Development	Market	
Possible end state	Stop	Stop	Success	Failure
End state code (s)	1	2	3a	3b
Conditional probability of success of stage (P_s)	0.6	0.2	0.5	0.5
Total probability of reaching the stage. P_{s-1}' (Product of P_0, P_1 etc till P_{s-1})	1	0.6	0.12	0.12
Probability of happening of state 's ' $\{Q_s = P_{s-1}'(1-P_s)\}$	0.4	0.48	0.06	0.06
Cash Flow ($ millions) (C_s)	-5	-50	500	100
Year (T)	1	2	3	3
Risk-free Rate (RFR)[a]	0.1	0.1	0.1	0.1
Discount Factor (F = 1 + RFR)	1.1	1.1	1.1	1.1
Discounted Cash Flow ($ millions) ($DCF_s = C_s/F^T$)	-4.5	-41.3	375.7	75.1
NPV ($ millions)[b] $(DCF_1+DCF_2+Q_{3a}*DCF_{3a}+Q_{3b}*DCF_{3b})$				-18.8
ENPV ($ millions)[b] $(Q_1*DCF_1+Q_2*DCF_2+Q_{3a}*DCF_{3a}+Q_{3b}*DCF_{3b})$				5.4

* multiplied by

[a]Government bond rate for appropriate time frame should be taken as RFR. In pharma R&D projects 12-13 years for R&D and 17-18 years of market life cycle can be assumed. Thus, a 30 year bond rate should be ideal in initial stages. Currently 30 year US bonds return about 5% per annum. RFR shown here is just to illustrate calculations.

[b]Note that ENPV is simply a sumproduct of conditional probabilities of all the possible end states generated by the decision tree analysis and the corresponding discounted cash flows. NPV assumes that all the investments are committed up-front.

scope of project, arising from improved information. The options of abandonment or growth are an important source of value, and, therefore, they need to be incorporated in any evaluation model.

The NPV model

NPV is a popular model for investment decision. The basic principle of this valuation method is the recognition of the fact that a dollar today is more valuable than a dollar tomorrow, and hence, future cash flows have to be discounted for the purpose of summation at a common date (present). The more distant a cash flow, the larger the discount factor becomes, and thus, projects with different cash life-cycles are valued differently.

The 'discount rate' used represents the expected rate of return from the project and, fundamentally, is a reward for the risk that is taken by investors. Typically, investors need to be rewarded for three types of risks; (a) country risk, (b) corporate risk and (c) project risk. Country risk reward is benchmarked with a comparable government bond, for example, for an USA-based long-term investor, the reward for country risk taken is equivalent to a 30-year American bond return (~5% per annum, currently). Corporate risk premium and project risk premium are added to this, and would obviously vary from company to company and project to project.

However, the NPV method is static, in the sense that it does not recognize that a company can control its future cash flows by decision-making as a project progresses and as more information becomes available. Thus, the NPV method can undervalue projects, especially those with greater uncertainty and greater flexibility; in effect, it does not value abandonment options. By contrast, growth options have the potential to be built into the model.

The second principle of the NPV model is that it tries to capture the variability of cash flow in a 'catch-all' discount factor; in pharmaceutical research projects, project risks outweigh the country risk and the corporate risk. Assignment of a numerical value to the project risk is a practice that is prone to error, therefore, the discount factors are also prone to error: a projected cash flow for two years from present would usually be discounted twice (with the same factor that would be used once for a cash flow happening one year from present). The error has a multiplying accumulation for distant cash flows and the slightest estimation error in the discount factor could lead to a huge error in NPV values, thus, making NPV values extremely unreliable.

The 'Real options' model

Real options (RO) methodology is based on the financial option theory in real investment cases, of Merton, Black and Scholes in 1973 [4]. The fundamental argument is that a multi-stage process with a 'go/stop' point at the end of every stage is a set of cumulative options, in which later investments are made only if results from the previous stage are satisfactory. Furthermore, it is argued that the rate of discount that is used to calculate present value is a function of risk; as the project moves towards the launch stage, uncertainties decrease and, hence, discount rates should become smaller - in effect, increasing the valuation of the project. The RO method enables this by allowing discounting of risk-adjusted expected cash flows at a risk-free discount rate. This methodology is designed to evaluate abandonment options through a complex procedure. The five parameters that are required for this evaluation are; (a) the present value of a project's operating assets, (b) the expenditure in acquiring the project assets, (c) the length of time the decision can be deferred, (d) the time value of money and (e) the 'riskiness' of the project assets. The Key assumption made is the tradability of the underlying asset in the free market.

Amram and Kulatilaka have clearly shown that these assumptions are not met in the case of pharmaceutical R&D investments [5]. Their argument is threefold:

(a) there is no traded underlying asset or portfolio of traded assets that tracks project value reasonably well,

(b) a large amount of project risk is not resolved until just before launch, and thus, the preceding go/stop decisions are largely triggered by the consideration of project risk, and

(c) the most important questions in drug development are centered around the value of information and, in such applications, RO has nothing to add beyond the current tools.

However, there have been many attempts to apply the RO method to real cases, a good illustration of which is found in a recent case study by Borissiouk and Peli [6]. They tried to measure the 'riskiness' of Serono's projects in the context of the volatility of biotech stocks. (Company stock is a portfolio of projects, and therefore, the measurement here does not represent project risk *per se*, but rather portfolio risk, which is usually much smaller, due to the diversification effect). The authors concur that the 'expected net present value' (ENPV) model is a better method for valuing an R&D project in question, their only contention being ENPV's incapability to capture economic risk (market risk), but, as will be discussed later, the ENPV method can be modified to capture this effect. It should be noted in the context of Amram and Kulatilaka's arguments, that economic risk for pharmaceutical R&D is a minor factor only. This is primarily because a pharmaceutical R&D project is abandoned or furthered depending on the merit of scientific data generated and the views of regulatory authorities on those data, and not on the changing market situation.

The ENPV model

In a pharmaceutical R&D project, the total investments are not committed upfront, but are contingent on the success of the previous stage. This abandonment option is the primary value creator in early stages of the research. ENPV methods enable the combination of NPV and decision tree analyses and, by enabling the factoring-in of the probability distribution of future outcome and consequent decision, make it possible to incorporate flexibility considerations; negative NPV projects can prove to be positive ENPV projects.

Owing to the integration of decision tree analysis, growth options can also be built in. Growth options include, primarily, the possibility of new indications for a drug, discovered later in development. They could also include different dosage forms or analogues and so on. To avoid subjectivity of discount rate, the risk-free rate (US government bond returns) for appropriate periods is used. Thirty-year bond rates would be appropriate for early-stage pharmaceutical R&D projects; a typical project life-cycle is 25–30 years (12–15 years before launch and 12–15 years after launch). When the drug reaches 'new drug approval' stage, a market life-cycle of 12–15 years is possible, and thus, a 10-year bond rate becomes a better approximation of the risk-free rate. All scientific risk is built into the probabilities associated at decision nodes, whereas, the market risk is incorporated by generating different scenarios and assigning probabilities for those scenarios.

As is shown in Table 1, for a simple, illustrative, three-stage model, involving investments of ~US$5 million in the first stage (probability of success = 0.6), US$50 million in the second stage (probability of success = 0.2), and the possibility of generating US$500 million (probability = 0.5) or US$100 million (probability = 0.5) in the third stage, the NPV is negative US$18.8 million, whereas the ENPV is positive $5.4 million. Such a project would be rejected on the basis of NPV calculations, but would be progressed on the basis on ENPV calculations. The value enhancement is due to incorporating the option that the project might be discontinued after stage 1, if the results are not positive.

Potential uses and applications of the ENPV method

The ENPV method enables the generation of different scenarios to resolve the dilemmas of process development, the importance of

Table 2. Comparison of various investment decision models

	NPV model	Real options model	ENPV model
Merits	1. Simple to use 2. Easy to understand 3. Differentiates different cash life-cycles	1. Good handling of economic uncertainty 2. Values abandonment options 3. Can incorporate growth options	1. Simple to use 2. Easy to understand 3. Values abandonment options 4. Can incorporate growth options
Limitations	1. Subjectivity in discount rates 2. Investments assumed to be committed upfront 3. Undervalues R&D projects	1. Assumptions made are not met by pharmaceutical R&D 2. Very complicated to use 3. Difficult to understand	1. Requires detailed decision tree analysis

which has been highlighted by Shultis [7]. The 'fallout' of starting process development at different stages of the development of the molecule can be incorporated, appropriate probabilities can be attached, and the ENPV can be calculated for the different scenarios. Obviously, the option that generates maximum ENPV would be selected. Again, a similar method can be used to decide the value of pursuing multiple indications, multiple formulations and so on, by superimposing the ENPV framework over the SmithKline method of resource allocation, as discussed by Sharpe and Keelin [8].

Another major application of the framework would be in licensing negotiations and milestone payment determinations, where, again, RO-based models are being suggested erroneously [9].

Conclusion

Table 2 summarizes the merits and limitations of the three alternative methodologies discussed here. There is a strong case for using the ENPV method in evaluation of pharmaceutical R&D projects; this method bridges the gap between R&D strategy and financial evaluations. Thus, it would improve decision-making and consequently help to increase value in Pharma.

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