A user friendly real option based model to optimize pharmaceutical R&D portfolio

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Abstract. Pharmaceutical industry pays great attention to its R&D process because it is a long, dynamic, very expensive, and uncertain process. On the other hand this process can be modelled as a step-wise process and each stage allows achieving better information and generally lower uncertainty. In order to build up the best portfolio a tool able to capture the intrinsic flexible nature of the process should be selected: real options analysis has this characteristic but as widely demonstrated in literature, is narrowed to very limited cases because its perceived complexity. Basing on OptFolio, a model available in literature, this paper proposes a user friendly programming model based on Real Options Analysis fitted to the pharmaceutical R&D process able to support managers in the selection of the best partially self-financing portfolio. So we propose a new closed-form model of low complexity in order to obtain a financially balanced portfolio; finally, a numerical example is used to illustrate the proposed approach.

Keywords: R&D management; portfolio selection; optimization; real options

Received September 2012. Accepted May 2013

Introduction

The winner-takes-all patent race and the focus on innovation, make R&D process extremely important in the pharmaceutical industry; this importance is witnessed by the financial effort that pharmaceutical firms carried out during the last decades to fund R&D activities. In the US, the R&D intensity, which is the ratio between expenditures for R&D and firm revenue, rose from 12% in the 1970 to over 20% in the late 1990’s and it’s now approximately steady around the value of 19% (PhRMA, 2011). In 2009, pharmaceutical companies invested US$ 65.3 billion in R&D, 37% more than 5 years before (Vernon et al. 2010). In addition, the pharmaceutical R&D process has a long and dynamic life, and further investments depend on the success/failure of previous ones. According to recent analysis (DiMasi, 2001), only one of 10,000 potential medicines investigated by American pharmaceutical companies makes it through its R&D process and is approved for patient use by the FDA. Potential new drugs pass through several stages on their way from research laboratories to pharmacy shelves. These phases are well defined and strongly regulated by regulatory agencies as the above mentioned FDA. An illustrative model of the pharmaceutical R&D process is shown in figure 1 (Cassimon et al. 2004).

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The timeline from discovery to marketing approval of a new drug can run 10-15 years and costs around $1.2 billion (Pharma, 2011). High expenditures and failure rates make the pharmaceutical R&D process extremely risky. These risks are usually divided in two components, namely economic and technical (Brealey and Myers, 2000). Economic risk deals with factors which increase market uncertainty, like interest rates, inflation and changes in industry prices. On the other hand, technical risk stems from the lack of certainty about the process success. So, being the pharmaceutical process very expensive and uncertain, it’s vital to evaluate R&D projects in the most proper and accurate way in order to decide whether to invest in them or not. Moreover there are fewer and fewer new molecular entities that are ready to be brought to the market per USD invested in R&D, so the importance of a promising portfolio selection assumes a growing importance.

Traditional evaluation methods, based on discounted cash flow (DCF) such as net present value, are not able to catch the actual value created by this kind of projects because of their inability to take account of the flexibility owned by managers, who might interrupt the drug development process and consequently abandon the project if it became no longer favourable. The ability of project managers to react to these uncertainties at future time adds intrinsic value to the project, and this value is not captured by standard DCF methods (Lawryshyn, Y. and Jaimungal, 2010). Thus, alternative tools, able to adapt to the features of pharmaceutical R&D projects, are required, in order to correctly assess their value. In addition, as above shown (fig.1), the development of a new drug is a step-wise process that starts with discovery and pre-clinical test phase, followed by clinical tests, the FDA approval and, ultimately, the commercialization phase. Particularly, each phase is an option on the following one: if the discovery phase turns to be successful, then pre-clinical phase can start. So the initial R&D phase is an option on the preclinical one. Similarly, preclinical phase is an option on the first clinical test, which is an option on the next test and so on, until the last phase, i.e. the commercialization phase (Cassimone et al., 2004).

Real options methods, as widely acknowledged in literature (Dixit and Pindyck, 1994; Trigeorgis 1988; 1995), allow to take account of uncertainty and flexibility inherent in the pharmaceutical R&D process and to reckon with the value of future chances deriving from the acquisition of knowledge during the drug development process. So the process can be modelled as a compound option, a set of subsequent options that are dependent on each other. In real options literature this option can be evaluated using both closed-form solutions (such as Geske formula) and numerical approaches, such as binomial model. An alternative way to binomial model is the decision tree analysis, which incorporates “the decision instances that allow the manager to maximize the value of the project conditioned on the information available at that point in time, after several uncertainties may have been resolved” (Brandio and Dyer, 2011). However, organizations, as pointed out by Hartmann & Hassann (2006), while recognizing the importance of ROA, do not apply it very often because it is perceived as a complex concept. This observation is especially true when the whole projects portfolio is considered.

The goal of this paper is twofold i) to deepen the discussion on different real options models able to optimize a portfolio of R&D projects and ii) to propose an accurate and simple model, called OptFolio Light (OL), to optimize a pharmaceutical R&D portfolio. As a matter of fact, the proposed model can be easily implemented into a spreadsheet. In the following section, different models for RO valuation are presented with major focus on tools to evaluate both single biopharmaceutical projects and the whole portfolio. The proposed model (OL) is introduced in section 3 and tested on a pharmaceutical portfolio selection case study in section 4. Finally, in section 5 some conclusions are drawn and some suggestions for possible further studies are proposed.
Literature review

A major advance in development of R&D project selection tools came with the application of options reasoning to R&D. An analysis of projects in a dynamic environment is often more complex than the standard (DCF) approaches may suggest, since they implicitly assume a static view of investment decisions and projected cash flow scenarios. The real options approach is more dynamic than the traditional approaches since it is capable of incorporating the above flexibility (Smit and Trigeorgis, 2003). A number of papers have addressed the importance of managerial flexibility. Myers (1987) suggests considering strategic investment opportunities as growth options, while Dixit and Pindyck (1994), Trigeorgis (1988; 1995), Smit (1996), and others, discuss many corporate options and provide various expositions of the real options approach to investment. These considerations are particularly true in sequential R&D projects, in which the staged process allows the management to move a product development project into the next stage only if the expected results appear to be satisfactory. Although traditional methods are still the most frequently used for evaluation of R&D projects, the enormous pressure to innovate, especially in the biopharmaceutical industry, forces the companies to use sophisticated instruments which are more accurate in evaluation of chances and risks of R&D projects, in order to choose the right ones and avoid the risk of missing profitable opportunities. So, in recent years, the evaluation of R&D projects through real options based methods has gained growing attention (Cassimon et al., 2004).

In particular, real options researches support R&D process mainly through two different approaches. The former evaluates the project using numerical methods, such as the binomial model (Cox et al., 1979), while the latter uses closed-form solutions such as the Black-Scholes (B&S) option pricing formula (Black and Scholes 1973) and the Geske model (Geske, 1979), based on B&S, which is able to evaluate compound options. According to Cassimon et al. (2004), by adopting binomial approaches a problem may arise, i.e. it is not known how many time steps are necessary in order to obtain an accurate option price. On the other hand, the main limit of closed-formulae is its inability to solve the American put option. However, the R&D process is seen as a sequence of the growth options (modeled by call options), so this limitation would not apply. Moreover, according to Cassimon et al. (2004), the Black-Scholes formula seems to work well in a general R&D environment without fixed and distinct phases but it seems less suited in a step-wise pharmaceutical process, that can be better modelled by Geske approach (which allows compound options).

In addition, according to Collan et al. (2009), there are also a number of later developed versions of the above mentioned methods, which include the use of fuzzy variables. For example, Carlsson and Fuller (2003) use the B&S formula, where the present values of expected cash flows and expected costs are estimated by trapezoidal fuzzy numbers. Similarly, a fuzzy compound option model based on the Geske model is proposed by Wang and Hwang (2007). Starting from the Cox et al. (1979) model, Muzzioli and Reynaerts (2008), use fuzzy logic in order to investigate which is the effect on the option price of assuming the volatility as an uncertain parameter.

Actually, different real options methods to evaluate the R&D process are been developed. Among these we can mention simulation based models, such as Monte-Carlo simulation based methods (Longstaff and Schwartz, 2001) or Datar-Mathews method (Datar and Mathews 2004), which calculates the real option value from a pay-off distribution that is derived from a probability distribution (generated with a Monte-Carlo simulation) of the net present value for a project. However, according to Cassimon et al. (2004) simulation has serious limitations. For example, the extreme high and low simulated values of the probability distribution are shown to be unreliable (Brealey and Myers, 2000). Moreover, these methods require statistical and programming skills which violate the goal of simple application for the real option analysis (Enevoldsen and Nordabaek, 2011).

Finally a new and simple method is the fuzzy pay-off method for real options valuation (Collan 2008; Collan et al. 2009). The model uses fuzzy numbers in order to represent the distribution of the NPV of the project, i.e. of the expected future outcomes of the project. The mean value of the positive values of the fuzzy NPV is the “possibilistic” mean value of the positive fuzzy NPV values. So the real options value calculated from the fuzzy NPV is the “possibilistic” mean value of the positive fuzzy NPV values multiplied with the positive area of the fuzzy NPV over the total area of the fuzzy NPV (Collan 2008). The structure of the method is similar to the probability theory based Datar–Mathews method for real option valuation but the method is not based on probability theory and uses fuzzy numbers and possibility theory in framing the real option valuation problem.

In addition, the pay-off method is different from the Black-Scholes and binomial models, because of the payoff distribution. In order to calculate the ROV (real option value) a process is needed to create an expected payoff
distribution (Enevoldsen and Nordabaek, 2011). To achieve this, closed solutions, like Black-Scholes, utilise stochastic processes while the binomial approach uses tree-like processes. By adopting the pay-off method, the real options value can be constructed directly from cash-flow scenarios (typically three or four scenarios which are most often created by an expert or a group of experts) data for a given project, that is the method is not dependent on a given process to model the future. In fact, the pay-off distribution is created simply by assigning each of the three/four cash-flow scenarios a corresponding definition with regards to a fuzzy number (triangular fuzzy number for three scenarios and a trapezoidal fuzzy number for four scenarios). This makes the procedure easy and transparent, and the method is very helpful when the available data has a fuzzy nature. However the choice and the estimate of the cash-flow scenarios remain arbitrary and this is not a trivial question.

Real options pharmaceutical project evaluation

Different authors address the R&D pharmaceutical process by adopting the above mentioned real options models. Particularly, these models were mostly used for a single R&D project evaluation. As Bowman and Moskowitz pointed out (Bowman and Moskowitz, 2001), the first application of ROA in the evaluation of a pharmaceutical R&D project was carried out by Merck, one of the most important pharmaceutical company, in the early 1990’s. At that time, Merck was evaluating the chance of investing on a new technology which would have allowed it to develop a new drug. Merck considered the whole project as a growth option. In fact, if this technology had failed to produce a commercially valuable product, then Merck would have been under no obligation to build the plant and incur the start-up costs. Since a growth option could be considered as a call option, and its value was therefore assessed by Merck using the Black & Scholes formula. After this first attempt, many scholars have devoted their attention to these closed-form solutions, and they refer to more accurate models such as the compound option model (Geske, 1979). Among these, we can mention the two-fold compound approach (Perlitz et al., 1999) or the generalized n-fold version of this (Cassimon et al., 2004).

A different approach to model a pharmaceutical R&D project, as shown by Ollila (2000) in the Orion Pharma case and Kellog and Charnes (2000) in the Agouron’s Viracept case, consists of adopting the binomial model. Schwartz (2004) uses a Monte Carlo simulation based on the Longstaff and Schwartz (2001) procedure to value pharmaceutical R&D projects. Finally, Sereno (2010) showed also how it is possible to evaluate a pharmaceutical R&D project modelled as a compound option, using a numerical method such as the binomial method. This method improves the flexibility of the evaluation but, at the same time, makes impossible to automate the calculation of the value through software.

Real options portfolio optimization tools

However, according to several authors it is better to evaluate the entire R&D project portfolio of a company instead of its single projects, in order to consider the relations and the interdependences between them. While there is a large amount of literature on project evaluation using ROA, little research has been conducted to evaluate a R&D projects portfolio (Copeland & Antikar, 2001). Consistently with this issue, Rogers et al. (2002) adopted a quadrational approach (a two-variable binomial tree) to develop a stochastic optimization model, called OptFolio. The aim of this method is to determine the optimal drug developmental portfolio that maximizes its real options value (ROV), overall value of the portfolio, given a set of candidate drugs in various stages of development. However, implementation and use of OptFolio turn out to be very complex. As a matter of fact, a pharmaceutical company may find it hard to set its optimal project portfolio solving a problem with hundreds of constraints and several dozen thousands of variables, with only 20 candidate drugs. Binomial trees are the most widespread tool for real options valuation; it is due to its intuitive simplicity in the modelling (Mun, 2002). However the more advanced trinomial, quadrational and multinomial trees should in theory yield more precise results as they incorporate more events at each node (Copeland & Antikar, 2001), but they are also computationally more complex to model (Kodukula & Papudesu, 2006). According to Hartmann and Hassan’s (2006) findings, the perceived technique complexity is the major reason of lacking of use of the real options methods by pharmaceutical firms. In addition, as pointed out by Poh and Buy (2001), both i) the ability of the evaluation method to incorporate risk and uncertainty in the analysis and ii) the simplicity of the model, are become important factors when the effectiveness of an evaluation tool is considered. This observation would suggest to adopt closed-form solutions
instead of numerical approaches such as binomial decision trees which can easily become difficult to manage because of the rapidly expanding number of trees increasing the size of the portfolio (Cassimon et al. 2004). In addition, binomial model is based on a discrete rather than continuous way of contemplation of the underlying. According to Perlitz et al. (1999), the continuous time assumption of Black & Sholes formula and Geske model, allows for closed-form solutions that makes the handling easier. Consistently with this issue, Wang and Hwang (2007) developed a closed fuzzy compound option model to estimate the value of a pharmaceutical portfolio. Particularly they test the model on the same case study adopted by Rogers et al. (2002). Specifically the authors adopt a fuzzy real options valuation method that is based on the method proposed by Carlsson and Fuller (2003) and use Geske model for all 20 drugs in the considered portfolio. While closed solutions, adopted by Wang and Hwang (2007), reduce the computational implementation, however, according to Hassanzadeh et al. (2011), the Wang and Hwang’s formulation, deserves attention. The first issue concerns the objective function that consists in the total ROV (fuzzy real option value) of selected projects minus all development costs in the planning horizon. However, deducting the total development costs of selected projects from their ROVs in the objective function implies that the total benefit of the portfolio is doubly affected (because they are also considered as exercise prices in the real options evaluation) by development costs (except for the initial cost). Another problem is the real options formula used to model the pharmaceutical process of each drug in the portfolio. Specifically, they use the Geske compound options valuation model for all 20 drugs which are in different phases of their development (see section 4). This means they assume to use the same mathematical process for all stages (Hassanzadeh et al. 2011), but we believe that the method should depend on the remaining phases. Finally they use the crisp value of the input parameters in the classical Geske method and so their model suffers of the same limitations of the Black and Scholes formula (that will be discussed in section 3). Starting from the same case study (Rogers et al. 2002), Hassanzadeh et al. (2012) address the above problem integrating the pay-off method, which is processed independently, to portfolio optimization. In particular the real options value of each candidate drug is calculated by using the pay-off method. Then, they formulate an optimization model and use a transformation method to transform the resulting fuzzy mathematical model to a classical optimization model, with budgetary constraints and other constraints. The obtained model is a practical mathematical model and very simple to understand, but it involves heavily subjectiveness being a fuzzy method.

The objective of this paper is to develop a new closed-form portfolio selection model to optimize the R&D portfolio in an uncertain R&D environment. Particularly we propose to use Geske model, or Black and Scholes formula, or the simple NPV (depending on the remaining phases of each project) in the considered portfolio (in the following section the model is presented in more detail). By adopting this approach, we obtain a model which is both accurate in project evaluation and simple to manage. As a matter of fact, we can solve the same case study proposed by Rogers et al. (2002) with only 40 binary variables and 20 continuous variables, instead of the 893 binary variables and 12843 continuous variables involved in OptFolio. In addition, our formulation, also account for the self financing opportunity. According to Kamien and Schwartz (1978), the urgency of self-financing R&D for a company has two reasons. First, the external financing may be difficult to obtain without substantial related tangible collateral to be claimed by the lender if the project fails. An R&D project that fails generally leaves behind few tangible assets of value. Second, the firm might be reluctant to reveal detailed information about the project that would make it attractive to outside lenders, fearing its disclosure to potential rivals.

**OptFolio Light (OL)**

The aforementioned complexity of OptFolio, both in terms of computational load and implementation difficulties, doesn’t boost the companies to entrust the optimal selection of their projects to a real option based method. Furthermore, financial interdependencies existing among the projects of a product portfolio have to be underlined. That’s why a new mixed-integer programming model, based on OptFolio, was developed to provide an affordable way to select the optimal R&D product portfolio from a set of candidate drugs in different phases of their development process (Enea and Lo Nigro, 2001a) and decide whether to reinvest part of their market incomes to fund further R&D activities (Enea and Lo Nigro, 2001a). The aim of this new model is to reduce the complexity of OptFolio in order to favour its use by the pharmaceutical companies, for example obtaining the chance of solving the optimization problem using a simple spreadsheet; this is why we called it OptFolio Light (OL).
OptFolio models the R&D process of each project as a series of continuation/abandonment decisions, where the choice whether to continue the development of a drug or not is made at the beginning of each phase. To estimate the value of a single project/drug, this method uses the quadrangular model, where the terminal nodes of a phase are called value scenarios. Thus, the overall value of the portfolio is given by the sum of the single drugs values. Particularly, the method uses binary variables \((y_{i,s})\) to model the presence of a drug \((i)\) in the portfolio in a particular phase \((s)\) and in a particular value scenario \((Ks)\). The single drug value has a recursive formulation: so starting from product lunch value, by backward induction, it is possible to obtain the drug value at \(s = 1\) (beginning phase development) and \(K_s=1\). This formulation, as the same authors say, involves a large number of binary variables and causes the objective function is not a linear function. So, in order to have a more tractable approach in a linear form, the authors have to solve a sub-problem with no budgetary restrictions (see in detail Rogers et al. 2002, pag 6616). This linearization procedure reduces the variables number but complicates the global problem resolution. Several constraints are present in the model, such budgetary constraints or others that are used to enforce the precedence between the different development phases of a drug and to prevent a drug which has been abandoned in an earlier stage to be selected. Using this approach, the mathematical model of the case study considered (the same presented in section 4), includes 893 binary variables and 12843 continuous variables. To reduce OptFolio complexity and create OpFfolio light some alterations are needed.

The first one is the way the R&D process is modelled: as above mentioned we opt for closed formulae instead of numerical approach, making easier the computations. Particularly, the Black & Scholes formula is used for candidate drugs which are about to complete their R&D processes and have only two development phases left, while the Geske formula is used for candidate drugs in earlier phases of their development. In fact, this situation represents a compound option, which is modelled through the Geske model. Lastly, if a drug has only one phase to pass through, generally the approval phase, neither Black and Scholes nor Geske formula are used, since this situation doesn’t represent an option but rather a common investment. Thus, the real options value of this type of drug is equal to its expected NPV.

OL also assumes that, if the development of a drug is interrupted in any phase, the drug will be dismissed from the optimal portfolio and that a drug could not be selected because of budgetary constraints. These two assumptions allow the new model to use a simpler binary variable, with only one subscript, \((y_i)\) where \(i\) is a generic candidate drug) to model whether a drug is selected to be part of the optimal portfolio, instead of the original OptFolio binary variable which has three subscripts \((y_{i,s,k}\) where \(s\) is a generic stage of drug development and \(k\) is a generic value scenario), simplifying its solving process. Additionally, a few assumptions are required in order to obtain a balanced portfolio (with self-financing). They include hypotheses on the annual cash flows distribution and on the commercial life of marketed drugs and are described in more detail in the following section.

Sets, parameters and variables

The starting point of the portfolio planning is the group of candidate drugs \(P\) which may be selected to be part of the optimal portfolio. At the beginning of the optimal portfolio selection, they can be in any stage of their development process. As in the OptFolio, the sets of OL are:

\[
\begin{align*}
i & = \text{product} \ (i = 1, 2, ..., P) \\
s & = \text{stage of drug development} \ (s = 1, 2, ..., S) \\
t & = \text{year of the portfolio planning horizon} \ (t = 0, 1, ..., T)
\end{align*}
\]

And, as OptFolio, for each candidate drug \(i\), portfolio selection decision made at the present time \((t = 0)\) classify the impending stage as \(s = 1\) regardless of where the candidate drug is in its development. Subsequent development stages are numbered in ascending order until termination at product launch.

The parameters of OL are:

\[
\begin{align*}
V_0 & = \text{current value of drug } i - \\
\sigma_s & = \text{estimated annual market volatility for drug } i \\
r & = \text{risk-free interest rate} \\
T_s & = \text{length in years of stage } s \text{ of drug development for drug } i \\
I_s & = \text{investment cost of developmental stage } s \text{ for drug } i \\
B_t & = \text{budgetary constraint for year } t \\
C_i & = \text{ - Value of drug } i \\
F_i & = \text{annual cash flow of drug } i
\end{align*}
\]
\( r \) = rate of return in the pharmaceutical industry
\( n \) = drugs commercial life
\( X_{i}^{R&D} \) = percentage of cash flows of drug \( i \) invested in R&D
\( F_i \) = amount of annual cash flow of drug \( i \) invested in R&D

The parameter \( V_{0i} \) represents the expected NPV - of drug \( i \), namely the sum of the discounted value of all cash flows that result from the drug commercialization. The market volatility \( \sigma_i \) is the standard deviation of \( V_{0i} \), which is usually estimated using historical sales data of similar products. The risk-free interest rate \( r \) corresponds generally to an observable market rate, such as US Treasury Bills. Every development stage \( s \) of each candidate drug could have different length \( T_s \) and investment cost to be carried out \( I_s \). The budgetary constraint \( B_t \) is the total amount of financial resources that a company can spend for its R&D projects in the year \( t \).

The drug value, \( C_i \), is calculated by different expressions (NPV/B&S/Geske), depending on the number of the stages left. As above mentioned, NPV is used for drugs which have only one stage to pass. Black & Scholes formula is used if a drug has only two development phase left and presents this expression:

\[
C_i = V_{0i} \cdot N(d_{1i}) - I_{i2} \cdot e^{-rT_{i1}} \cdot N(d_{2i})
\]

with:

\[
d_{1i} = \frac{\ln \left( \frac{V_{0i}}{I_{i2}} \right) - rT_{i1}}{\sigma_i \sqrt{T_{i1}}} + \frac{\sigma_i \sqrt{T_{i1}}}{2}
\]

\[
d_{2i} = d_{1i} - \sigma_i \sqrt{T_{i1}}
\]

and \( N \) is the cumulative normal distribution function.

On the other hand, Geske formula, not the Black and Scholes one, should be used when a drug has to pass through more than two phases before being commercialised. If the development phases left are only 3, traditional Geske formula can be used:

\[
C_i = V_{0i}N_2(a_{i1}, a_{i2}, \rho) - I_{i2}e^{-r(T_{i2}-t)}N_2(b_{i1}, b_{i2}; \rho) - I_{i2}e^{-r(T_{i1}-t)}N(b_{i2})
\]

with:

\[
b_{i1} = \frac{\ln \left( \frac{V_{0i}}{\tilde{V}_i} \right) + \left( r - \frac{1}{2} \sigma_i^2 \right)(T_{i1} - t)}{\sigma_i \sqrt{T_{i1}}} - \frac{\sigma_i \sqrt{T_{i1}}}{2}
\]

\[
b_{i2} = \frac{\ln \left( \frac{V_{0i}}{I_{i2}} \right) + \left( r - \frac{1}{2} \sigma_i^2 \right)(T_{i2} - t)}{\sigma_i \sqrt{T_{i2}}}
\]

\[
a_{i1} = b_{i1} + \sigma_i \sqrt{T_{i1} - t}
\]

\[
a_{i2} = b_{i2} + \sigma_i \sqrt{T_{i2} - t}
\]

\[
\rho = \frac{T_{i1} - t}{\sqrt{T_{i2} - t}}
\]

\( T_{i1} \) = time to maturity of the option \( C_i \)
\( T_{i2} \) = time to maturity of the underlying call option

With \( V_{i1}^{-} \) is the solution of \( C_i(V_{i1}, T_{i1}) - I_{i2} = 0 \) Where \( N_2 \) is the bi-variate cumulative normal distribution function with \( a_{i1} \) and \( a_{i2} \) as upper and lower limits and \( \rho \) as the correlation coefficient between the two variables.

With drugs which have more than three development stages left, the aforementioned extended Geske model, developed by Cassimon et al., is needed. However, in order to simplify the analysis, for example in a spreadsheet where an \( n \)-variety cumulative normal distribution is hard to implement, the traditional expression could be used. To do this, if a drug with four stages left is considered, \( s = 2 \) and \( s = 3 \) stages, for instance, could be merged, as the decision to undertake both of them is made at the beginning of the \( s = 2 \) stage. This allows the drug to appear as it has only 3 stages left instead of 4. The investment/exercise price of this new single stage can be calculated as:

\[
I_{i2,3} = I_{i2} + I_{i3}e^{-rT_{i2}}
\]
The same might be done for \( s = 3 \) and \( s = 4 \) or for more stages.

As mentioned before, further assumptions are needed to achieve a balanced R&D portfolio. The first one of them, which concerns the annual revenues distribution of a marketed product, assumes that, after its commercialization, a drug provides a company with uniform cash flows \( F_i \) for \( n \) years. The value of these annual incomes for drug \( i \) is:

\[
F_i = V_{oi} \left( \frac{(1 + r_{ph})^n}{(1 + r_{ph})^n - 1} \right) \tag{11}
\]

In this paper, the rate of return in the pharmaceutical industry \( r_{ph} \) has been assumed equal to 12\%, as suggested by DiMasi (2001). On the other hand, the life of a drug after its commercialization \( n \) has been considered equal to 10 years, since after this lapse of time a drug normally loses its patent protection, causing its annual incomes to fall dramatically. However, only a share \( X_{i}^{R&D} \) of the annual cash flow is potentially reinvested to fund the development of further drugs. Thus, the actual amount of financial resources \( F_i^* \), deriving from the commercialization of drug \( i \) and planned to be yearly invested in R&D, is:

\[
F_i^* = X_i^{R&D} V_{oi} \delta \tag{12}
\]

where

\[
\delta = \left( \frac{(1 + r_{ph})^n}{(1 + r_{ph})^n - 1} \right) \tag{13}
\]

In the new model there are two binary variables as well as a continuous one for each drug. The first variable \( y_i \) models its presence in the optimal portfolio and it is defined as:

\[
y_i = \begin{cases} 
1 & \text{if drug } i \text{ is selected for the optimal portfolio} \\
0 & \text{otherwise}
\end{cases}
\]

Using only one variable of this kind per drug allows a massive reduction in the overall variables number and has a great positive impact on computational load.

The second binary variable \( z_i \) models the decision whether to reinvest part of the cash flows of drug \( i \) or not, and it is defined as:

\[
z_i = \begin{cases} 
1 & \text{if part of the cash flows of drug } i \text{ is reinvested} \\
0 & \text{otherwise}
\end{cases}
\]

Finally, the continuous variable \( X_{i}^{R&D} \) represents the optimal cash flows share of drug \( i \) reinvested to fund the development of further drugs.

Constraints and objective function
OL does not need many OptFolio constraints because of its use of closed-form model instead of the binomial model. Thus, the only essential constraints group is the one related to budget limitations which is expressed as:

\[
\sum_{i,s} I_{is} y_i w_{ist} - \sum_i \omega_i F_i^* z_i \leq B_t \quad \forall t \tag{14}
\]

The first part of this constraints group refers to the overall R&D expenditures. The binary parameter \( w_{ist} \) appears in the OptFolio model as well and allows to include in budgetary constraints only those drugs beginning a stage of development in the period \( t \). The second part, on the other hand, includes the financial contributions brought to R&D by those commercialized drugs whose revenues have been partially allocated for this specific purpose. The binary parameter \( \omega_i \) allows the contribution of drug \( i \) in the period \( t \) to be considered only if the drug has been already introduced to market in that period.

Of course, a drug cannot fund further R&D activities if it has not been selected for the optimal portfolio. Thus, the following group of constraints is required:

\[
z_i \leq y_i \quad \forall i \tag{15}
\]

Finally a constraint on \( X_i^{R&D} \) that expresses a percentage variable:

\[
0 \leq X_i^{R&D} \leq 1 \tag{16}
\]
Complexity reduction is evident also in terms of constraints number which is considerably lower than the original OptFolio. By adopting the above formulation, we can solve the same case study proposed by Rogers et al. (2002), with only 40 binary variables and 20 continuous variables, instead of the 893 binary variables and 12843 continuous variables involved in OptFolio. It is also possible to insert further constraints groups regarding the consumption of limited resources (i.e. human resources) with little increase in computational load.

As in OptFolio, the objective function deals with maximization of the overall ROV of the product portfolio at \( t = 0 \), but it is calculated in a different way:

\[
max ROV = \sum_i (C_i - I_{t_i})y_i - \sum_{t, i} \frac{\omega_{it}F_i'z_i}{(1 + r_{ph})^t}
\]  

(17)

As well as the budgetary constraint, the objective function is divided in two parts, where the former deals with the selection of the candidate drugs to insert in the optimal portfolio while the latter concerns the decision to use part of the incomes of a selected drug to fund further R&D activities. Drug \( i \) could be selected to be part of the optimal portfolio if its real options value exceeds the investment required to start its current development stage. Furthermore, part of the incomes of drug \( i \) may be reinvested in order to allow other drugs to enter the optimal portfolio. In this case, the discounted cash flows used for this purpose must be subtracted. Unlike OptFolio objective function, this one is fairly easy to be implemented and solved in a spreadsheet which is the aim of OL.

However, our model has a limit deriving from a limit of B&S formula. In order to calculate the ROV we used B&S formula and Geske model, based on the B&S formula - that assumes Brownian Motion as distribution for the underlying. This particular motion implies a continuous arrival of information that changes the underlying value (Pennings & Lint, 1997), like information arises “every day” (Loch and Bode-Greul 2003). However, this does not fit a research environment, where information tends to arise at on discrete points in time, e.g. after a test or an experimental test has been evaluated (Loch and Bode-Greul 2003).

On the other hand, the main advantage of the Brownian Motion is that it is a Markov process. According to Dixit and Pindyck (1994), the Markov property is particularly important, because it “implies that the probability distribution for all future values of the process depend only on its current value, and is unaffected by past values of the processes or by any other current information” (Dixit and Pindyck, 1994).

**Model formulation**

The complete OL formulation is:

\[
max ROV = \sum_i (C_i - I_{t_i})y_i - \sum_{t, i} \frac{\omega_{it}F_i'z_i}{(1 + r_{ph})^t}
\]

subject to:

\[
\sum_{i, t} I_{t_i}y_iw_{ist} - \sum_{t, i} \omega_{it}F_i'z_i \leq B_t \quad \forall t
\]

\[
z_i \leq y_i \quad \forall i
\]

\[
0 \leq X_i^{R&D} \leq 1
\]

\[
y_i, z_i \in \{0, 1\}
\]

Therefore, the model provides a set of drugs constituting the optimal portfolio and a subset of them whose future incomes will be partially used to fund the development of other candidate drugs. The resulting portfolio is balanced as it contains both profitable products as well as supporting drugs which help the pipeline of a company to partially finance itself. The model gives back also the optimal market revenues share of this kind of drugs to reinvest.

The simplicity of OL allowed its implementation in a Microsoft Excel spreadsheet, the industry standard for business case models. Particularly, the model needs inputs regarding budget limitations as well as about candidate drugs, such as their expected current values, volatilities, technical success rates and investment costs of each stage, and types, which indicates what is the impending development stage of a drug at the time of portfolio selection.
Case study

In order to show how the model works and demonstrate its simplicity and effectiveness, a case study concerning a balanced optimal portfolio selection is provided. The starting product portfolio chosen to test the model comes from the paper by Rogers et al. (2002) where OptFolio has been introduced, and contains 20 candidate drugs in different stages of their development process. Given the finite level of resources available, it is not possible to take all of them into clinical development simultaneously, so, different distributions of budget constraints have been tested. The drugs characteristics are summarised in Table 1, while candidate drugs inputs are reported in Table 2. The model calculates options parameters and the evaluation method required. A comparison between the optimal portfolio ROV in case of presence and absence of self-financing, for different budget combinations, is shown in Table 3 (in brackets the corresponding optimal portfolio composition). It is evident that having the chance to reinvest part of drugs profits provides pharmaceutical companies with higher overall ROV.

Table 1. Description of the candidate drugs

<table>
<thead>
<tr>
<th>Candidate drugs</th>
<th>Type</th>
<th>Beginning phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2,3,4,5,6</td>
<td>1</td>
<td>Phase I</td>
</tr>
<tr>
<td>7,8,9,10,11</td>
<td>2</td>
<td>Phase II</td>
</tr>
<tr>
<td>12,13,14</td>
<td>3</td>
<td>Phase III</td>
</tr>
<tr>
<td>15 and 16</td>
<td>4</td>
<td>2nd year Phase III</td>
</tr>
<tr>
<td>17,18,19,20</td>
<td>5</td>
<td>FDA Approval</td>
</tr>
</tbody>
</table>

Table 2. Candidate drugs inputs

<table>
<thead>
<tr>
<th>P</th>
<th>$V_0$ [MS]</th>
<th>Type</th>
<th>$\sigma_i$</th>
<th>$I_{11}$ [MS]</th>
<th>$I_{12}$ [MS]</th>
<th>$I_{13}$ [MS]</th>
<th>$I_{14}$ [MS]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>1</td>
<td>80%</td>
<td>2</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>1</td>
<td>60%</td>
<td>5</td>
<td>15</td>
<td>50</td>
<td>170</td>
</tr>
<tr>
<td>5</td>
<td>600</td>
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<td>50%</td>
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<td>40</td>
<td>45</td>
<td>200</td>
</tr>
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<td>80</td>
<td>2</td>
<td>50%</td>
<td>10</td>
<td>25</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>2</td>
<td>70%</td>
<td>20</td>
<td>35</td>
<td>50</td>
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<tr>
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<td>20</td>
<td>55</td>
<td>80</td>
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<tr>
<td>10</td>
<td>380</td>
<td>2</td>
<td>35%</td>
<td>30</td>
<td>55</td>
<td>120</td>
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<tr>
<td>11</td>
<td>80</td>
<td>2</td>
<td>45%</td>
<td>10</td>
<td>25</td>
<td>30</td>
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</tr>
<tr>
<td>12</td>
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<td>3</td>
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<td></td>
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<tr>
<td>13</td>
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<td>30%</td>
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<td>14</td>
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<td>90</td>
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<td></td>
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<tr>
<td>15</td>
<td>500</td>
<td>4</td>
<td>35%</td>
<td>50</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>300</td>
<td>4</td>
<td>100%</td>
<td>80</td>
<td>150</td>
<td></td>
<td></td>
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<tr>
<td>17</td>
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<td>5</td>
<td>60%</td>
<td>180</td>
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</tr>
<tr>
<td>18</td>
<td>550</td>
<td>5</td>
<td>30%</td>
<td>220</td>
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<tr>
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<td>800</td>
<td>5</td>
<td>60%</td>
<td>250</td>
<td></td>
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<td></td>
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<tr>
<td>20</td>
<td>1150</td>
<td>5</td>
<td>20%</td>
<td>350</td>
<td></td>
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<tr>
<td>Phase</td>
<td>Length</td>
<td>$r_{ph}$</td>
<td>$\rho$</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>$n$</td>
<td>10</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>$r$</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>$\delta$</td>
<td>0.176984</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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</table>
Table 3. Comparison between the optimal portfolio ROVs [MS]

<table>
<thead>
<tr>
<th>Next year budget [MS]</th>
<th>1st year budget [MS]</th>
<th>Self financing (SF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400.00</td>
<td>500.00</td>
</tr>
<tr>
<td>100.00</td>
<td>1,494.28</td>
<td>(P2, P5, P15, P20)</td>
</tr>
<tr>
<td>SF</td>
<td>1,494.28</td>
<td>(P5, P7, P14, P15, P20)</td>
</tr>
<tr>
<td>no SF</td>
<td>1,389.15</td>
<td>(P3, P10, P15, P20)</td>
</tr>
<tr>
<td>200.00</td>
<td>2,118.40</td>
<td>(P5, P10, P14, P15, P16, P19)</td>
</tr>
<tr>
<td>SF</td>
<td>1,368.40</td>
<td>(P2, P5, P10, P14, P15, P16, P19)</td>
</tr>
<tr>
<td>no SF</td>
<td>1,368.40</td>
<td>(P2, P5, P10, P14, P15, P16, P19)</td>
</tr>
<tr>
<td>300.00</td>
<td>2,173.66</td>
<td>(P3, P5, P10, P14, P15, P16, P19)</td>
</tr>
<tr>
<td>SF</td>
<td>1,923.66</td>
<td>(P3, P5, P10, P14, P15, P16, P19)</td>
</tr>
<tr>
<td>no SF</td>
<td>1,923.66</td>
<td>(P3, P5, P10, P14, P15, P16, P19)</td>
</tr>
</tbody>
</table>

In particular, referring to the first case (a budget of 400 MS for the first year and of 100 MS for the others) the selected drugs have been P2, P5, P7, P15 and P20, with an overall ROV of M$ 1,494.28, while 83.34% of the future incomes of drug P15 will be used to partially fund subsequent R&D activities. It is indeed worth noting that if this problem had been solved with the same budget constraints but without any self-financing chances, it would have led to a lower overall ROV, equal to M$ 1,401.34. In fact, just the reinvested market revenues of drug P15 would allow, for example, the development of the profitable drug P5, and leading to higher portfolio ROV.

Conclusions

This paper focuses on application of real options methods to evaluate pharmaceutical R&D projects, presenting the state of the art regarding models and techniques which suit this particular aim. We propose an optimization method based on a method already available in literature, OptFolio model by Rogers et al. (2002); it is able to solve all the problems OptFolio can address giving some additional features like the self financing possibility. Particularly, this article proposes a mixed-integer model able to select among the products available the optimal portfolio and the self financing strategy that suggests to the company to use part of the future financial incomes of its commercialized drugs to fund the development of other products. The model proposed is able to select a balanced R&D portfolio in the pharmaceutical industry: the model has been implemented and tested with a case study, based on the selection of an optimal drugs portfolio among twenty products. Since only data entry and a click of a button are required to launch this model, it might be helpful to many pharmaceutical companies as a support for their strategic decisions and then the study has managerial implications; in the meanwhile it wants to contribute to the literature with a new theoretical approach in modelling the R&D process through ROA. Our main goal is to foster managers in adopting ROA models, to evaluate their projects portfolios. To achieve this, we suggest to use closed formulæ instead of, for example, numerical approach, such as binomial lattice, which is inferior to closed-form models (Chance, 1998). Literature offers, to the best of our knowledge, two approaches able to address, with minor adjustments, the issues OL treated with, preserving simplicity. The first approach is based on simulation, like the Datar-Mathews method (Mathews and Datar, 2007) the second one is based on Real Options fuzzy evaluation methods (Collan et al., 2009). These methods, even if they overcome the rigidity of some assumptions of Black and Scholes formula that we have adopted in the OL, are based on some subjective hypotheses: in particular the Datar-Mathews model results, like the simulation-based method, depends on the number of iterations while the fuzzy-based methods (Hassanzadeh et al., 2012; Wang and Hwang, 2007) encounter limitations typical of fuzzy method like the subjectivity in defining input variables distribution and also constraints degree of satisfaction.

Further developments can follow three distinct directions: the first two refer to the field of application, indeed the model can be fitted, with minor revisions, to other industries and within biopharmaceutical industry the model would be useful to evaluate open innovation opportunities. In particular, it could be possible to use it to evaluate
licensing deals and alliances between pharmaceutical and biotechnology companies, as already done by Rogers et al. with the OptFolio model (Rogers et al., 2005). The third direction aims at overcoming the assumption of Brownian motion for the underlying. In order to overcome the limitations of the Brownian motion, different authors propose jump-process models both for Black and Sholes formula (Brach and Paxson, 2001) and Geske model (Pennings and Sereno, 2011). In fact, this particular motion implies a continuous arrival of information that changes the underlying variable. Actually, information that affects future net cash flows of research projects arrives at discrete points in time, causing that managers not continuously adjust the underlying, but only when information arrives. A Poisson (jump) process would be able to describe these movements in the underlying variable in a more realistic way (Pennings and Lint, 1997).

Acknowledgments—The authors are very gratefully to the anonymous referees whose suggestions greatly contributed to improve the paper.

References


