A real options based model to select a balanced R&D portfolio

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Abstract

The R&D process in the pharmaceutical industry has a long and dynamic life then it is an ideal field of application for ROA. Actually, ROA implementation, as widely demonstrated in literature, is narrowed to very limited cases because its perceived complexity.
This research wants to suggest a simplified method, respect the ones available in literature, that could foster the use of ROA: we built up an integer linear programming model, based on a model available in literature, useful for selecting a balanced R&D portfolio from a set of candidate drugs. The model has been tested through a case study.

Keywords: Real Options Analysis; Pharmaceutical Industry; R&D portfolio

1. Introduction

Drugs have great social relevance, since their use has a considerable influence on people's quality of life, wellness, diseases progress and recovery chances. For these reasons, pharmaceutical companies have always focused their attention on innovation, in order to find a cure to the illnesses which still do not have satisfactory treatments and to improve already existing drugs. However, there are other reasons pushing pharmaceutical firms into making large efforts on Research and Development (R&D). In fact, developing a new drug allows pharmaceutical companies to ask regulatory agencies, like FDA (Food & Drugs Administration) in the US, for a patent which protects the innovative drug incomes, preventing other companies from using the same chemical structure. Therefore, pharmaceutical firms struggle to discover and develop promising compounds before competitors do. This allows them to beat competitors in the winner-takes-all patent race and, once the drug is introduced in the market, to gain great revenues useful also to fund other R&D projects. This is particularly true if the drug eventually becomes a blockbuster, namely a successfully drug whose annual revenues exceeds one billion dollars.
Thus, due to its focus on innovation, R&D process is extremely important in pharmaceutical industry, as it allows a company to achieve high profits and growth rates. 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% (see Fig. 1) [1].

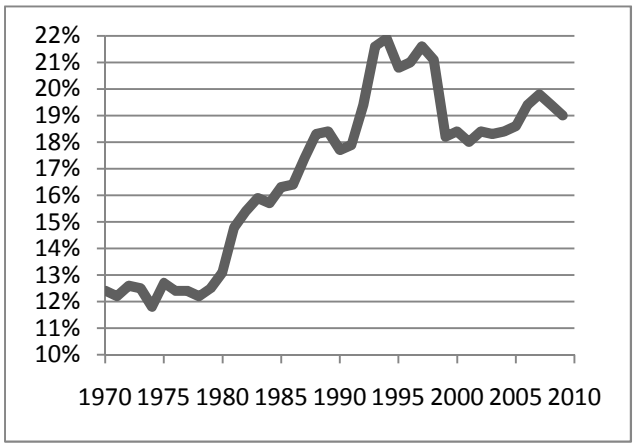

Fig. 1. R&D as a percent of US sales for pharmaceutical companies (1970-2009) (source: PhRMA)

In 2009, pharmaceutical companies invested US$ 65,3 billion in R&D, 37% more than 5 years before [2].
Since the above mentioned importance of R&D for pharmaceutical companies, 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 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. Therefore, these models could underrate some projects, especially those that are riskier and set in a dynamic environment, eventually leading to reject some profitable opportunities. Thus, alternative tools, able to adapt to the features of pharmaceutical R&D projects, are required, in order to correctly assess their value. This article deals with real options based methods used to evaluate pharmaceutical R&D projects. Indeed, they 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. As a result, real options methods are able to quantify this added value in a more accurate way than the traditional ones.
Section 2 describes the R&D process of a new drug, pointing out the risks inherent in it, while Section 3 shows the methods to evaluate pharmaceutical R&D projects, comparing the traditional ones with those based on real options and presenting the most used applications of them. Literature review is reported in Section 4. The proposed model is introduced in section 5: it is a mixed-integer linear programming model useful for selecting a balanced optimal product portfolio from a set of candidate drugs at different stages in their R&D process. This model results from the adjustment of a pre-existing model to which some simplifications, useful for favouring its spread among the companies, and some modifications, useful for achieving balance in the portfolio selection, have been introduced. As a result, this model is quiet easy to implement in a spreadsheet for computing its solution, as shown in Section 6, where it is applied to solve an actual pharmaceutical portfolio selection case study. In the same section, a sensitivity analysis is also shown, which was carried out to study the variation of portfolio value and composition caused by changes in budget limitations of a company. Finally, in section 7 some conclusions are drawn and some suggestions for possible further studies are proposed.

2. Pharmaceutical R&D: new drug development

According to recent analysis [3], 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. That's why the pharmaceutical R&D process, whose length swings between 10 and 15 years, can be fairly modelled as shown in figure 2.

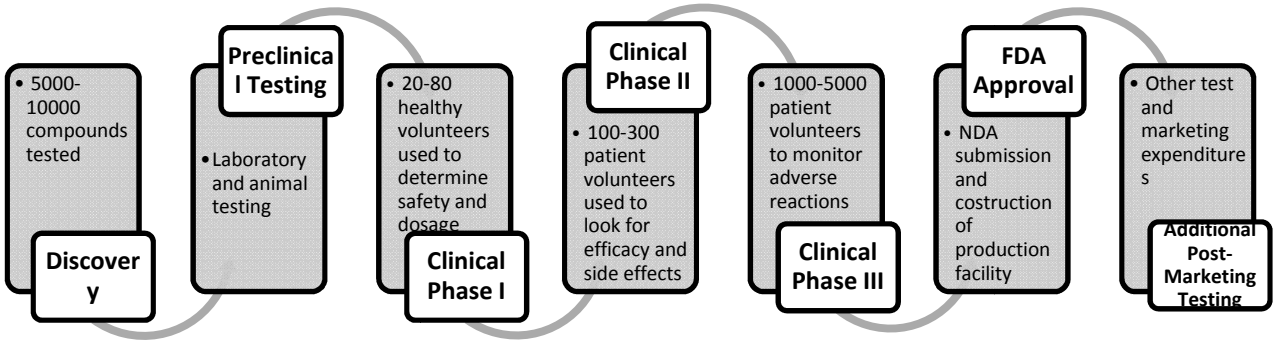

Fig. 2. Pharmaceutical R&D process

The development of a new drug starts with a complex and highly expensive research of potential candidates compounds, in which more than 10,000 chemical compounds are tested in order to find some of them able to affect the under analysis disease. About 250 of the starting molecules enter the following phase, called *pre-clinical phase*, during which the survived compounds are tested on laboratory animal in order to investigate the presence of possible side effects. If this happens and risks for humans are detected, the R&D process of the drug will be interrupted. Conversely, a company may ask regulatory agencies such as FDA for approval, in order to begin the subsequent phase named *clinical phase*, in which the tests are carried out on human beings. On average, out of the 250 chemical compounds that entered the pre-clinical phase, only 5 are able to continue to the following one. Clinical studies are divided in three sub-phases. In the first one, *phase I*, 20-30 healthy volunteers, treated with different doses of the examining drug, are used to determine safety and dosage of the medicine. In the next one, *phase II*, the tests are carried out on 100-300 patient volunteers who are plagued by the targeted sickness, in order to look for efficacy and side effects. This is usually done by comparing the effect of the molecule on the volunteers with the one stem from the use of a placebo. Finally, in *phase III*, 1,000-5,000 sick patient volunteers, unaware of the basic information about the experiment, are used to test the effectiveness of the new drug, in order to demonstrate that it works better than the already existing treatments. If clinical tests are successfully completed, a company will send the FDA an approval request for a New Drug Application (NDA), submitting all the data obtained during the clinical testing. On average, only one of the five chemical compounds, which underwent clinical tests, is approved by regulatory agencies. Once obtained the approval, a pharmaceutical company has the right to sell the drug under the aforementioned patent protection. In this terminal phase, named *commercialisation phase* (or *phase IV)*, further clinical tests are usually performed in order to detect possible side effects which could manifest themselves only when the drug is widely spread. The entire R&D process commonly takes until 15 years to be completed and it costs around US$ 15 million. Furthermore, expenditures per approved drug are magnified by the development costs of those drugs which failed to be marketed or whose revenues didn't match their own R&D costs.

2.1 Risk components

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*. [4] *Economic risk* deals with factors which increase market uncertainty, like interest rates, inflation and changes in industry prices. This kind of risk is systematic because a company can't affect it. In the pharmaceutical industry, economic risk manifests itself in the volatility of the drugs future values which may be caused either by a market reduction or by the commercialisation of a rival product. On the other hand, *technical risk* stems from the lack of certainty about the process success. Researchers cannot guarantee in advance for safe and effective drugs, able to successfully complete all clinical tests and gain the FDA approval as well. As a matter of fact, side effects or drug ineffectiveness might manifest themselves in any phase of the process, leading to early end of the development process. *Technical risk* deals with factors related to the projects such as approval probability and uncertainty in development costs, and it's thereby referred to as unsystematic.

3. Pharmaceutical R&D project evaluation

The evaluation of investment projects is generally done by using discounted cash flow based methods such as *net present value*. However, in the field of R&D projects, where high uncertainty and risks are prominent, these methods lose a large amount of their effectiveness. In fact, as said before, they fail to correctly assess the real value of these projects which results, among other things, from the flexibility possessed by the management and from the several opportunities these kinds of investments offer. Using traditional methods like NPV to evaluate R&D projects might lead to two different kinds of errors. The first one concerns the assumption of static cash flows. This hypothesis ignores the flexibility available to management such as the chance to interrupt a project in order to avoid losses, for example in case of failures in drug testing (technical risk) or negative market variations (economic risk). The second one, which is perhaps the biggest source of inaccurate R&D project evaluation, is the assumption that risk always reduces the projects value. Actually, the higher the volatility of the project cash flows is, which is directly connected to project riskiness, the higher the likelihood of large future incomes is. This is particularly true in pharmaceutical R&D projects, in which the staged process allows the management to move a drug development project into the next stage of its process 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 pharmaceutical industry, forces the companies to use more 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 pharmaceutical R&D projects through *real options* based methods has gained growing attention. As a matter of fact, real options methods are able to model the uncertainty and the flexibility embedded in the R&D process and to consider the value of future opportunities.
Real options are options whose underlying asset is a capital investment and not a financial instrument. Thus, a real option gives the right, but not the obligation, to undertake a business decision, which generally is the chance to make, abandon, expand, or contract a capital investment. The *real options analysis* (ROA) applies the financial options evaluation techniques, like Black & Scholes formula or binomial method, to capital budgeting decisions [5]. This real options based method, unlike the traditional ones, allows modelling the particular features of pharmaceutical R&D projects as uncertainty and flexibility and that is why it suits better than cash flow based methods to evaluate this kind of projects. The basic idea of ROA is

to consider the opportunities embedded in a project, or the whole project itself, as real options whose value is estimated and subsequently added to the project's basic NPV. As said before, financial options models are used to evaluate a project modelled as a real option and usually require six input variables which are *underlying value*, *exercise price*, *volatility*, *time to maturity* and *riskless interest rate*. These input variables have a real counterparts in actual capital investments, as shown in Table 1, and have to be estimated before valuing a real option.

Variable	Financial option	Real option
S	Underlying asset value	Present value of project expected incomes
X	Exercise price	Present value of project investment cost
T	Time to maturity	Length of time in which the investment opportunity exists
σ	Volatility of returns on stock	Volatility of project cash flows
r	Riskless interest rate	Riskless interest rate

Table 1. Input variables used in financial options and real options evaluation

The first step to take for the evaluation of a capital investment through ROA consists of detecting which kind of real option is inherent in the project itself. There are five main different kinds of real options which may be embedded in a project, namely: the growth *option*, the option to *abandon* an investment project, the option to *defer* an investment project, the option to *contract*, *expand* or *temporarily shut down* an investment, the option to *switch* input or output. Abandon options and growth options are generally used to model the pharmaceutical R&D projects. Abandon options are used to model the chance owned by the managers to interrupt the development of a drug in any stage of its R&D process, if they consider it no longer profitable. The growth options approach, on the other hand, considers a new stage of the R&D process as an option which will be exercised if its expected outcomes are satisfying. Growth options are also used to model the opportunity of a future new molecule development using the knowledge deriving from the current project.

4. Literature review

Real options researches support pharmaceutical R&D process basically through two different approaches: the first one aims at evaluating a single R&D project, while the second focuses on the entire R&D portfolio. In the following sub-sections, a literature review, which shows the most notable applications of these approaches, is provided.

4.1 Single options evaluation

As above mentioned, the first approach identifies the single real options embedded in a project and considers them as they were independent of each other. In literature, it is dealt with fundamentally in two ways: the first one is the simplest one since it allows evaluating the options one by one, using standard models as the Black & Scholes formula or the binomial method, while the second one models the entire project as a compound option. As Bowman and Moskowitz pointed out [6], 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. The input variables identified by Merck in this process were the ones that will be used afterwards in almost all the following pharmaceutical R&D project evaluations. For the underlying asset value, Merck took the expected present value of the cash flows deriving from the commercialization of the drug. The exercise price was the cost of building the plant and its associated start-up costs. The time to expiration was based on the expected time to develop the product while the volatility was based on the annual average standard deviation of returns for pharmaceutical industry. With this approach, an investment is favourable if the theoretical value of the growth option exceeds the sum of the cost of the new technology plus the present value of the R&D costs. A different approach to model a pharmaceutical R&D project, as shown by Ollila in the Orion Pharma case [7] and Kellog and Charnes in the Agouron's Viracept case [8], is to consider the chance owned by the management to abandon the project in any stage of its development process. Obviously, the real option embedded in the project is the abandon option, which is generally considered as an American put option. A closed-form model, such as the Black & Scholes formula, cannot be used to calculate the value of this type of option, so it's necessary to use a numerical method like the binomial one. The same input variables of the Merck case may be used also in this abandon option approach, with the exception of the exercise price which in this case is the R&D cost that the company pays to continue the development process of a drug. Kellog and Charnes provided also an empirical proof about the advantage of using ROA instead of traditional methods as NPV. They compared the actual Agouron's market value in certain periods, with its theoretical value calculated both with ROA and NPV, proving that the ROA value was closer to the real value of the stocks than the NPV value. As said before, there is another way to model and evaluate a pharmaceutical R&D project using ROA, which is through the compound options. To evaluate this kind of options, and thus the projects modelled with them, it is possible to use either *ad hoc* methods as Geske model or numerical methods as the binomial model. Perlitz et al. [9] displayed how to apply the Geske model to fulfil this purpose, providing a case study application. The model requires the R&D process, which is typically divided into 5 phases, to be split into two main parts, where the first one concerns the three phases of clinical tests while the second one regards the commercialization phase. Each of them can be assimilated to single growth options, with their own exercise prices and time to maturity, which altogether form a compound option where the latter serves as underlying asset of the first one. Once the input variables of both options have been estimated, the value of the compound option can be assessed analytically using the Geske formula, which is based on the Black & Scholes formula and has therefore a closed-form expression as well. Although this approach makes easier the project value assessment, it has a rather big limitation in its way of modelling the R&D process since it can be divided in only two parts, causing a decreased granularity of analysis. Cassimon et al. [10] overcame this issue introducing a generalisation of the Geske model which provides a closed-form formula able to calculate the value of a *n*-fold compound option (traditional Geske model can estimate only the value of a 2-fold compound option). They applied this extended Geske model to the evaluation of a NDA, modelling the R&D process as a series of 6 growth options, each of them related to a particular phase of the process. Therefore, the resulting compound option was a 6-fold compound option. Finally, Sereno [11] 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.

4.2 Optimal portfolio selection

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. These interdependences, ignored if projects are evaluated one by one, usually deal with limited resources consumption, risk balancing and company strategies.

. The second approach, which is slightly more complex but also more realistic, considers the pharmaceutical R&D process as a set of subsequent options dependent of each other. This group of options is called *compound option* whose value is estimated through non-standard method as Geske model. A great contribution in this field to scientific literature was brought by Roger et al. [12] who developed a stochastic optimization model, called OptFolio, able to identify the most valuable projects among the entire R&D project portfolio of a company. The aim of this method is to determine the optimal drug developmental portfolio that maximizes real options value (ROV) , overall value of the portfolio, given a set of candidate drugs in various stages of development, estimates of the probability of clinical success, duration, investment required for the remaining stages and forecasts for the future market. This method 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 as a Bermuda option[1]. To estimate the value of a single project/drug, this method uses the binomial 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. OptFolio uses binary variables to model the presence of a drug in the portfolio in a particular phase and in a particular *value scenario*, while the objective function aims at maximizing the portfolio overall value. The model selects which drugs have to be included in the portfolio basing on their expected current values, their development costs and their technical and commercial success probabilities. Since companies usually have limitations to their R&D expenditures, OptFolio has constraints which limit the annual R&D efforts preventing them to exceed a given budget value. Other constraints 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. The resulting model formulation has a recursive objective function and eight constraints groups. Despite being particularly close to reality, 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. This is confirmed by the results of a survey conducted by Hartmann and Hassan [13] among the most important pharmaceutical firms in 2005 in order to investigate the methods used by companies in the evaluation of their R&D projects. The survey clearly confirmed the assumed dominance of NPV-based valuation approaches as, on average, only 20% of the pharmaceutical companies use ROA to evaluate their projects. Furthermore, the major reason of this lacking of use appeared to be the perceived complexity of this method, since about 30% of the sample companies answered that real options are considered too complex. A step toward simplifying this issue was made by Wang et al. [14], who developed a fuzzy compound option model to estimate the value of each R&D project in a pharmaceutical company pipeline. Particularly, they formulated the R&D portfolio selection problem as a fuzzy zero-one integer programming model. Limited resources generally deal with the amount of a company's financial assets assigned to its R&D projects. Therefore, they are usually shared by them, meaning that only few projects may be carried out but also that part of the financial outcomes resulting from the successfully commercialized drugs could be used to fund the development of new drugs. According to Kamien et al. [15], the urgency of self-financing R&D for a company has two reasons. First, the

[1] A type of option that can only be exercised on predetermined dates.

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. Furthermore, Brighi et al. [16] remarked that the highest risk related to R&D projects leads to more difficulties to find external financial funds, implying some forms of financial constraints. However, self-financing may appear as a signaling mechanism, correcting such a market imperfection.

5. The proposed model: Optfolio Light

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. This could mean both that selecting a drug to be developed may deduct financial resources from the development of other drugs as well as it may provide funds to feed the development of new products. In fact, if a drug manages to be commercialized and to achieve satisfactory economic results, a company might use part of its incomes to finance other R&D projects. This is, as a matter of fact, one of the prominent features of blockbuster drugs. These considerations underline the importance for a pharmaceutical company to select a balanced R&D portfolio, composed both of profitable drugs ensuring high revenues and successful drugs able to provide profits as well as to finance new drugs development. That's why a new mixed-integer linear 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 [17] and decide whether to reinvest part of their market incomes to fund further R&D activities. 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 Opfolio Light (OL).

5.1 Assumptions

To reduce OptFolio complexity and create the new model some alterations are needed. The first one is the way the R&D process is modelled, since, instead of being considered as an abandonment option, it is considered either as a growth option, or as a series of growth options, depending on how many development phases a candidate drug has to pass through (two in the first case, more than two in the second case). This modification allows assessing the value of a candidate drug using a closed-form formula instead of the binomial method, making easier the calculations. 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. 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. Moreover, the new model assumes that if the development of a drug is interrupted in any phase, the drug will be dismissed from the optimal portfolio. 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_{isk} where s is a generic stage of drug development and k is a generic value scenario), simplifying

its solving process. This is why it is not necessary anymore to account for the possible presence of a drug in the optimal portfolio in a certain phase rather than another one, or in a certain *value scenario*. Additionally, a few assumptions are required in order to obtain a balanced portfolio. They include hypothesis on the annual cash flows distribution and on the commercial life of marketed drugs and are described in more detail in the following section.

5.2 Mathematical Problem Formulation of Optfolio Light

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:

i = product (i = 1, 2, ..., P)
s = stage of drug development (s = 1, 2, ..., S)
t = year of the portfolio planning horizon (t = 0, 1, ..., T)
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:

V_{0i} = current value of drug i at t = 0
σ_i = estimated annual market volatility for drug i
r = risk-free interest rate
T_{is} = length in years of stage s of drug development for drug i
I_{is} = investment cost of developmental stage s for drug i
Φ_{is} = probability of technical success in stage s of development for drug i
B_t = budgetary constraint for year t
C_i = Real options value of drug i
F_i = annual cash flow of drug i
r_{ph} = 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 at t = 0 of drug i, namely the sum of the discounted value of all cash flows that result from the drug commercialization. The market volatility σ_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_{is}, investment cost to be carried out I_{is} and probability of technical success Φ_{is}. 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 real options value C_i is the value of drug i which takes account of the abandonment option embedded in the project itself and, as said before, may be calculated by two different expressions. Black & Scholes formula must be used if a drug has only two development phase left and presents this expression:

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

with:

$$d_{1i} = \frac{ln\frac{V_{0i}}{I_{i2}e^{-rT_{i1}}}}{\sigma_i\sqrt{T_{i1}}} + \frac{\sigma_i\sqrt{T_{i1}}}{2} \quad (2)$$

$$d_{2i} = d_{1i} - \sigma_i\sqrt{T_{i1}} \quad (3)$$

and N is the cumulative normal distribution function.

On the other hand, Geske formula must 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:

$$C_i = V_{0i}N_2(a_{1i}, a_{2i}; \rho_i) - I_{i3}e^{-r(T_{i2}-t)}N_2(b_{1i}, b_{2i}; \rho_i) - I_{i2}e^{-r(T_{i1}-t)}N \quad (4)$$

with:

$$b_{1i} = \frac{\ln(V_{0i}/\bar{V}_i) + \left(r - \frac{1}{2}{\sigma_i}^2\right)(T_{i1} - t)}{\sigma_i\sqrt{(T_{i1} - t)}} \quad (5)$$

$$b_{2i} = \frac{\ln(V_{0i}/I_{i3}) + \left(r - \frac{1}{2}{\sigma_i}^2\right)(T_{i2} - t)}{\sigma_i\sqrt{(T_{i2} - t)}} \quad (6)$$

$$a_{1i} = b_{1i} + \sigma_i\sqrt{(T_{i1} - t)} \quad (7)$$

$$a_{2i} = b_{2i} + \sigma_i\sqrt{(T_{i2} - t)} \quad (8)$$

$$\rho_i = \sqrt{\frac{T_{i1} - t}{T_{i2} - t}} \quad (9)$$

with $\bar{V}$ is the solution of $C_1(V, t_1) - K_1 = 0$

Where N_1 is the cumulative normal distribution function, while N_2 is the bivariate cumulative normal distribution function with a_1 and a_2 as upper limits and ρ 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 a *n*-variate cumulative normal distribution is hard to implement, the traditional expression could be used. To do this, 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:

$$I_{i2,3} = I_{i2} + I_{i3}e^{-rT_{i2}} \tag{10}$$

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:

$$F_i = V_{0i}\frac{(1+r_{ph})^n r_{ph}}{(1+r_{ph})^n - 1} \tag{11}$$

In this paper, the rate of return in the pharmaceutical industry r_{ph} has been assumed equal to 12%, as suggested by DiMasi et al. [18]. 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 annual cash flows 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:

$$F_i' = X_i^{R\&D} V_{0i}\delta \tag{12}$$

where

$$\delta = \frac{(1+r_{ph})^n r_{ph}}{(1+r_{ph})^n - 1} \tag{13}$$

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:

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

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:

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

Finally, the continuous variable $X^{R\&D}{}_i$ 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:

$$\sum_{i,s} I_{is}\phi_{i,s-1}y_i w_{ist} - \sum_i \omega_{it} X_i^{R\&D} V_{oi}\delta z_i \leq B_t \qquad \forall t \tag{14}$$

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 technical success rate $\Phi_{i,s-1}$ is included in order to consider the expected cost of each selected drug for the period *t*, and not the actual one. 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 ω_{it} allows the contribution of drug *i* in the period *t* to be considered only if the drug has been already introduced to the 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:

$$z_i \leq y_i \qquad \forall i \tag{15}$$

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. 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:

$$max\, ROV = \sum_i (C_i - I_{i1})y_i - \sum_{i,t} \frac{\omega_{it} X_i^{R\&D} V_{oi}\delta z_i}{\left(1 + r_{ph}\right)^t} \tag{17}$$

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.

Model formulation

The complete OL formulation is:

$$\max ROV = \sum_i (C_i - I_{i1}) y_i - \sum_{i,t} \frac{\omega_{it} X_i^{R\&D} V_{oi} \delta z_i}{\left(1 + r_{ph}\right)^t}$$

subject to

$$\sum_{i,s} I_{is} \phi_{i,s-1} y_i w_{ist} - \sum_i \omega_{it} X_i^{R\&D} V_{oi} \delta z_i \leq B_t \qquad \forall t$$

$$z_i \leq y_i \qquad \forall i$$

$$0 \leq X_i^{R\&D} \leq 1$$

$$y_i \in \{0,1\}$$

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.

5.3 Spreadsheet implementation

The simplicity of OL allowed its implementation in a Microsoft Excel spreadsheet. Any company interested in evaluating and selecting its pharmaceutical R&D projects could create its own optimal products portfolio simply entering drugs information and clicking a button. 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. Thus, the spreadsheet identifies whether Black & Scholes formula, Geske formula or none of them is needed for a certain drug and calculates the options parameters (as exercise prices, d_1 and d_2 for Black & Scholes formula, a_1, a_2, b_1 and b_2 for Geske formula) useful for estimating its real options value C_i. At last, it is sufficient to click on a macro button which launches the Excel solver, finding the balanced optimal portfolio composition. Fig.3 summarizes the described steps.

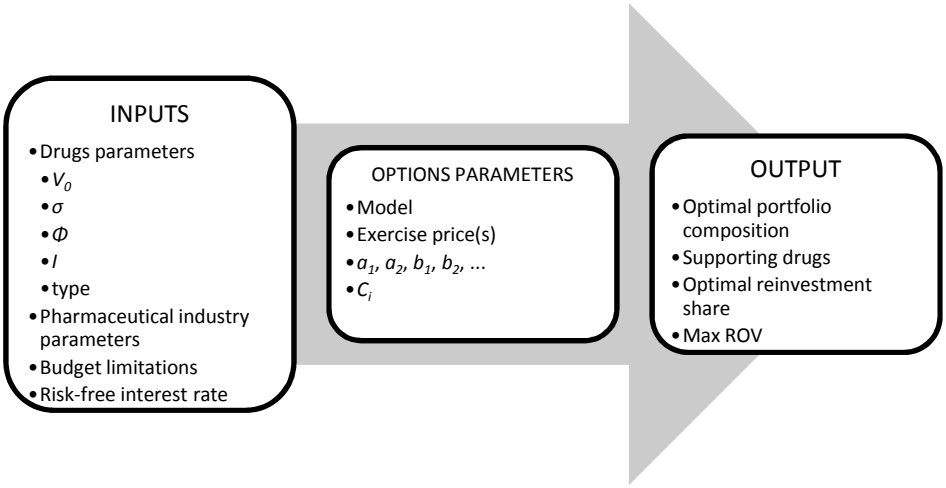

Fig. 3. Optimal portfolio selection process using the new model spreadsheet

6. 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. [12] 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 2.

Candidate drugs	Type	Beginning phase
1	1	Phase I
2	1	Phase I
3	1	Phase I
4	1	Phase I
5	1	Phase I
6	1	Phase I
7	2	Phase II
8	2	Phase II
9	2	Phase II
10	2	Phase II
11	2	Phase II
12	3	Phase III
13	3	Phase III
14	3	Phase III
15	4	2nd year Phase III
16	4	2nd year Phase III
17	5	FDA Approval
18	5	FDA Approval
19	5	FDA Approval
20	5	FDA Approval

Table 2. Description of the candidate drugs

The length of phase I and II have been assumed equal to 1 year, while the length of phase III and approval equal to 2 years, with an overall 6 years length R&D process. Budget limitation have been initially considered as M$ 400 for the first year and M$ 100 for the remaining ones, with a planning horizon of 5 years. Finally, the risk-free interest rate has been set at 3.41% which corresponds to a December 2010 5-years US treasury bond[2]. The screenshot of the model implemented in Excel, shown in fig. 4, summarizes the overall candidate drugs inputs.

Candidate drugs parameters											
P	V0 [M$]	Type	σ	ϕ1	ϕ2	ϕ3	ϕ4	I1 [M$]	I2 [M$]	I3 [M$]	I4 [M$]
1	50	1	80%	0.6	0.7	0.8	0.95	2	10	20	30
2	100	1	70%	0.65	0.55	0.75	0.9	3	10	40	45
3	200	1	50%	0.7	0.8	0.9	0.9	10	15	60	100
4	200	1	60%	0.5	0.7	0.8	0.9	5	15	50	170
5	600	1	50%	0.6	0.6	0.7	0.9	20	40	45	200
6	100	1	20%	0.85	0.9	0.9	0.95	15	15	25	45
7	80	2	50%	0.6	0.8	0.95		10	25	30	
8	100	2	70%	0.6	0.8	0.95		20	35	50	
9	180	2	55%	0.75	0.7	0.85		20	55	80	
10	380	2	35%	0.6	0.8	0.95		30	55	120	
11	80	2	45%	0.6	0.8	0.95		10	25	30	
12	100	3	80%	0.8	0.9			30	60		
13	400	3	30%	0.8	0.9			75	180		
14	700	3	40%	0.6	0.85			90	280		
15	500	4	35%	0.8	0.95			50	100		
16	300	4	100%	0.7	0.9			80	150		
17	350	5	60%	0.75				180			
18	550	5	30%	0.9				220			
19	800	5	60%	0.7				250			
20	1150	5	20%	0.9				350			

Phase	Lenght	Budget	0	1	2	3	4
1	1	[M$]	400	100	100	100	100
2	1	rph	12%				
3	2	n	10				
4	2	δ	0.176984				

Fig 4. Screenshot showing the candidate drugs inputs

The screenshots depicted in figures 5 and 6 show the automatically assessed options parameters. The model recognizes which method is needed to evaluate a drug and calculates the parameters useful for this purpose as well as the final drug value.

[2] Source: www.bloomberg.com (January 2011)

Options parameters					Eval.
V	K2	K3	t1	t2	Method
50	29.3295	30	1	4	Geske
100	48.659	45	1	4	Geske
200	72.9885	100	1	4	Geske
200	63.3237	170	1	4	Geske
600	83.4914	200	1	4	Geske
100	39.1619	45	1	4	Geske
80	25	30	1	3	Geske
100	35	50	1	3	Geske
180	55	80	1	3	Geske
380	55	120	1	3	Geske
80	25	30	1	3	Geske
100	60	/	2	/	BS
400	180	/	2	/	BS
700	280	/	2	/	BS
500	100	/	1	/	BS
300	150	/	1	/	BS
350	/	/	/	/	/
550	/	/	/	/	/
800	/	/	/	/	/
1150	/	/	/	/	/

Fig. 5. Screenshot showing options parameters and evaluation method required

Geske									Vlim	M1	M2	N	C	Black & Scholes			No option
ρ	b1	b2	a1	a2	d1	d2	C(V,t1)-K2							d1	d2	C	C
0.5	-0.25512	-0.39548	0.54488	1.204516	1.076269	-0.30937	0	Vlim 1	46.07264	0.664968	0.214246	0.399315	16.32149				
0.5	0.059645	-0.03221	0.759645	1.367791	1.140808	-0.07163	0	Vlim 2	77.67384	(9222	0.338237	0.523781	36.01003				
0.5	0.446011	0.329547	0.946011	1.329547	0.989049	0.123023	0	Vlim 3	146.1176	0.779908	0.496368	0.672206	65.25542				
0.5	0.160765	-0.3509	0.760765	0.849099	0.541228	-0.498	0	Vlim 4	156.9549	0.672251	0.280092	0.563861	58.39708				
0.5	1.886563	0.735012	2.386563	1.735012	0.625537	-0.24049	0	Vlim 5	213.3103	0.952965	0.759207	0.97039	360.9954				
0.5	1.211724	2.137269	1.411724	2.537269	2.114727	1.768317	0	Vlim 6	79.59294	0.918225	0.879295	0.887191	23.72022				
0.57735	0.755622	0.817677	1.255622	1.683703	1.174247	0.467141	0	Vlim 7	50.06468	0.871247	0.675148	0.775062	32.68795				
0.57735	0.219242	0.049856	0.919242	1.262292	0.895983	-0.09397	0	Vlim 8	69.46346	0.773209	0.400582	0.586769	39.39099				
0.57735	0.561287	0.482329	1.111287	1.434957	0.971658	0.193841	0	Vlim 9	117.5777	0.827963	0.567327	0.712699	70.17624				
0.57735	2.435552	1.76707	2.785552	2.373288	0.93699	0.442015	0	Vlim 10	157.6816	0.989146	0.957058	0.992565	219.4353				
0.57735	0.858465	0.999944	1.308465	1.779367	1.254046	0.61765	0	Vlim 11	50.8341	0.884892	0.726607	0.804682	31.67018				
								Vlim 12						1.077477	-0.05389	59.11883	
								Vlim 13						1.171389	0.747125	221.8276	
								Vlim 14						1.319695	0.75401	431.9884	
								Vlim 15						1.881866	1.531866	394.4563	
								Vlim 16						1.227247	0.227247	181.5243	
								Vlim 17									350
								Vlim 18									550
								Vlim 19									800
								Vlim 20									1150

Fig. 6. Screenshot showing the parameters of the drugs evaluation methods and the drugs values

Finally, the last screenshot in figure 7 shows the solution for a budget of 400 M$ for the first year and of 100 M$ for the others. Particularly, 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, leading to higher portfolio ROV.

Objective function							
P	C	I1	(C-I1)	y	(C-I1)*y	z	Xi
1	16.32149	2	14.32149	0	0	0	0.00%
2	36.01003	3	33.01003	1	33.01003	0	0.00%
3	65.25542	10	55.25542	0	0	0	0.00%
4	58.39708	5	53.39708	0	0	0	0.00%
5	360.9954	20	340.9954	1	340.9954	0	0.00%
6	23.72022	15	8.720225	0	0	0	0.00%
7	32.68795	10	22.68795	1	22.68795	0	0.00%
8	39.39099	20	19.39099	0	0	0	0.00%
9	70.17624	20	50.17624	0	0	0	0.00%
10	219.4353	30	189.4353	0	0	0	0.00%
11	31.67018	10	21.67018	0	0	0	0.00%
12	59.11883	30	29.11883	0	0	0	0.00%
13	221.8276	75	146.8276	0	0	0	0.00%
14	431.9884	90	341.9884	0	0	0	0.00%
15	394.4563	50	344.4563	1	344.4563	1	83.34%
16	181.5243	80	101.5243	0	0	0	0.00%
17	350	180	170	0	0	0	0.00%
18	550	220	330	0	0	0	0.00%
19	800	250	550	0	0	0	0.00%
20	1150	350	800	1	800	0	0.00%
	max ROV			ROV	$1,494.28		

Fig. 7. Screenshot showing the optimal portfolio composition and the overall ROV

In order to study the effect of the investment constraint on the optimal portfolio composition, different yearly budget limitations have been tested. Particularly, different combinations between the first year budget and the following ones have been tried out. They are shown in Table 3, together with the resulting optimal portfolio composition and overall ROV, the supporting drugs and their correspondent percentage of reinvested cash flows.

1st year budget	Next years budget	Porftolio composition	ROV	Supporting drugs	R&D share
400	**100**	P2, P5, P7, P15, P20	$1,494.28	P15	83.34%
400	**200**	P2, P5, P10, P14, P15, P16, P19	$1,868.40	-	-
400	**300**	P2, P4, P5, P10, P14, P15, P16, P19	$1,948.61	P15	18.36%
500	**100**	P5, P7, P14, P15 P20	$1,646.40	P20	46.68%
500	**200**	P5, P10, P14, P15, P16, P20	$2,118.40	-	8.35%
500	**300**	P2, P4, P5, P10, P14, P15, P16, P20	$2,198.61	P15	11.02%
600	**100**	P5, P7, P15, P18, P20	$1,812.72	P15	45.20%
600	**200**	P5, P10, P14, P15, P16, P20	$2,118.40	-	-
600	**300**	P2, P4, P5, P7, P8, P9, P10, P11, P12, P14, P15, P16, P20	$2,341.65	P16	18.36%

Table 3. Optimal portfolio composition for different budget limitations

The same results are displayed in the following graphs, which shows the trend of the optimal ROV as the budget limitations change.

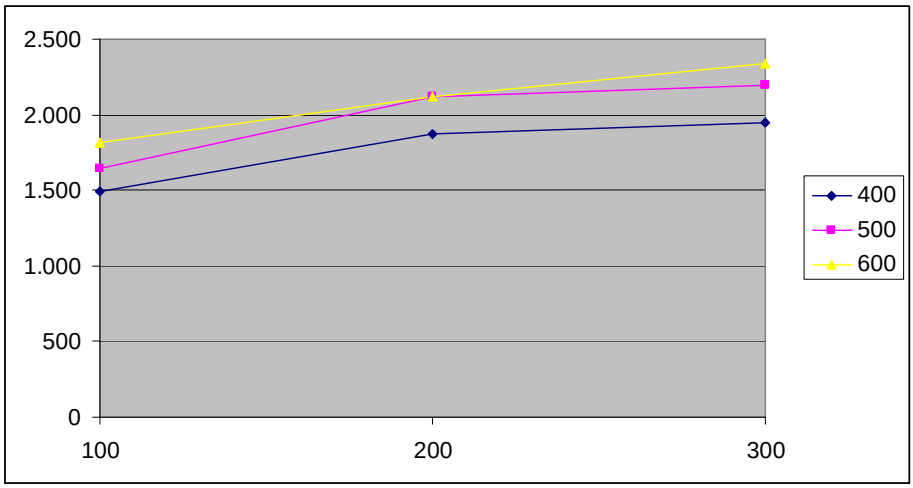

Fig. 8. Graph of optimal ROV for different budget limitations

It is possible to observe that almost every budget combination has a supporting drug which gives a certain amount of its future revenues allowing more drugs to be part of the optimal portfolio. Furthermore, a comparison between the optimal portfolio ROV in case of presence and absence of self-financing, for different budget combinations, is shown in Table 4 (in brackets the corresponding optimal portfolio composition).

		Self financing (SF)	1st year budget		
			400.00	**500.00**	**600.00**
Next years budget	**100.00**	**SF**	1,494.28 (P2, P5, P7, P15, P20)	1,646.40 (P5, P7, P14, P15 P20)	1,812.72 (P5, P7, P15, P18, P20)
		no SF	1,389.15 (P3, P10, P15, P20)	1,418.27 (P3, P10, P12, P15, P20)	1,694.46 (P15, P19, P20)
	200.00	**SF**	1,868.40 (P2, P5, P10, P14, P15, P16, P19)	2,118.40 (P5, P10, P14, P15, P16, P20)	2,118.40 (P5, P10, P14, P15, P16, P20)
		no SF	1,868.40 (P2, P5, P10, P14, P15, P16, P19)	2,118.40 (P5, P10, P14, P15, P16, P20)	2,118.40 (P5, P10, P14, P15, P16, P20)
	300.00	**SF**	1,948.61 (P2, P4, P5, P10, P14, P15, P16, P19)	2,198.61 (P2, P4, P5, P10, P14, P15, P16, P20)	2,341.65 (P2, P4, P5, P7, P8, P9, P10, P11, P12, P14, P15, P16, P20)
		no SF	1,923.66 (P3, P5, P10, P14, P15, P16, P19)	2,173.66 (P3, P5, P10, P14, P15, 16, P20)	2,329.16 (P4, P5, P7, P8, P9, P10, P11, P12, P14, P15, P16, P20)

Table 4. Comparison between the optimal portfolio ROVs [M$]

It is evident that having the chance to reinvest part of drugs profits provides pharmaceutical companies with higher overall ROV.

7. Conclusion

This paper focused 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. These methods were compared with traditional evaluation methods like NPV, which fail to properly assess the value of this kind of projects, since they don't take account of the opportunities usually embedded in R&D projects. Moreover, as the value of these chances is very high in risky and long term projects, such as those carried out by pharmaceutical companies, the use of real options based methods allows to improve the accuracy in their evaluation. Particularly, this article dealt with selection of an optimal R&D project portfolio, through real options, which is also able to establish whether is favourable for a company to use part of the future financial incomes of its commercialized drugs to fund the development of other products, in order to achieve balance in its strategic planning. This is done by presenting a model available in literature and providing a new one which aims to overcome the drawbacks of the already existing one that limited its spread across the companies and to provide balance in terms of self-financing. To do this, some modifications were made to the original model, in order to built up a new one which is more comprehensible and fairly easy to implement in a simple spreadsheet. The resulting portfolio is balanced since it contains both drugs whose aim is to provide pharmaceutical companies with large revenues and drugs which are able to fund further R&D activities sharing part of their financial incomes. This may lead pharmaceutical companies to higher profits and increasing growth rates. A case study, based on the selection of an optimal drugs portfolio among twenty products, is provided to prove the simplicity and effectiveness of the new model. 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. As a further study, it may be worth to slightly modify the new model in order to extend its field of application. The possible extension is twofold: it can be fitted, with minor revisions, to other industries and within biopharmaceutical industry the model would be useful to evaluate open innovation opportunities. Particularly, 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 [18]. Using the same approach focused on simplification, a decision support system might be created in order to help pharmaceutical companies to develop their strategic plans.

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