Valuing a portfolio of dependent RandD projects: a Copula approach

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1. Introduction

The aim of this work consists of pricing a real biotechnology firm that is based on a portfolio of several drug development projects at different phases. Duffie and Singleton (1999) formulate a system of n correlated jump mean-reverting intensity equations to capture a portfolio of n entities' default times. The drawback of their approach is that there are a lot of parameters and we have no enough information so as to estimate all. This is the reason why the copula approach has been very well accepted in recent years as an alternative tool for these situations since we can model the extreme situations (or default in this case) under a dependence framework by selecting those copula functions with a very few number of parameters. Summing up, this is the reason why we use them in this study. We simulate situations of common rare events under this approach.

The abandonment flexibility - which is the only one that we consider in this study and it is quite different from the idea to abandon due to a common (specific) catastrophic event which can be extended to the remaining projects (one project) – affects each project independently. This option is exercised under those situations of expected costs to completion higher than the expected cash flow, that is, during the investment period for research and development. Including this flexibility in a patent is the same as valuing a project with an implicit American put option.

2. A portfolio of Research and Development projects

The assets for the company that will be value consist in a portfolio of research and development drugs projects which are patent protected. The flexibility inherent in these projects is captured by real option methodology. The patent life for these projects is in average twenty years. Once the R&D process is completed, the new drug is marketed and the company enjoys of a monopolistic situation until the expiration of the patent life. From the time being, the drug has to share the market with generics, and a sales decreasing is produced until reach profits zero[1].Another possibility would be that the firm runs out all the patent life for R&D without completion.

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[1] The possibility of two different drugs development process would lead a duopoly situation, but the basis would be the same (Schwartz 2004).

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We can identify three types of uncertainties: the first one is about the investment cost required for the completion of the R&D stage of the project. The reason is a learning process that occurs while there is investment. We capture this one with a cost dynamic described in Pindyck (1993) and Schwartz (2004). The second uncertainty concerns about the possible free cash flows (FCF) that the drug will obtain once that have been marketed. For capturing this one, we will proposal three types of processes as Piñeiro and León (2004) recommended. The third uncertainty is described by catastrophic events that could lead the failure of the project. This one will be described by a Poisson process.

In all stages the possibility of abandon can be exercise if the completion expected cost is higher than the expected cash flow, that is, in the research and development period. We also introduce a new dimension to our valuation: dependence between projects, that is, in the hypothetical case of a catastrophic event that affected to one project, it could lead a contagious effect in the others, which would give a higher probability of going bust than the initial predicted for our portfolio. The dependence will be introduced in the instantaneous intensity of default for each project. This dependence will be simulated with two tools: on one hand, we will introduce a process that capture common and specific projects effects and sum up in an affine process. On the other hand, we will use a well-known tool in credit risk: copula functions.

3. Continuous time model

The research process for one drug is long and it has an associated costs that can vary depend on the development phase will take place. If the drug overcomes every phase, it will ready for commercial lunch. In our model we implemented a different expected cost to completion in each phase for our empirical evaluation. We let the possibility of generic entrance once the patent expires and also we use different models to capture the dependence among projects to avoid overvaluation or undervaluation of our portfolio.

3.1 Cost Dynamic

We follow, in spirit, the modeling of cost uncertainty in irreversible investment projects described in Schwartz (2003) and León y Piñeiro (2004). The dynamics of the conditional expected remaining costs to completion are given by:

$$dK_s(t) = -I_s dt + \sigma_s \sqrt{I_s K_s(t)} dw_s(t), \tau^*_{s-1} < t < \tau^*_s \qquad (1)$$

Where $K_s(t)$ is the expected real cost to complete the ongoing phase before starting the next phase. The interpretation for equation (1) is straightforward. As the firm continues investing in the R&D, the expected remaining cost to completion decreases. However, the firm also learns more about its ability to complete the project on time and on budget. Prior to the beginning of Phase i, the firm expects that the total cost to complete the Phase i research to be $K_i(0)$. Negative shocks to the R&D delay the Phase i completion and increase the total development cost for the phase, while positive shocks shorten development time and reduces the development cost. The drift component in equation (1), which is the rate of investment I_j, is a control variable: the larger is the investment rate, the lower is the expected cost to completion. This means that the investment implies a "learning process" and the expected cost decreases only when there is investment. The uncertainty $dw_s(t)$ is called by Pindyck (1993) *"technical uncertainty"* and only can be solved by investing. Due to the variance is linear in investment; there will be only two possible solution values for the control: invest zero or the maximum possible rate.

Remark that the stochastic process for the cost dynamic is a reasonable representation of uncertainty about expected cost in R&D investment for drugs as suggest DiMasi et al (2003) and Schwartz (2001).

3.2 Free Cash Flow Dynamic

We implemented a life cycle model that consists in three parts: from the R&D completion date until the sales peak[2]; from the sales peak to the expiration date of the patent; and from the expiration date to the time that the firm obtains zero profits.

3.2.1 Stage 1

For the first stage, we use a Brownian motion model given by:

$$dC_1(t) = \alpha^* C_1(t) dt + \phi C_1(t) dz_c^*(t) \qquad (2)$$

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[2] According to some papers, it is achieved in the ninth year.

Where alpha is the risk-adjusted drift:

$$\alpha^* = \alpha - \eta \tag{3}$$

And η is the risk premium. ϕ is the volatility parameter and $dz_c^*(t)$ is the increment of a wiener process under the risk neutral measure.

3.2.2 Stage 2

For the second stage we propose three alternative life cycle models, that is, a Brownian motion, an Orstein-Uhlenbeck and a random walk. The key for introducing them is to avoid a possible overvaluation of the project (Bollen 1999, León y Piñeiro 2004).

3.2.3 Stage 3

And for the third stage, we assume that the behavior of the FCF will be decreasing till getting to zero when the profits are zero, because since the patent has expired, the monopolistic advantage decreasing for the leader firm due to the entrance of generics until reach zero profits:

$$dC_2 = -\delta(t)C_1(T)dt, T \le t \le T^* \tag{4}$$

Where T is the patent expiration date, $C_1(T)$ is the FCF starting value for stage two and T^* is the time in that the profits are zero and $\delta(t)$ is the delta function with values decreasing from T to T^* (it captures the decreasing effect in profits):

$$\delta(t) = \begin{cases} \delta_1; t \in [T, t_1) \\ ... \\ \delta_m; t \in [t_{m-1}, T^*] \end{cases} \tag{5}$$

We also let correlation between $dw_i(t)$ and $dz_c^*(t)$ given by:

$$dw_i(t)dz_c^*(t) = \rho_{ci}dt \tag{6}$$

4. Introducing dependence between projects

We consider two approaches for introducing the dependence among projects. On one hand, we consider a process for specific factors and another for common factors. On the other hand, we will use copula functions. Both of them try to solve the *stylized facts* to describe the dependence with extreme values: asymmetric as indicated nonzero skewness and fat tails as indicated by excess of kurtosis.

The dependence is introduced by the intensity of default[3]. Then, the survival probability will be given by a Poisson process as Schwartz (1999) and León & Piñeiro (2004) suggest:

$$prob(Tc > Ts) = e^{-\int_0^t \lambda_i dt} \tag{7}$$

We consider two ways for introducing the dependence. The first one is specifying a copula function consistent with the studied empirical dependence structure. The problem of this approach is the absence of empirical data for intensities of default in R&D companies. The second one is specified given marginals ex-ante and inducing then the related copula functions. We use the second one for two main reasons: first, as we have said before, we do not have empirical data of the intensities of default for fitting any copula, and second, this approach lets us to compare the grade of undervaluation or overvaluation with the different copulas that have been chosen in our pool.

4.1. Fan Yu Approach

We have introduced a model to give us a first approach of the dependence between projects and let us to compare these results with a later copula approach. We use Fan Yu approach (2003), which consists in modeling the dependence through the individual intensity of default with common and specific factor processes given by:

$$\lambda_i(t) = \alpha + \beta F(t) + G_i(t) \tag{8}$$

Where *beta* is the factor loading for the common factor process *F(t)*, *alpha* is a free-adjust parameter and *G(t)* is the specific factor. And

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[3] We assume that $\lambda_i(t)$ exhibit continuous margins for modeling it with the pool of copulas of our study.

because the individual intensities are linear functions of the processes considered, then they are affine processes and we can apply known mathematical tools. The parameter beta controls the proportion of the total variation in the default intensity that is attributed to the common factor. With beta zero the default correlation will be zero. The common and specific factors will follow CIR's processes that ensure a positive value for the variable under study. The expressions are given by:

$$dF(t) = k_1(\theta_1 - F(t))dt + \sigma_1\sqrt{F(t)}dw(t) \qquad (9)$$

$$dG_i(t) = k_2(\theta_2 - G_i(t))dt + \sigma_2\sqrt{G_i(t)}dz_i(t) \qquad (10)$$

Where $dw(t)$ and $dz_i(t)$ are independent Wiener processes.

The initial value for the factors will be set to their respective long-run means. The factor loading beta will be treated as a free parameter. The constant coefficient alpha is chosen such that the cumulative default probability at the ten year horizon is equal to 1%, according with some estimation in Duffie (1999) and Driessen (2005). Since the model will be numerically implemented because it has not a closed-form solution, a discrete explicit solution of CIR process will be necessary as we will see in section five.

4.2. Copula Approach

For the copula approach, we use a pool of both extreme value Archimedean copulas and elliptical copulas. The pool consists in Gumbel, Clayton, t and Gaussian copula. We will compare different scenarios with different parameters and copulas to capture the grade of overvalue or undervalue compare with a non-contagious effect scenario. We generate random samples of these and we introduce in our model in order to capture the dependence through the intensity of default[4]. Notice that the idea is not fitting a data with a specified copula because we have not time series data of the company, but capture the dependence through

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[4] The key is to insert the intensity of default in the survival probability given by

$$prob(Tc > Ts) = e^{-\int_0^t \lambda_i dt}$$

different copula functions among projects[5]. The way for introducing the dependence will be generate samples for a chosen copula and these samples will be taken as intensities of default for one project. Note that the dependence is capture through the copula function that generates the samples and that dependence affect to all intensities of default.

4.2.1 Brief introduction to copulas

Copula functions are adapted tools to construct multivariate distributions. The copula extends the concordance notion to the continuous framework. We take the marginal distributions, each of which describes the way in which a random variable moves "on its own," and the copula function tells us how they "come together" to determine the multivariate distribution of the portfolio of variables considered; that is,

Definition 1 *A copula is a function that joins a multivariate probability distribution to a collection of univariate marginal probability functions.*

Properties *According to Nelsen (1998) a N-dimensional copula is a function C with the following properties:*

1. Dom C is $[0,1]^N$,
2. C is grounded and N-increasing[6],
3. C has margins C_n which satisfy $C_n(u)=(1,1,...,u,...,1,1)=u$ for all u in the domain.

Copulas are invariant through strictly increasing transformations of the random variables considered. The copula also takes into account phenomena due to depended extreme events. Really, this is the most important point of interest for us: copula provides more information due to rare events that occurs with lower probability in the distribution tails but occurs. So, copula lets us to capture them. Sklar theorem let us to study the dependency structure of multivariate distributions without studying marginal distributions; that is,

Theorem 1 *If F is a N-dimensional distribution with continuous marginals $F_1...F_N$ then F has a unique copula representation (Sklar, 1959):*

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[5] Of course is straightforward to introduce time series data one time the scenarios have been implemented (a likelihood method –it has been implemented by us- would be the most recommended option to this proposal).

[6] C is *N-increasing* if the *C-volume* of all *N-boxes* whose vertices lies in I^N are positive.

$$F(x_1, ..., x_n, ..., x_N) = C(F_1(x_1), ..., F_n(x_n), ..., F_N(x_N)) \qquad (11)$$

Also *Deheuvels* (1981) showed that each multivariate distribution has at least one associate copula function, and this copula is unique when margins are continuous. However, as *Frees and Valdez* (1997) notes, is not always obvious to identify the copula. More exactly, *Durrleman, Nickeghbali and Roncalli* (2000) noted that a misspecification of marginals leads to a biased estimation of the copula function, and the solution would be consider the copula function without any marginal law.

Within of the large family of copulas, we will be interested in two groups: *Elliptical copulas* and *Archimedean copulas*. The first one includes *Gaussian copulas* and *t copulas*. The second one includes *Gumbel, Clayton and Frank copulas*.

Gaussian copulas provide a very simple framework for studying the dependence effect[7]. This one does not permit tail dependence, but it could help to match the effects of introducing the dependence. A drawback, also shared by t copulas, is the big number of parameter necessary: a correlation matrix of $n.\dfrac{(n-1)}{2}$ elements. If the Gaussian copula fits the data well, the correlation matrix suffices to describe the dependence.

T copulas need to specify the degrees of freedom and the correlation matrix[8] too. However, this one captures extreme value effects because it is asymptotically dependent in both the upper and the lower tail. For fixed correlation structure, the strength of the tail dependence increases as the degrees of freedom decreases; and for fixed degrees of freedom, the tail dependence increases as the correlation structure increases. So, the parameters needed are $n.\dfrac{(n-1)}{2}+1$.

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[7] Lower tail dependence with parameter λ_L means that as $u \rightarrow 0$, the probability mass that is in the lower square [0,u]x[0,u] tends to zero like λ_L.u and not like u^2, the area of the square. This means that there must be a rather strong singularity of the copula's density in the lower left corner (0,0). Analogous judgment for higher tail dependence is followed.

[8] Note if we increase the degrees of freedom, t copula converges to Gaussian copula, more exactly, with $\upsilon \rightarrow 30$ the different are negligible.

On the other hand, the advantage of Archimedean copulas is given by the lower number of parameters needed for modeling them. More exactly, we only need to specify the generator function for the copula chosen. Also we have generators with a lower number of parameters (in our case with one or two parameters). Archimedean copulas are also *exchangeable*; the dependency between any two or more different variables does not depend on the question which pair is chosen. This is a good notice for assessing portfolio with homogeneous projects as in our case (all drugs projects in R&D phases). *Gumbel* copulas are interested because they have higher tail dependence. The idea is that a higher intensity of default for one project due to catastrophic events will be followed by a higher intensity of default by others projects. So, this one is, a priori, the best election for our proposal. *Clayton* copulas have lower tail dependence, and *frank* copulas are symmetric.

Details about sampled generations will be given in section five.

5. Model Implementation

Due to the interest in giving the details about copula sampling and the algorithms used by us, we divided this section in three parts. In the first one we give the discrete expression that has been implemented; in the second one, we give a more exhaustive analysis of sampling methods and in the third one, we explain the stopping rule algorithm.

5.1 Discrete versions of cost and FCF dynamics

Because we cannot obtain the portfolio value with a closed-form solution we need to consider the discrete version of given equations, and employ for solving a numerical solution algorithm as we have said before. The discrete version of cost dynamic equation (1) is given by:

$$K_s(t+\Delta) = K_s(t) - I_s\Delta + \sigma_s K_s(t)\Delta\varepsilon_s(t) \tag{12}$$

The discrete version of equations (2) and (4) are respectively:

$$C_1(t+\Delta) = C_1(t)\exp[(\alpha^* - 0.5\phi^2)\Delta + \phi\sqrt{\Delta}\varepsilon_c(t)] \tag{13}$$

$$C_2(t+\Delta) = C_2(t) - C_1(T)\int_t^{t+\Delta} \delta(u)du \tag{14}$$

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Where $\varepsilon_c(t)$ is a correlated standard normal variable with parameter ρ_{ci} between $dw_i(t)$ and $dz_c^*(t)$. The correlation between two different phases is assumed equal to zero (León y Piñeiro 2004). T is defined as the remaining life in years of the patent from nowadays till expiration or stage one. And for equations (9) and (10) we use the transition density function of them which is known[9] for getting a discrete solution of the CIR processes:

$$F(t) = \frac{\sigma_1(1 - e^{-k_1\Delta})}{4k_1}[\chi_d{}'(v)] \tag{15}$$

$$v(t) = \frac{4k_1 e^{-k_1\Delta}}{\sigma_1{}^2(1 - e^{-k_1\Delta})} F(t - \Delta) \tag{16}$$

$$G_i(t) = \frac{\sigma_2{}^2(1 - e^{-k_2\Delta})}{4k_2}[\chi_d{}'(v)] \tag{17}$$

$$v(t) = \frac{4k_2 e^{-k_2\Delta}}{\sigma_2{}^2(1 - e^{-k_2\Delta})} G_i(t - \Delta) \tag{18}$$

$$\Delta = \frac{T}{N} \tag{19}$$

Where $\chi_d{}'(v)$ is the non-centered Chi function that can be expressed as a centered Chi function and Δ is the time step size. k_1 and k_2 are parameters of the CIR processes, and also the volatilities.

5.2 Methods for simulating draws from a chosen copula

Assume a bivariate copula in which all of its parameters are known (fixed or estimated them). The task is to generate pairs (u,v) of observations of [0,1] uniformly distributed random variable. (u,v) whose joint distribution function is C. To reach this goal, we can use two methods: the conditional distribution technique, and the Marshall and Olkin's algorithm for the compound construction of copulas.

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[9] For a detailed study see Glasserman 2003.

5.2.1 The conditional distribution technique

The algorithm for the conditional distribution technique (Cherubini, 2001) is:

-Compute two independent r.v.s. $(u,v) \in [0,1]$,
-U is the first draw we are looking for.
-Compute the cuasi-inverse function of $C_u(v) \Rightarrow v = C^{-1}_u(w)$.

For multivariate generation, we only need to consider that the draw F_n is extracted of the conditional distribution $Cn(F_n | F_1,...,F_{n-1})$.

The drawback of the conditional distribution technique is that it fails very quickly if the number of dimensions becomes just moderately large (bigger than 4), because either the analytical expressions become impossible to handle or because deriving the conditional distribution on the *k-th* level involves taking *k* cross-derivatives of the distribution function. Each numerical evaluation of a derivative of a function involves the subtraction of two numbers very close to each other, and scaling up the different. At each of these subtractions several significant digits in accuracy are lost. So, other methods more robust and easy to compute are needed.

5.2.2 Marshall and Olkin's method

The key point in the M&O method is that conditional on the realization of γ, the random variables U_i are independent. This conditional independence property was exploited in the proof of the algorithm[10]. It has a similar function to the conditional independence which allowed Schömbucher to derive the large portfolio loss distribution in the one factor Vasicek model[11].

The algorithm is[12]:

-Generate a latent r.v. γ having Laplace transform τ.

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[10] See Marshall and Olkin (1988) for details: Algorithm for the compound construction of copulas.
[11] See Credit Derivatives pricing models, Schömbucher (Wiley and Sons).
[12] See Frees and Valdes (1998) for details of the Marshall and Olkin's algorithm implementation.

-Independently of the previous step, generate $U_1,\ldots,U_n$ independent random variables.

-For k=1…n, calculate $X_k = F_k^{-1} = (U_k^*)$, where $U_k = \tau(-\dfrac{1}{\gamma}\ln U_k)$.

-F is given by $F(x_1,\ldots,x_n) = \tau\left[\tau^{-1}(F_1(x_1)) + \ldots + \tau^{-1}(F_n(x_n))\right]$.

-Each X_k is the draw looked for.

Draws from the M&O algorithm are straightforward calculated for most copulas of interest that are generated by compounding methods. It can be easily implemented for high dimension. Needless to say, this additional latent variable is not always easy to simulate and to calculate the Laplace transform.

5.3 Algorithm for the stopping rule

Our election will be based on the optimal stopping algorithm of Longstaff and Schwartz (2001) that combine Monte Carlo simulation with least squares regression that was implemented in León and Piñeiro (2004).   The algorithm searches for the optimal stopping along each path by backwards induction. It is assumed that the option to abandon the project can be only exercised once and before the approval for the market launch of the drug. Note the optimal stopping time rule consist of obtaining for each path the minimum value that the abandon is better than continuing.

More exactly, once we have simulated random samples from copulas, or we have introduce the values obtained by Fan Yu approach in the Poisson process that describe the probability of success at each phase, we simulate our model getting different paths in the simulation, and we advance by each one until to reach the expiration date or to execute the abandon option. Then we discount the FCF until the time in that we are valuing the firm, and doing the mean of all paths implied in the process we get the value that we are looking for.

We obtain a payoff matrix with elements $V(i, j\Delta)$. The procedure to get $V(i, j\Delta)$ is: (a) start at time zero, (b) move forward along each path till the first stopping occurs and we will denote j_i^* as the optimal stopping date for path i, (c) then discount all the cash flows to time zero and (d) take the average of the N_p paths. In the end, we estimate the value of the

portfolio by discounting the FCF to time zero and averaging them over all paths according to the next expression[13]:

$$V_0 = \frac{1}{N_p} \sum_{i=1}^{N_p} \sum_{j=1}^{N_1} \exp[-(r + \lambda_j)] \Delta_j V(i, j\Delta) \tag{20}$$

Note that the intensity of default is introduced in the valuation as an increment in the discounted rate. We also need to consider the (possible) cash of the firm that must be added to the total value of the firm that is obtained in our algorithm.

6. Data and parameters

We use data of different sources to adjust our models. In concrete, we use the data of León and Piñeiro (2004) for the PharmaMar valuation, and also data from financial analysts' reports corresponded to this year. All monetary values are expressed in euros.

6.1 Portfolio composition

The process of drug development is lengthy, complex and risky. Before a new drug can reach the market, it must pass through the following sequential stages: discovery; preclinical testing; phases I, II and III from clinical trials; submission to either the European Medical Evaluation Agency or Food and Drug Administration (FDA) and finally, phase IV trial.

The most advance drug is Yondelis that is waiting for the approval of EMEA (European Medical Evaluation Agency). Aplidine is the second more advanced that has shown to be active in a larger number of cancer types. Kahalahide-F has as main indication prostate cancer and ES-285 has shown evidence of solid tumors. Meanwhile for the preclinical one, since it is in a very early stage of R&D joint with the lack of information from PharmaMar, it is unknown what sort of pathology this compound could be effective.

Our portfolio consists in five drugs: *Yondelis, Aplidine, Kahalahide-F, ES-285* and *Preclinical 5*. To be precise, at simulation moment there are two drugs in phase I (Kahalahide-F and ES-285) and

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[13] See León and Piñeiro (2004) for a detailed explanation of the algorithm.

two in phase II (Aplidine and Yondelis). Also a exist four compounds more in preclinical testing, but we consider only the compound in the most early phase as bound of all of them (Preclinical 5). The reason is simple: on one hand, Preclinical 5 has the bigger time expected to completion and the lower initial FCF, on the other hand, the bigger expected cost of all preclinical drugs (it works as lower bound for costs). Also it permits us to simplify the dimension of our problem for copula constructing.

6.2 Copulas parameters

Copula functions have been implemented with marginal distributions as exponential functions, with parameter T. More concretely, the parameter is fixed to the expected remained time to completion for each drug. So we have: 16.75, 17.75, 18.50, 19.25 and 22.25 years for each component respectively. The explanation for our marginal distribution function election is to ensure the positive value of our latent variable (intensity of default) and due to the exponential distribution function shape, to get the greater part of values in the lower part of the shape, and only higher values in the tail with a lower probability. This idea capture the catastrophic event process: if not usual to occur, but if it occurs, values can be very high. Of course, it is a priori specification, and a more detailed study with empirical data could help to choose another one (Gaussian or gamma distributions could be an correct election). But due to the characteristic of our study, that is, to introduce dependence between projects as a early approximation, such marginal functions are considered by us a good idea.

Also for Archimedean ones, the dimension specified has been *5* and the parameters chosen have been *2* or a vector with two parameters *(2,4)*. For the Gaussian copula also we introduce correlation between each project with parameter *0.5*, and for the t copula the same correlation and 9 as the degrees of freedom. Again the copula parameters and correlation choice are arbitrary: we weigh up both types of copulas with correlation factor *0.5* to introduce the homogeneity of the entry of a possible catastrophic event for all projects independently of the drug[14]. Finally, we have generated a matrix for each type of copula with 60000

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[14] Of course an exercise of calibration would be the most appropriate tool for getting fitted values according to the empirical dependence structure. However, we do not have empirical data for default intensities so a trial and error method has been followed by us to obtain these values.

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paths and five columns (one for each drug's intensity of default). So we have matrixes of size *60000 x 5.*

6.3 Phases parameters

The expected average lifetime, in years, for each phase is fixed according to Sweeny (2002) and Tang (2002): 3.5 (preclinical), 1.5 (phase I), 2 (phase II), 2.5 (phase III) and 1.5 (approval).

6.5 Costs parameters

According to analyst' reports, we will assume as total costs to PharmaMar exactly 2/3 of the standard pharmaceutical costs. This reduction is due to the short toxic level since these compounds are obtained from marine organism. The expected cost to a certain phase is the same for each therapeutical line for any compound. For preclinical compound, the forecast of the cost is the same for phases I, II, III and approval due to the lack of data. The expected cost for a given phase will be the same for any therapeutical line and this value will be independent of the compound that the therapeutical line belongs to. The reason is the number of pathologies treated with each compound is the same in each phase. For obtaining the annual rate of investment per phase I_s, we divide the expected cost to complete phase s, k_s, by the expected lifetime of phases s given in subsection 6.3. The volatility parameter σ_s can be obtained from:

$$\text{var}_t[\tilde{k}_s(t)] = \frac{\sigma_s^2}{2 - \sigma_s^2} k_s^2 \tag{21}$$

We need also estimations for both the square root of $\text{var}_t[\tilde{k}_s(t)]$ and k_s, which can be found in DiMasi et al (2003). The resultants estimates of σ_s are 0.96, 0.91, 0.97 and 0.81 to phases preclinical, I, II and III respectively. In the approval phase, due to all events that affect to a drug are of civil service, the volatility is fixed to zero.

6.6 FCF parameters

FCF are the 33.45% of the sales. We compute the annual peak sales considering that the sales in Europe are a 35% of total sales and the royalties. We will take as percentage the average of the total sales with value 15.12%. The peak sales for the preclinical compounds are obtained as the average of the clinical compounds' peak sales times five (five

compounds). For computing the peak sales for Yondelis, we consider the amount of 538.27 million for PharmaMar business in Europe. The annual peak FCF is 331.25 million which comes from adding up both 180.05 and 151.20, where 18.05(151.20) is equal to 538.27x0.3345 (999.64x01512). So the quarterly FCF is 82.81 million. For all other compounds the procedure is similar.

We use two drifts in our model to compare the sensitivity of the model to changes in the drift. The first one -0,291- was used in León and Piñeiro (2004) and it was obtained from Yondelis and it was the same for all drugs dynamics since we have not enough information for the rest. The second one -0.115- is proposed by DiMasi and it is calculated from different studies of R&D pharmaceutical companies. This second one assumes lower expectations about future FCF, so the expected results must be lower than with the first one because FCF is lower now. We set a small correlation between the stochastic process for cost and cash flows (-0.10) according to León y Piñeiro (2004). This value will be increasing in absolute value as we move to more advanced phases in R&D. The idea is based on that more successful projects take a shorter time to develop, so their cost are lower and their cash flows are higher. The annual volatility parameter ϕ is fixed to 0.38 which is the sample standard deviation based on daily returns of Zeltia (2003, January to April period). In the end, when the patent expires the sales decreasing because of generics. The drop set for the first 6 years is fixed according to analysts: 30%, 20%, 15%, 15%, 10% and 10% respectively.

6.7 Other parameters

The interest rate –denoted as *r*- will be assumed constant for simplicity, and it has been fixed to 1.68%[15]. The risk premium considered is 6% than correspond to a α^* of 0.232.

PharmaMar has in cash an amount of 120 millions of euros that we will have to add to the total value of the compounds for the valuation.

In each compound we use 60000 simulations with quarterly steps, that is, $\Delta = ¼$.

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[15] Since the internal rate of return –*i*- for the ten-year German bond is 3.73% at May 30, 2003, and given the inflation target denoted by π_e by the ECB of 2%: $r = \ln \dfrac{(1+i)}{(1+\pi_e)}$.

7. Simulation results

Our task is to evaluate the portfolio value introducing dependence and compare the results without dependence. Table 3 shows the value obtained by León and Piñeiro (2004). Table 4 shows our results. We have divided it in two: table 4.a shows the results with drift value of 0.291, and table 4.b with 0.115. Note that there is three columns: value with flexibility (abandon option and dependence is included), without flexibility (only dependence is included) and option value. In all of them stochastic character is given to the variables. The value of the whole portfolio is given by adding all individual values and the cash of PharmaMar. Again the higher value correspond to Yondelis equal that in León and Piñeiro (2004) due to the lower uncertainty, and the value decrease when increase the cost and FCF volatility, that is, in preclinical compound.

Results obtained with drift 0.291 and Archimedean copulas – tables from 4.1 to 4.6- have higher value than obtained in León and Piñeiro (2004). Two possible answers: on one hand, the intensity of default is introduced via copulas have a lower effect on the drugs' values, on the other hand, calibration no play any role in the simulations and the bias could be evident. However, we are worried on how to obtain higher option values and in this case are three times in average bigger. Effects introduced by two parameters do not change the results so much. The random walk introduced in both papers for the drugs' behavior avoids a possible overvaluation and reject a negligible value for the abandon option. An Orstein-Uhlenbeck (OU) process produces very similar results to the random walk as we have checked in the simulations. Values obtained with elliptical ones are negative. Why is it? The reason is simple: t and Gaussian copulas give very higher values for intensities of defaults due to the input values for sampling them. Remember that these values are not calibrated and the correlation matrix is introduced at random as an exercise of introducing dependence among projects. Also, a marginal misspecification and or their parameters could lead a very different result (*Durrleman, Nickeghbali and Roncalli*, 2000).

Another approach used for introducing dependence is with Fan Yu model (table 4.9). In this case, control variable –a vector in our case- is introduced weighting up heavier the preclinical compounds than the other one. The idea underplayed is that preclinical stages are more sensible to contagious effects. Values obtained with this proceed are one magnitude order lower than copulas approach but positive. The reason

could be the CIR process followed by the intensity of default which values are very different of the copulas approach[16]. Of course, again calibration plays no role in our results and it could lead an important bias in the results. So, we conclude that the default correlation in reduced-form models can be quite sensitive to the common factor structure imposed on individual default intensities. It leads to consider as an option easier to calibrate copulas due to the lower number of parameters to chose.

Changes in the drift introduce a big effect in the compounds' prices. Tables 4.10 to 4.18 show the results. Again Yondelis has the higher value, and it decrease as we increase the time to maturity of the drugs due to higher uncertainty in costs and FCF. The results obtained are lower than original drift values. However, option values increases a lot. Concretely, we observe that a significant increase in the option value punishes much the drugs' values. Another important feature to emphasize is that, with new drift, the introduction of the abandon option leads a positive value that the model without abandon does not capture as we can see in table 4.10 and row ES-285 (with a option value of €7.43 millions). We avoid a possible undervaluation that would have been taken without flexibility (and of course with Net Present Value method)[17]. Again elliptical copulas punished a lot the price for each drug due to the reasoning previously exposed (negative values are obtained). Now Fan Yu model shows values more accorded to copulas values, and the option value is increased as we have more volatility in the drugs (control value parameters have not been change from the previous drift).

8. Sensitivity Analysis

We have performed three analyses: first one is oriented to capture the changes in prices versus drifts. In the second one we illustrate the idea that an increase in the time horizon is accompanied by a decrease in the survival probability. In the third one, we show that an increase in the interest rates leads an increase in the option value to abandon. The first one has been calculated for Yondelis because drifts for all compounds are based on Yondelis (more advanced compound).The second one is for the whole portfolio and all copulas are showed. In the last one, Yondelis again is studied for the same reason as before.

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[16] If we set control variable beta to cero, project values are only a little bigger, and the option value changes only about 2%.

[17] Exactly we obtain a NPV for ES-285 of -€89.856 millions (clearly the drug is undervalued and the project would be avoided with this method).

The idea of a time decreasing survival probability captures the increased in the completion phase expected cost. Figure 1 shows the whole portfolio survival probability if we increase the time horizon (in years). We observe that the portfolio survival probability starting from one year decreases a lot of. Concretely, bigger effects are produced by elliptical copulas, while Archimedean ones punish less (remember the higher values for intensities default obtained with elliptical ones). Then decreasing time survival probability drives higher option values for shorting time of the patent life and lower option values for bigger ones.

Changes in drift have been explained in section 7. Sensibility to these changes is very large: depending on what expectation about future growth is chosen –materialized in the drift value-, very different results are obtained indepently of the copula studied. This result could explain the very different target price for Zeltia fixed by analysts. Figure 2 showed the exponential character of the drift for Yondelis value. We observed that small increments in drift value lead to large increments in Yondelis value so also increase a lot the whole portfolio valuation. Remember that as we have stressed before, small drift values are associated with higher option values for abandoning which is showed in figure 3 (also for Yondelis). It is according to the results obtained by León and Piñeiro (2004). Figure 4 shows that higher expectations about profits are associated with lower total percentage of abandoned paths[18].

Figure 5 shows that a higher real interest rate drives to a higher option value to abandon according to León and Piñeiro (2004).

9. Extensions

An extension applicable to the cost dynamics would permit to obtain closed-form solutions and a dynamic learning process. We follow, in spirit, the modeling of cost uncertainty in irreversible investment projects described in Schwartz (2003) and León y Piñeiro (2004). The dynamics of the conditional expected remaining costs to completion would be given by:

$$dK_i(t) = -I_i dt + \sigma_i dw_i(t), 0 < t < \tau_i \qquad (22)$$

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[18] Because all drifts for all components are based on Yondelis due to lack of data for the rest, we perform sensibility analysis only for Yondelis.

$$dK_j(t) = \sigma_j dw_j(t), 0 < t < \tau_i \qquad (23)$$

$$dK_j(t) = -I_j dt + \sigma_j dw_j(t), 0 < t < \tau \qquad (24)$$

The interpretation for equation (22) and (24) is straightforward. As the firm continues investing in the R&D, the expected remaining cost to completion decreases. However, the firm also learns more about its ability to complete the project on time and on budget. Prior to the beginning of Phase i, the firm expects that the total cost to complete the Phase I research to be $K_i(0)$. Negative shocks to the R&D delay the Phase i completion and increase the total development cost for the phase, while positive shocks shorten development time and reduces the development cost. Equation (23), on the other hand, captures the idea of learning process, that is, revisions in the firm's expectation on the cost for completing Phase i research also brings about revisions in the Phase j expected cost to completion ($i<j$).

The drift component in equation (22) and (23), which is the rate of investment I_j, is a control variable: the larger is the investment rate, the lower is the expected cost to completion. This means that the investment implies a "learning process" and the expected cost decreases only when there is investment. The uncertainty $dw_i(t)$ is called by Pindyck (1993) *"technical uncertainty"* and only can be solved by investing. Due to the variance is linear in investment in equation (22) and (23), there will be only two possible solution values for the control: invest zero or the maximum possible rate. Also with equations (22) and (24) we can get a closed-form solution for the *"first hitting time density"* (which is not normal) of an arithmetic Brownian motion with drift I_j and variance σ_j :

$$\phi_1(\tau_1) = \frac{K_1(0)}{\sigma_1 (2\pi)^{1/3} \tau_1^{3/2}} \exp\left\{ \frac{-[K_1(0) - I_1\tau_1]^2}{2\sigma_1^2 \tau_1} \right\} \qquad (25)$$

And the cumulative density function for the first hitting time is[19]:

$$\phi_1(\tau_1) = 1 - N(\frac{K_1(0) + I_1\tau_1}{\sigma_1 \tau_1^{1/2}}) + \exp\left\{ \frac{-2I_1 K_1(0)}{\sigma_1^2} \right\} N\left\{ \frac{-K_1(0) + I_1\tau_1}{\sigma_1 \tau_1^{1/2}} \right\} \qquad (26)$$

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[19] For details see Karatzas and Shreve (1991) and León (2005).

Since the $dw_1(t)$ and $dw_2(t)$ are correlated we can rewrite the expected research cost as:

$$K_2(\tau_1) = K_2(0) - \rho \frac{\sigma_2}{\sigma_1}(K_1(0) - I_1\tau_1) - \sqrt{1-\rho^2}\sigma_2 Z_2(\tau_1) \qquad (27)$$

Where $Z_2(\tau_1)$ is a normal random variable with mean zero and variance τ_1.

Therefore we can write $K_2(\tau_1)$ conditionally normal with mean $K_2(0) - \rho \frac{\sigma_2}{\sigma_1}(K_1(0) - I_1\tau_1)$ and variance $1-\rho^2\sigma_2^2\tau_1$. Remark that the stochastic process for the cost dynamic is a reasonable representation of uncertainty about expected cost in R&D investment for drugs as suggest DiMasi et al (2003) and Schwartz (2001).

Another possible solution for getting more accuracy solutions could be to introduce multivariate dynamic models for copulas. It has been studied by Schömbucher and Schubert (2001) and would permit us to understand the particular specification of copula has on the dynamics of survival probabilities in the model. For more details and proofs the reader is referred to this paper[20]. Also specific construction of copulas or change in marginal functions may be to lead different solutions of given above. Of course, a calibration exercise would be the best adjust for choosing the right copula and its parameters.

Finally, we could model the intensity of default introducing different copulas where the marginal distribution of $\lambda_i(t)$ is Pareto and it follows a gamma distribution[21].

10. Conclusions

This paper studies the valuation of a portfolio of R&D projects with real options and introducing dependence between them to capture catastrophic events. The approach proposed by us could be used for valuing companies with assets that consist in a R&D projects –patent or

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[20] See also Multivariate Continuous Time Models through copulas, by Shang Chan Chiou.

[21] It is being developed by Gea and León (2006).

not protected- and highly volatiles in FCF or costs. We allow the flexibility of abandonment at any time during the R&D process. We also permit extreme value situations that lead dependence in the projects behavior. We capture these with two models: a reduced-form model and copula functions. Copulas permit us to consider a lower number of parameters for introduced dependence effects. Also we consider a reduced-form model proposed by Fan Yu (2005) by capture extreme values effect. A real simulation is run with a real company. Concretely, in our study we use a real portfolio coming from PharmaMar company to illustrate numerical examples. It is a portfolio of patents for oncological drugs. Patent protected projects considered are in preclinical phase or in clinical phases. The value of the portfolio is calculated as the sum of the R&D projects. We capture uncertainty in the cost to completion of the project, uncertainty in the FCF once the drug is launched and dependence between projects modeled as extreme situations of defaults with copulas. We have modeled the evolution of the FCF according to León and Piñeiro (2004) and allowing the possibility of the generic entranced once the patent expires. Costs are modeled indepently for each drug according to Schwartz (2004) and León and Piñeiro (2004). Catastrophic events are captured in our model and contagious effects bring about them too. More exactly, dependence is introduced by a reduced-form model proposed in Fan Yu (2005) and copulas functions, with a static model permitting dependence among projects and different phases. It is shown that Archimedean copulas give a more approximated result to the market value specifying a lower number of parameters; and the sensibility to increase these are very low. Also is showed that the reduced-form model considered is quite sensitive to the common factor structure imposed on individual default intensities. The higher drift value considered, the lower abandon option value is obtained. We also have obtained that the project value –and then the whole portfolio- increases exponentially with the drift value. So it can explain very different values fixed by analysts' for Zeltia share. Also percentage of abandon paths is decreasing in the drift value. Another variable with an important effect in our model is the interest rate: higher interest rates lead bigger option values. Finally, we showed that an increased in the time to completion for the project to cause a decreasing in the probability of survival for the whole portfolio, and the intensity of this fallen depends on the copula considered (in our case t copula produces the most big effect in the survival probability).

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Table 1. Expected cost per phase (euro million 2003)

	$K_{prec,0}$	$K_{I,0}$	$K_{II,0}$	$K_{III,0}$	$K_{ap,0}$
Yondelis			9.28	40.58	2.07
Aplidine			18.55	40.58	2.07
Kahalalide		0.99	7.95	17.39	0.89
ES-285		1.99	7.95	17.39	0.89
Preclinical 5	57.84	3.31	13.25	28.99	1.48

Table 2. Data to model FCF (euro million 2003)

	Peak sales	**Peak FCF**	**Initial FCF**
Yondelis	1537.90	82.81	1.59
Aplidine	1534.47	82.63	1.18
Kahalalide	799.22	43.04	0.49
ES-285	799.22	43.04	0.39
Preclinical 5	1214.65	65.41	0.24

Table 3. Valuation of PharmaMar without dependence between projects
(euro millions, 2003)

	Value with option	Value without option	Option Value
Yondelis	436.52	436.36	0.16
Aplidine	283.01	282.79	0.21
Kahalalide	106.20	106.06	0.14
ES-285	81.87	81.69	0.18
Preclinical 5	18.86	8.70	7.17

Table 4.a Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.291 Gumbel param 2	Value with option	Value without option	Option Value
Yondelis	547.44	547.11	0.33
Aplidine	503.36	503.00	0.36
Kahalalide	236.84	236.66	0.17
ES-285	212.66	212.44	0.44
Preclinical 5	158.59	157.66	0.93

Table 4.2.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 Gumbel param 2,4	Value with option	Value without option	Option Value
Yondelis	546.82	546.49	0.32
Aplidine	503.13	502.75	0.37
Kahalalide	237.24	237.07	0.17
ES-285	212.65	212.35	0.30
Preclinical 5	155.68	154.98	0.70

Table 4.3.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 Frank param 2	Value with option	Value without option	Option Value
Yondelis	547,16	546,83	0,32
Aplidine	503,13	502,75	0,37
Kahalalide	237,24	237,07	0,17
ES-285	212,65	212,99	0,33
Preclinical 5	157,84	157,39	0,45

Table 4.4.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 Frank param 2,4	Value with option	Value without option	Option Value
Yondelis	547,81	547,48	0,33
Aplidine	503,25	503,00	0,25
Kahalalide	235,57	234,99	0,57
ES-285	211,00	210,54	0,45
Preclinical 5	156,73	156,23	0,50

Table 4.5.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 Clayton param 2	Value with option	Value without option	Option Value
Yondelis	547,19	546,86	0,32
Aplidine	502,70	502,33	0,36
Kahalalide	236,48	236,11	0,37
ES-285	210,76	210,29	0,47
Preclinical 5	157,17	157,33	0,16

Table 4.6.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 Clayton param 2,4	Value with option	Value without option	Option Value
Yondelis	545,96	545,64	0,31
Aplidine	500,36	499,65	0,70
Kahalalide	234,54	234,01	0,53
ES-285	212,53	212,11	0,41
Preclinical 5	156,33	156,03	0,29

Table 4.7.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 Gaussian	Value with option	Value without option	Option Value
Yondelis	-1,38	-2,66	1,27
Aplidine	-1,45	-2,89	1,44
Kahalalide	-0,40	-1,02	0,61
ES-285	-0,89	-1,44	0,55
Preclinical 5	-2,86	-5,44	2,5792

Table 4.8.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 t	Value with option	Value without option	Option Value
Yondelis	-1,38	-2,60	1,21
Aplidine	-1,65	-2,99	1,33
Kahalalide	-1,08	-2,11	1,03
ES-285	-0,66	-1,89	1,23
Preclinical 5	-3,00	-6,93	3,91

Table 4.9.a Valuation of PharmaMar with dependence between projects(euro millions, 2003)

Drift 0.291 Fan Yu	Value with option	Value without option	Option Value
Yondelis	25,24	25,06	0,19
Aplidine	14.96	14.77	0,18
Kahalalide	4,54	4,49	0,05
ES-285	2,65	2,57	0,07
Preclinical 5	-6,92	-12,56	5,63

Table 4.10.b Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 Gumbel param 2	Value with option	Value without option	Option Value
Yondelis	42,70	37,92	4,77
Aplidine	20,27	10,70	9,56
Kahalalide	7,54	2,69	4,85
ES-285	3,26	-4,17	7,43
Preclinical 5	-8,18	-80,88	72,70

Table 4.11.b Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 Gumbel param 2,4	Value with option	Value without option	Option Value
Yondelis	42,33	34,65	7,68
Aplidine	22,34	11,22	11,12
Kahalalide	6,79	1,99	4,80
ES-285	3,56	-5,68	9,25
Preclinical 5	-8,99	-82,89	73,89

Table 4.12.b Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 Frank param 2	Value with option	Value without option	Option Value
Yondelis	42,60	37,81	4,78
Aplidine	21,67	11,88	9,78
Kahalalide	7,82	3,00	4,82
ES-285	2,99	-7,88	9,64
Preclinical 5	-7,99	-80,17	72,17

Table 4.13.b Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 Frank param 2,4	Value with option	Value without option	Option Value
Yondelis	42,97	37,99	4,97
Aplidine	21,95	1,59	20,36
Kahalalide	7,98	3,00	4,97
ES-285	3,89	-5,74	9,64
Preclinical 5	-7,88	-79,99	72,10

Table 4.14.b Valuation de PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 Clayton param 2	Value with option	Value without option	Option Value
Yondelis	42,64	37,88	4,75
Aplidine	21,09	12,00	9,09
Kahalalide	8,00	3,65	4,35
ES-285	3,29	-7,33	10,63
Preclinical 5	-8,55	-79,80	71,25

Table 4.15.b Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 Clayton param 2,4	Value with option	Value without option	Option Value
Yondelis	42,76	37,99	4,77
Aplidine	22,78	12,55	10,22
Kahalalide	7,99	3,78	4,20
ES-285	3,05	-7,72	10,78
Preclinical 5	-7,34	-89,22	81,87

Table 4.16.b Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 Gaussian	Value with option	Value without option	Option Value
Yondelis	-0,66	-0,19	0,47
Aplidine	-0,38	-1,22	0,83
Kahalalide	-0,40	-1,02	0,61
ES-285	-0,39	-0,93	0,53
Preclinical 5	-1,03	-1,89	0,85

Table 4.17.b Valuation of PharmaMar with dependence between
projects(euro millions, 2003)

Drift 0.115 t	Value with option	Value without option	Option Value
Yondelis	-14,88	-27,88	13,00
Aplidine	-16,78	-25,88	9,10
Kahalalide	-16,88	-19,29	2,40
ES-285	-12,99	-23,11	10,11
Preclinical 5	-19,88	-28,88	9,00

Table 4.18.b Valuation of PharmaMar with dependence between projects
(euro millions, 2003)

Drift 0.115 Fan Yu	Value with option	Value without option	Option Value
Yondelis	32,83	29,06	3,77
Aplidine	12,95	5,22	7,73
Kahalalide	3,88	0,12	3,76
ES-285	0,94	-5,18	6,12
Preclinical 5	-8,00	-48,77	40,76

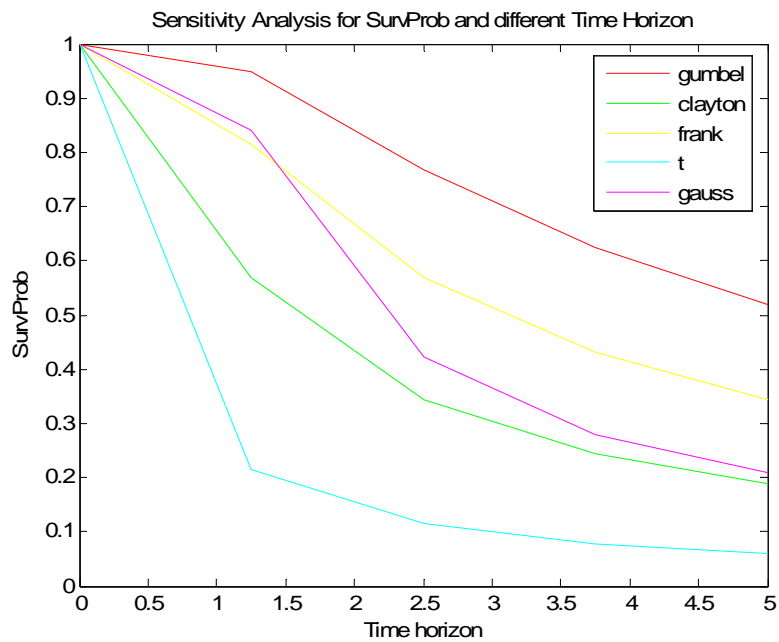Figure 1. Sensitivity Analysis: portfolio survival probabilities vs. Time horizon values

Figure 2. Sensitivity Analysis for Yondelis: Drug value
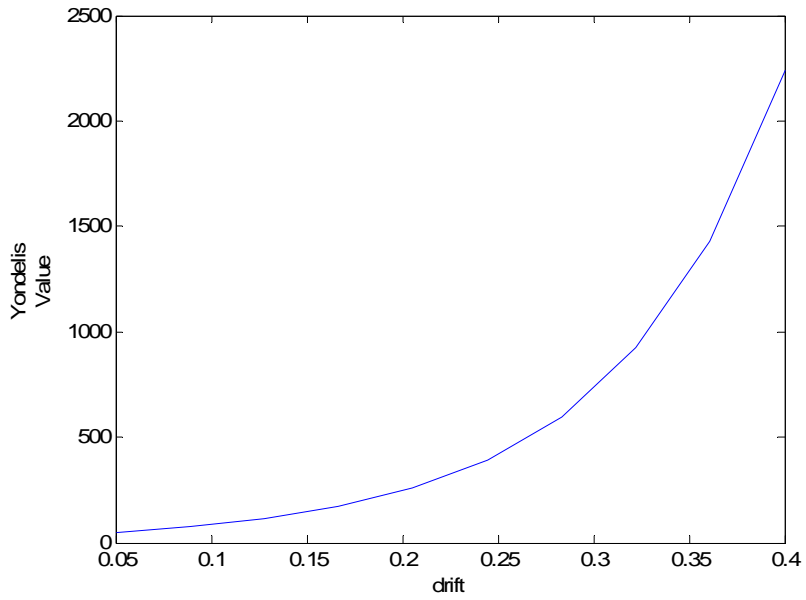And different drift values

Figure 3. Sensitivity Analysis for Yondelis: Abandon
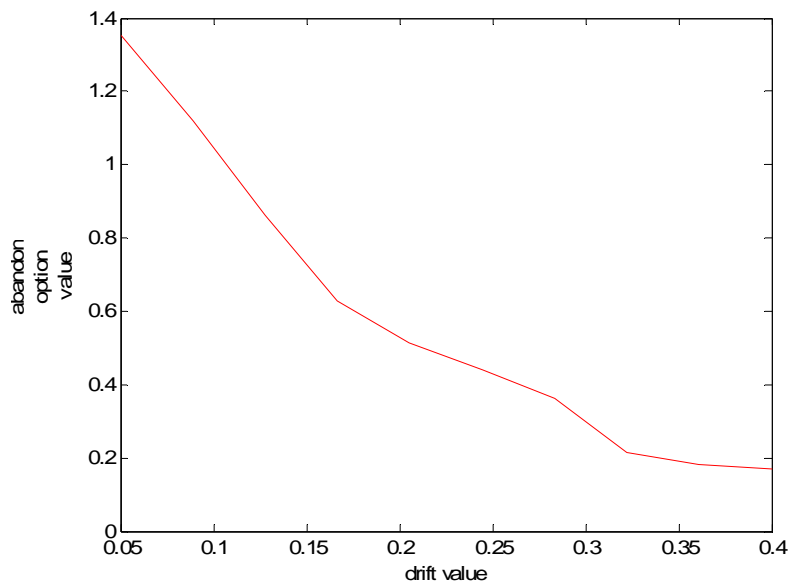Option Values for different drift values

Figure 4. Sensitivity Analysis for Yondelis:
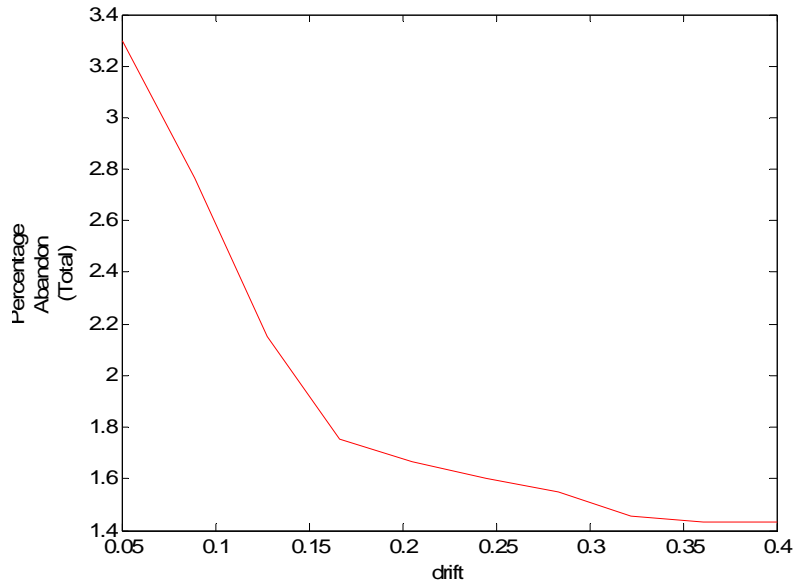Abandon paths percentage for different drift values

Figure 5 Sensitivity Analysis for Yondelis:
Option Value to abandon for different interest rates