VALUATION OF A BIOTECH COMPANY: A REAL OPTIONS APPROACH

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CEMFI Working Paper No. 0420

November 2004

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This paper is based on the Master project by Diego Piñeiro at CEMFI, 2003 under the supervision of Angel León. We are very indebted to J.M. Jimeno (PharmaMar) and J.I. Morales (BBVA) for their helpful comments. We would also like to thank to seminar participants at both the XI Foro de Finanzas in Alicante on November 13-14, 2003 and Bolsa de Madrid on July 1, 2004. The contents of this paper are the sole responsability of the authors.
Angel León acknowledges the financial support provided by the Ministerio de Ciencia y Tecnología grant BEC2002-03797 and the Generalitat Valenciana grant CTIDIA/2002/103.
Diego Piñeiro acknowledges the financial support for the Master project provided by the Bank of Spain and Caixa Galicia.

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Abstract

The aim of this paper consists of valuating a real biotechnology firm that is based on a portfolio of several drug development projects at different phases. They are patent-protected R&D projects and their values are obtained by implementing an extension of the real options approach in Schwartz (2004). To be precise, the life cycle of the drug is modeled by considering an alternative and more realistic behavior for the evolution of the FCF, different from the standard Geometric Brownian motion, once the peak sales is reached till the patent expiration, we will also allow for the possibility of the generic entrance once the patent expires. Different expected costs to completion are considered here, that is one equation to each compound; a different probability of catastrophic event depending on the phase and so on. It is shown that the abandonment value is higher for those compounds being in preclinical testing than those in clinical trials.

JEL Codes: C15, C61, C63, G13, G31.
Keywords: Patent, R&D phase, drug, real options, investment cost, free cash flow, generics, life cycle, Monte Carlo simulation.

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1 Introduction

This article is about the valuation in the early stages of a real biotech company without any drug brought to the market yet. The assets for this company consist of a portfolio of promising research and development (R&D) projects which are patent protected for the development of a new drug each. It is well known that the discounted cash flow (DCF) technique results inadequate to valuate these firms because it does not capture the flexibility inherent in these projects. This flexibility is captured through the well known real options methodology. This paper will focus on the real options approach by Schwartz (2004), with some extensions, to valuate this sort of firms with no revenues yet. The firm value will be based on the sum of the values of its drug development projects.

The patent life for these projects are on average about 20 years. The R&D process implicit in these projects takes up plenty of time for completion. Once the research is completed, the new drug is marketed and the firm enjoys a monopolistic situation till the expiration of the patent. From that moment, the entrance of generics is allowed and it starts decreasing the competitive advantage for the leader firm. It might happen that the firm runs out all the patent life for research without completion. Different uncertainties are implied under a R&D project: the first uncertainty is about the investment cost required for the completion of the project. There is a learning process that only occurs while there is investment. The dynamics for the expected investment costs will be described in Pindyck (1993). Once the cost for completion is finished, the drug is marketed and there is a second uncertainty about the future profits or free cash flows (FCF) which can be driven by alternative processes assumed in this study. We will start with the benchmark

process for the FCF behavior that is the Geometric Brownian motion. A drawback for this process is that it could lead to a possible overvaluation of the project as Bollen shows (1999). Because of this, we will model the life cycle of the drug under different alternatives for the FCF behavior. Finally, another uncertainty is about catastrophic events that lead suddenly to the failure of the project. This uncertainty will be considered as a rare event that will be driven by a Poisson process. The possibility for abandonment may be 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.

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 order of stages: discovery, preclinical testing, phases I, II and III from clinical trials, submission to either the Food and Drug Administration (FDA) or the European Medical Evaluation Agency (EMEA) and finally, phase IV trial. As Schwartz and Moon (2000) quote: "*for pharmaceutical drugs 1 in 4000 compounds discovered eventually results in an FDA approved drug, and 1 in 5 drugs to enter phase I clinical trials results in an FDA approved drug. There is some evidence that the probabilities of success are higher for biopharmaceutical drugs*".

In this paper, we will compute the valuation of PharmaMar which is the research-intensive subsidiary of Zeltia, the Spanish listed biotechnology company mainly focussed on the development of novel cancer drugs. The four leading projects of PharmaMar correspond to compounds at either phases I or II while the others are at the preclinical testing. We will show that those preclinical projects exhibit larger abandonment option values than those at

clinical trials.

Other methodologies under the real options framework but different to the approach exhibited here for the valuation of early stage biotech firms or pharmaceutical ones are, for example, the work by Kellog and Charnes (2000) that is based on the binomial lattice with the addition of a growth option; Copeland and Antikarov (2001) implement compound rainbow options with binomial trees;[1] a similar approach is the one by Shockley et al. (2003) who also use compound options and Schwartz and Moon (2000) who deal with some issues discussed in Schwartz (2004) such as the same three uncertainties explained before but there are other differences. They obtain a solution by solving a partial differential equation. This kind of solution is possible because the time to end the costs to completion does not enter into the solution of the problem, while it does in Schwartz (2004). The owner of the project will start receiving cash flows depending on the duration of the R&D investment. The investment duration is under Schwartz (2004) a random variable and now the solution cannot be solved as before but using simulation techniques, exactly the Monte Carlo simulation methodology by Longstaff and Schwartz (2001).

The rest of this paper is organized as follows. The next section provides PharmaMar's portfolio of patents. Section 3 presents the continuous time model for valuation. Section 4 shows how to implement the continuous model. Section 5 deals with both the data and parameter values needed in practice to implement the model. Section 6 presents the first simulation results of the valuation for each compound. Section 7 provides an exhaustive sensitive analysis. Section 8 concludes.

[1] See chapter 11 from their book.

2 PharmaMar as a portfolio of patents

The key driver of Zeltia's valuation and performance is PharmaMar which is Zeltia's drug development subsidiary. According to analysts, PharmaMar's valuation is about 80% to 90% of Zeltia's valuation. Since 1986 PharmaMar has been researching novel cancer drugs based on compounds derived from marine sources. The remainder of Zeltia's assets are less significant in terms of valuation. These will be the non-core assets[2] that have been historically important for the R&D financing purposes.

As we mentioned before, PharmaMar consists of a portfolio of R&D projects or patents. To be precise, at that moment there were four drugs in clinical trials, half in phase II and half in phase I, and five compounds in preclinical trials. The most advanced clinical compound was Yondelis (ET-743) that was granted the "orphan status"[3] in November 2001 by EMEA for the treatment in patients with Soft Tissue Sarcoma (STS) and at that moment, on May 2003, it was still waiting for the approval of EMEA. It also showed promise in patients with other cancer types such as ovarian cancer, breast cancer and so on. Given the different indications in Yondelis, the treatment for STS patients was the most developed one. Aplidine is the second more advanced product that has shown to be active in a large number of cancer types, of which colorectal cancer has the largest incidence. Another product is Kahalalide-F and its main potential indication is prostate cancer, though it has also shown activity on breast cancer and hepatoma. Finally,

[2] Zeltia's non-core assets include: PharmaGen, Zelnova, Xylazel and real estate (in concrete, three buildings in the Madrid area).

[3] This status is granted to those drugs showing activity against a pathology that affects a *minimum percentage* of the population and there is no any available effective drug. This status allows for tax benefits, aids to research, a monopoly situation for seven years since the drug is approved and so on.

the compound ES-285 has shown evidence of solid tumors.

To conclude, the number of pathologies for the clinical compounds are 7, 7, 3 and 3 for Yondelis, Aplidine, Kahalalide-F and ES-285 respectively. Meanwhile for the preclinical ones, since they are in a very early stage of R&D joint with the lack of information from PharmaMar, it is unknown what sort of pathology these compounds could be effective. In consequence, we will assume the amount of 5 which is the mean for the clinical pathologies of the four clinical products of PharmaMar. We will consider this average as an estimate of the possible therapeutical lines for any preclinical compound.

3 Continuous time model

Once a molecule has been discovered and patented for a potential therapeutical use, a long research process starts where several costs depending on the development phase will take place. If the compound overcomes every phase, it will be ready for commercial launch. Our model is based on a short extension of Schwartz's (2004) model. Specifically, we implement a different expected cost to completion in each phase for our empirical valuation, we let the possibility of generic entrance once the patent expires and also an alternative behavior for the FCF dynamics before the patent expiration.

3.1 Investment cost uncertainty

The dynamics of the expected cost to completion of a R&D project is described in Pindyck (1993) and it is implemented in both Schwartz and Moon (2000) and Schwartz (2004) for the valuation of pharmaceutical patents and R&D projects.[4] The dynamics of the expected cost to completion for a given

[4]Schwartz and Zozaya (2000) also use the Pindyck's model (1993) for the expected cost to completion in the valuation of information technology investments.

phase s is

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

where $K_s(t)$ is the expected real cost to complete the ongoing phase before starting the next phase, that is, $K_s(t) \equiv E\left[\widetilde{K}_s(t)\right]$ where $\widetilde{K}_s(t)$ denotes the remaining real cost to complete phase s, τ^*_s represents the total random time needed for completing phase s, I_s is the rate of annual real investment which is assumed constant, σ_s is the volatility parameter, $dz_s(t)$ is the increment of a Wiener process which is uncorrelated with both the market portfolio and the aggregate wealth though it will be correlated with the free cash flow diffusion process defined later, and finally s denotes the phase indicator: preclinical, phase I, phase II, phase III and approval. To simplify, the instantaneous correlation between $dz_i(t)$ and $dz_j(t)$ is assumed to be zero where i and j denote any two different stages mentioned before.[5]

Prior to the beginning of any phase s, the firm expects that the total cost to complete the phase s research, $K_s\left(\tau^*_{s-1}\right)$, is equal to $K_{s,0}$ which is the starting value associated with the phase s cost equation (1). It is worth mentioning that, at the moment of the valuation of PharmaMar, neither compound will meet at the beginning of any phase but a certain period of time will have passed in the current phase s for the compound under consideration. It means that $K_{s,0}$ will really denote the remaining expected real cost to complete the phase s, meanwhile for every subsequent phase h it holds that $K_h\left(\tau^*_{h-1}\right)$ is equal to $K_{h,0}$ which is the total expected real cost in phase h. Notice that those expected costs that will happen later (denoted

[5] Hsu and Schwartz (2003) assume that this correlation is different from zero. A non-zero correlation would mean that revisions in the firm's expectation on the cost for completing phase i would carry out revisions in a more advanced stage j about its expected costs to completion.

as $h > s$) are evaluated now.

The drift component in equation (1), which is the rate of investment I_s, is a control variable: the larger is the investment rate, the lower is the expected cost to completion. This means that investment implies a "learning" process and thus, the expected cost decreases only when there is investment. The uncertainty $dz_s(t)$ corresponds to the type of uncertainty that Pindyck (1993) calls *technical uncertainty* which can only be resolved by investing. Note that the variance of the diffusion process is linear in both I_s and K_s. This implies again that uncertainty decreases with a lower $K_s(t)$. Note that, when $I_s = 0$ then the cost to completion does not change. Since the variance is linear in investment, there will be only two possible solution values for the control variable I_s: to invest zero or at the maximum possible rate.[6] It is also shown that the variance for the cost to completion $\widetilde{K}_s(t)$ has the following analytical expression:

$$Var_t\left[\widetilde{K}_s(t)\right] = \frac{\sigma_s^2}{2-\sigma_s^2}K_s^2. \tag{2}$$

This variance equation represents a conditional variance, denoted as $Var_t[\cdot]$, where the conditional term is the remaining expected cost to complete phase s evaluated at time t with value $K_s(t)$ equals K_s.[7] For more details, see equation (A.5) from Appendix A.1 in Pindyck (1993). Note that the larger is either σ_s^2 or K_s, the larger is the variance.

Given the process (1), we can obtain the probability that the total cost to completion at phase s of the project is less than k, conditional on $K_{s,0}$, is given by

[6] The equation (1) gives rise to a bang-bang solution for the optimal control problem. For more details, see Schwartz and Moon (2000).

[7] That is, $Var_t\left[\widetilde{K}_s(t)\right]$ is the shortening of $Var\left[\widetilde{K}_s(t)\,|K_s(t) = K_s\right]$.

$$P\left[K_s\left(t\right) \leq k \left| K_{s,0}\right.\right] = 1 - \sum_{n=0}^{\infty} \frac{e^{-y} y^{n+1+x}}{\Gamma\left(n+2+x\right)} \tag{3}$$

where $y = 2K_{s,0}/k\sigma_s^2$, $x = 2/\sigma_s^2$ and $\Gamma\left(\cdot\right)$ denotes the gamma function. The above cumulative density function can be obtained from Cox and Ross (1976) by making several substitutions carried out by Schwartz and Moon (2000) in their Appendix A. To shorten, we will denote (3) as $H_s\left(k\right) = p$, with p representing the probability that is the right-hand side of the above equation. So, given a value of p, we could obtain the value of k which guarantees equation (3). In our Appendix, we will show some quantiles of the distribution $K_s\left(t\right)$ conditional on $K_{s,0}$ per phase for each compound.[8]

We conclude by remarking that the stochastic process (1) is a reasonable representation of uncertainty about expected cost in R&D investment for drugs.[9] There is empirical evidence on estimates of the costs of pharmaceutical innovation by DiMasi et al (2003) showing[10] that those phases with higher average costs show more dispersion and so, equation (2) holds.

3.2 Free cash flow uncertainty

Once the R&D investment has finished succesfully and the drug has achieved the approval for market launch, the firm will obtain profits until the patent expiration. From this moment, sales will decrease gradually and at the end, the drug will dissappear due to the market is flooded with the generics. This

[8] To compute the p-quantile of $K_s\left(t\right)$, denoted as k_p, we will truncate the value of n in (3) to $n = 30$. The k_p value will be that value of k which is the solution of minimizing the following objective function: $\left(H_s\left(k\right) - p\right)^2$. The values of $K_{s,0}$ and σ_s that we need to compute (3) can be seen later, to be precise in subsection 5.2.

[9] A different equation to model the cost of uncertainty from (1) can be found in Hsu and Schwartz (2003). This alternative equation is nested in Pindyck's model (1993). In concrete, $dK_s\left(t\right) = -I_s dt + \sigma_s dz_s\left(t\right)$.

[10] See Table 5 on page 171.

would be the life cycle of the drug.[11] We implement a life cycle model that consists of two stages: the first ends with the patent expiration where we assume that only one firm is investing in R&D for a drug targeted to cure a certain disease. Summing up, there is no competitor and so, the firm is under a monopolistic situation while the patent is alive.[12] The second stage is about the entrance of generic drugs which is a period of free competition. Here, we will assume that the market share for the monopolistc firm will tend to decrease gradually till reaching zero.

3.2.1 Stage 1

To begin with, we assume the standard Geometric Brownian motion,[13] henceforth GBM, for the FCF holding the period from the R&D completion date until the patent expiration. The GBM under the real measure is driven by the following equation:

$$dC_1(t) = \alpha C_1(t)\,dt + \phi C_1(t)\,dz_c(t) \tag{4}$$

where $C_1(t)$ denotes the real FCF, α is the drift, ϕ is the volatility parameter and $dz_c(t)$ is the increment of a Wiener process that is correlated with the market portfolio. Under the risk neutral measure, the dynamics of the FCF is given by

$$dC_1(t) = \alpha^* C_1(t)\,dt + \phi C_1(t)\,dz_c^*(t) \tag{5}$$

such that α^* is the risk-adjusted drift, that is $\alpha^* = \alpha - \eta$ where η is the risk premium, and $dz_c^*(t)$ is the increment of a Wiener process under the risk-neutral measure, i.e. $dz_c^*(t) = dz_c(t) + (\eta/\phi)\,dt$.

[11] See, for example, Myers and Howe (1997), Grabowski (2002) for the life cycle of drugs.

[12] The possibility of two different drugs for the same disease can be seen in Miltersen and Schwartz (2004). If both drugs are succesful, there will be a duopoly situation.

[13] This process for the FCF behavior is also implemented for drug patents in both Schwartz and Moon (2000) and Schwartz (2004).

3.2.2 Stage 2

Once the patent expires, we consider the entrance of generics and assume that the behavior of the FCF will be decreasing till getting to zero at the end. The FCF dynamics corresponding to this period is described as

$$dC_2(t) = -\delta(t) C_1(T) dt, \qquad T \leq t \leq T^* \tag{6}$$

where T denotes the patent expiration date, $C_1(T)$ is the FCF starting value for stage 2, T^* is the date where FCF equals zero, i.e. $C_2(T^*) = 0$, and $\delta(t)$ is a deterministic step function defined as

$$\delta(t) = \begin{cases} \delta_1; & t \in [T, t_1) \\ \delta_2; & t \in [t_1, t_2) \\ \cdots & \cdots \\ \delta_m; & t \in [t_{m-1}, T^*] \end{cases}$$

where δ_i represents the annual growth rate of FCF verifying that $1 > \delta_1 > \delta_2 > \cdots > \delta_m > 0$ because of the generic competition.

We will also let correlation between any increment of a Wiener process $dz_s(t)$ and $dz_c^*(t)$:

$$dz_s(t)\, dz_c^*(t) = \rho_{sc} dt. \tag{7}$$

Later on, in subsection 7.1, we will introduce a different life cycle pattern where the only difference will be on modelling stage 1. We will divide this stage into two periods: the first would go from the R&D completion date to the peak sales date, denoted as τ_p, and we will again assume a GBM while for the second period, going from τ_p to T, the GBM will be replaced with another process. The reason for this alternative way of modelling stage 1 is that, although (4) would seem a quite reasonable behavior for the evolution of the FCF until date τ_p, we believe according to Bollen (1999) that the same

equation would not capture adequately the FCF behavior from τ_p to T since it is not expected to grow the FCF at the same level before τ_p but at a lower or constant one, and so on. Once that τ_p is reached, a different model for the dynamics of the FCF can be implemented as a solution in order not to get a possible biased valuation of the project. In our case, an overvaluation under the model introduced before, or benchmark model, will occur as shown in subsection 7.1.

4 Model implementation

Unfortunately, we cannot obtain the patent valuation as a closed form solution for the continuous model presented before. The algorithm employed here for a numerical solution is based on Schwartz's (2004). It consists in the optimal stopping algorithm of Longstaff and Schwartz (2001), which is implemented originally to solve numerically American options by using a technique that combines Monte Carlo simulation with least squares regression. This methodology is suitable to value patents for drugs since we let the possibility of giving up the project, that is to exercise the abandonment option, at any moment under the whole investment period to completion. Since its implementation involves working under a discrete time framework, we will need previously an approximation of the continuous model.

4.1 Discrete approximation

The discrete approximations to equations (1), (5) and (6) are respectively:

$$K_s(t+\Delta) = K_s(t) - I_s\Delta + \sigma_s\sqrt{I_s K_s(t)\,\Delta}\,\xi_s(t) \tag{8}$$

$$C_1(t+\Delta) = C_1(t)\exp\left[(\alpha^* - 0.5\phi^2)\Delta + \phi\sqrt{\Delta}\xi_c(t)\right] \tag{9}$$

$$C_2(t+\Delta) = C_2(t) - C_1(T)\int_t^{t+\Delta} \delta(u)\, du \tag{10}$$

where Δ is the time step size, $\xi_s(t)$ and $\xi_c(t)$ are correlated standard normal variates with ρ_{sc} as the correlation parameter and the correlation between any two variates $\xi_{s_1}(t)$ and $\xi_{s_2}(t)$, where s_1 and s_2 represent two different phases, is assumed to be equal to zero. Define T more exactly as the remaining life in years of the patent from nowadays till expiration or stage 1, M as the last period, measured in years, in obtaining FCF such that $M > T$, $N_1 \equiv T/\Delta$ as the number of periods, without including the starting period, per path in the simulation and finally N_p is the number of paths. For each path i, where $i = 1, ..., N_p$, we will simulate vectors of length N_1 corresponding to both equations (8) and (9). Its elements are denoted respectively as $K(i, j\Delta)$ and $C_1(i, j\Delta)$ where $j = 0, 1, ..., N_1$. Note that for $j = 0$ we will have the the corresponding starting values. To shorten, they will be denoted as $K(0)$ and $C_1(0)$ since they are the same value for any path i. The element $K(i, j\Delta)$ denotes the expected real cost in path i to complete the investment totally:

$$K(i, j\Delta) = K_{s(i,j)}(i, j\Delta) + \sum\nolimits_{h>s(i,j)} K_{h,0}$$

where $s(i, j)$ denotes that phase happening in period $j\Delta$ conditioned to path i and $K_{h,0}$ is the total expected real cost of any subsequent phase h. After the cost to *approval* completion reaches zero at a given period $q_i\Delta$ such that $q_i \leq N_1$, then $K(i, j\Delta) = 0$ for $j \geq q_i$. Note that from period $q_i\Delta$ till the patent expires at period T, the firm will obtain a stream of cash flows under the monopolistic situation, or stage 1, and we will only select from path i those elements $C_1(i, j\Delta)$ such that $j \geq q_i$. Meanwhile, at stage 2 ,or the generic entrance, we will simulate vectors of length N_2 where N_2 represents the number of periods at this stage, that is $M/\Delta - N_1$. We will

set any element of this vector as $C_2(i, k\Delta)$ where $k = 1, ..., N_2$. To shorten, let $C(i, l\Delta)$ represent the FCF for period $l\Delta$ such that $l = 0, 1, ..., M/\Delta$ for a given path i, then

$$C(i, l\Delta) = \begin{cases} C_1(i, l\Delta); & l \leq N_1 \\ \\ C_2(i, l\Delta); & l > N_1. \end{cases}$$

We will select for each row i those elements verifying that $l \geq q_i$.

4.2 Algorithm

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, that is, $\forall j < q_i$ since $K(i, j\Delta) > 0$. Let $W(i, j\Delta)$ denote the value of the patent to each point in time for a given path. Conditional on not having abandoned the project before, the patent expiration date is characterized by the following boundary condition:

$$W(i, T) = \sum_{k=0}^{N_2} \exp(-r\Delta k) C(i, T + \Delta k) \tag{11}$$

where r is the risk-free interest rate per year. At any date j before the patent expiration and after completing R&D investment, that is $q_i \leq j < N_1$, the patent value is computed recursively by

$$W(i, \Delta j) = \exp(-r\Delta) W(i, (j + 1)\Delta) + C(i, j\Delta).$$

Meanwhile for $j < q_i$ (unfinished R&D investment), the project could be given up because of two different failures: one, due to the optimal exercise of the abandonment of the option and second, the presence of catastrophic events such as a financial disaster of the firm, the departure of lead scientists

from any R&D project, high toxicity, and so forth. Since these events are rare, they could be defined as Poisson events as Schwartz and Moon (2000) suggest and so, the probability of a rare event per year would be the intensity parameter λ. We will consider a different intensity, denoted as λ_s, per phase. According to Brennan and Schwartz (1985), we will measure the impact on the valuation caused by these events as an increment of the discount rates since the project before investment completion is riskier in the light of these kind of events. Summing up, the discount rate per year will be set to $r + \lambda_s$. If we take all those paths in which investment is not completed, the conditional expected value of continuation is obtained by regressing the discounted value of the project, $\exp\left(-\left(r + \lambda_{s(i,j)}\right)\Delta\right) W(i, (j+1)\Delta)$, onto a set of basis functions of the state variables[14] at time $j\Delta$. If we denote $\widehat{W}(i, \Delta j)$ the fitted dependent variable of the above regression, we determine the project value $W(i, j\Delta)$ at date $j\Delta$, as in Schwartz (2004), according to the following rule:

$$W(i, j\Delta) = \begin{cases} \widehat{W}(i, j\Delta) - I_{s(i,j)}\Delta; & \widehat{W}(i, j\Delta) > I_{s(i,j)}\Delta \\ \\ 0; & \widehat{W}(i, j\Delta) < I_{s(i,j)}\Delta \end{cases}$$

where $I_{s(i,j)}\Delta$ denotes the marginal investment carried out at period $j\Delta$. Note that $I_{s(i,j)}$ is a piecewise function having the same value for those steps j in path i that correspond to the same phase. We also set $W(i, k\Delta) = 0$ $\forall k > j$ when abandonment is better than waiting at period $j\Delta$. By rolling back in time and repeating the procedure at each date $j\Delta$, we can fill out the corresponding columns of the matrix $W \equiv [W(i, j\Delta)]$. Note that the optimal stopping time rule consists of obtaining for each path i the minimum $j\Delta$ such

[14] We will consider here as independent variables the following ones: constant, K, C, K^2, C^2, $K * C$, $K^2 * C^2$, $K * C^2$ and $K * C^2$.

that the abandonment is better than continuing. Once W is filled out, the value of the project is generally not equal to the average of the $W(i,0)$'s. Indeed, we will use the optimal stopping rule generated by the algorithm so as to 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 $j_i^\star$ as the optimal stopping date for path i, (c) discount all the cash flows to time zero and (d) take the average of the N_p paths. Note that there are two possibilities under (b): either a stopping time before T, that is $j_i^\star < q_i$, then

$$V(i,j\Delta) = \begin{cases} -I_{s(i,j)}\Delta; & j \leq j_i^\star \\ \\ 0; & j_i^\star < j \leq N_1 \end{cases}$$

or no stopping time:

$$V(i,j\Delta) = \begin{cases} -I_{s(i,j)}\Delta; & j \leq q_i \\ \\ C\left(i,j\Delta\right); & q_i \leq j < N_1 \\ \\ W(i,T); & j = N_1. \end{cases}$$

Finally, we will obtain the estimated value of the patent V_0 by discounting the free cash flows to $t = 0$ and averaging them over all paths:

$$V_0 = \frac{1}{N_p} \sum_{i=1}^{N_p} \sum_{j=0}^{N_1} \exp\left(-rj\Delta\right) V(i,j\Delta).$$

5 Data and parameter estimates

The data used in this work come from several sources. In concrete, data from the PharmaMar firm, the pharmaceutical industry and some financial analysts' reports. The valuation of PharmaMar was carried on May 30, 2003. All the values are expressed in monetary amounts corresponding to that time.

5.1 R&D phases

At the moment of the valuation, Yondelis was about the middle of phase II, the beginning of phase II for Aplidine, half phase I for Kahalalide-F, the start of phase I for ES-285 and five compounds in preclinical phase, denoted as preclinical J such that $J = 1, ..., 5$, where depending on the compound: only 1 (preclinical 1), 1.5 (preclinical 2), 2 (preclinical 3), 2.5 (preclinical 4) or 3 (preclinical 5) years remained till finishing this phase. The expected average lifetime, in years, each phase will be:[15] 3.5 (preclinical), 1.5 (phase I), 2 (phase II), 2.5 (phase III) and 1.5 (approval).

5.2 Costs

The costs per patient associated with PharmaMar's clinical trials are €10,000, €8,000 and €5,000 to phases I, II and III respectively. According to Kelly (2003), it holds for the U.S. pharmaceutical sector that the average of patient volunteers at phases I, II and III range from 20 to 100, 100 to 500 and 1,000 to 5,000. In this paper, we will consider the average quantities: 60, 300 and 3,000 respectively. The clinical trial costs to phases I to III comprise 29% of total US pharmaceutical cost as shown at Table 1.

Since these data come from the pharmaceutical sector, they do not really correspond to the biotech sector where PharmaMar really belongs to. According to analysts' reports, we will assume as total costs to PharmaMar exactly 2/3 of the standard pharmaceutical costs. This cost reduction for PharmaMar is due to the short toxic level since these drugs are obtained from marine organisms. In August 2001 PharmaMar signed an agreement with Ortho Biotech, a subsidiary of Johnson & Johnson (J&J), for devel-

[15] See Sweeny (2002), Tang (2002) and some analysts' reports.

opment and marketing of Yondelis around the world. Some points of the agreement are: (a) J&J will market around the world except Europe where PharmaMar will have exclusive rights to market the drug while it will receive royalties from J&J, and (b) both companies will share the cost of future clinical development, with J&J funding 65% and PharmaMar 35% of the costs. We will assume that this last point will also hold for every potential drug. As a result of this available infomation and other that we do not report here to shorten, we finally construct Table 2 which shows the expected cost per phase $K_{s,0}$ for each compound from PharmaMar. It is worth mentioning that the expected cost corresponding to a certain phase is the same for each therapeutical line for any compound. So, $K_{s,0}$ for a given compound in Table 2 is the result of adding all the expected costs in that phase together corresponding to every pathology from the product under consideration. For instance, note that for all the preclinical compounds, the forecast of these costs are the same for phases I, II, III and approval (ap) where each cost is obtained by adding the costs of the five therapeutical lines as we mentioned in section 2. It is also shown in Table 2 that the differences in the cost amounts for the preclinical products in the preclinical stage, that is $K_{prec,0}$, are different. The reason is based on the following idea: if the five compounds had started at the same time, then $K_{prec,0}$ would be the same for every compound but this is not the case here, so we have adjusted the total expected cost corresponding to the preclinical phase by the remaining expected average lifetime in the preclinical stage in each case, so $K_{prec,0}$ will denote the remaining cost to end that phase for a given product. Something similar occurs for the clinical ones, note for instance in Table 2 that $K_{II,0}$, $K_{III,0}$ and $K_{ap,0}$ are the same for the products Kahalalide-F and ES-285, the reason is because both have the same number of pathologies equal to 3 and so on. Summing up, the total

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. So, if we look at our Appendix notice that we do not show some quantiles for several phases from some compounds since they are the same as other that appear in any of the tables from the Appendix due to the reason explained above.

How do we obtain the parameters I_s and σ_s from equation (1)?. The annual rate of investment per phase, I_s, will be obtained by dividing the expected cost to complete phase s, K_s, by the expected lifetime of phase s given in subsection 5.1. Meanwhile, the volatility parameter σ_s can be obtained from equation (2) once we get estimates for both the square root of $Var_t\left[\widetilde{K}_s(t)\right]$ and K_s,[16] which can be found in DiMasi et al. (2003).[17] The resultant estimates of σ_s are 0.96, 0.91, 0.97 and 0.81 to phases preclinical,[18] I, II and III respectively. We will assume that $\sigma_s = 0$ for the approval phase, so the expected cost equation (1) at this stage will consist of a linear function with a negative slope of $-I_s$.

5.3 Free cash flow

Following analysts' reports, the FCF represents 33.45% of sales. Table 3 exhibits the annual peak sales[19] and the corresponding quarterly FCF for every compound. In order to compute the peak sales, we have considered both the sales in Europe which represents a 35% of total sales and the royalties which

[16] The conditional variance (2) is indeed evaluated at the beginning of the phase s period and thus, the value of K_s is equal to $K_{s,0}$.

[17] To be precise, these estimates come from the right-hand side of Table 5 (columns of "mean cost" and "standard deviation" from "full sample") on page 171.

[18] We approximate the long-term animal testing phase to the preclinical one in Table 5 from DiMasi et al. (2003). The reason is that preclinical testing is based on laboratory and animal studies.

[19] These data are collected from the Zeltia valuation report by ING on April 7, 2003.

range from 11.25% to 19% of 65% of total sales through the agreement with J&J group. In this work, we will take as percentage the average with value 15.12%.

Note that the peak sales for the five preclinical compounds is the same: €1,214.65 million. We obtain this value[20] as an "approximated" weighted average of the clinical compounds' peak sales times five.

Next, the peak FCF, how is it obtained?. Take, for example, the case of Yondelis with peak sales of €1,537.90 million. We get an amount of €538.27 million (€999.64 million) for PharmaMar bussiness in Europe (rest of the world). The annual peak FCF is €331.25 million which comes from adding up both 180.05 and 151.20, where 180.05 (151.20) is equal to 538.27∗0.3345 (999.64∗0.1512). So, the quarterly FCF is €82.81 million (see first row in Table 3).

For the ovarian therapeutical line in Yondelis, we have only available FCF values for both the launch year, τ_l, and the peak year, τ_p, which amount to $C^{(\text{ovarian})}(\tau_l) = 10.48$ and $C^{(\text{ovarian})}(\tau_p) = 113.77$ in real million euros. We can estimate Yondelis' FCF at the launch date, i.e. $C^{(\text{yondelis})}(\tau_l)$, by assuming the ratio $C(\tau_l)/C(\tau_p)$ to be the same for both Yondelis and the ovarian therapeutical line. So, $C^{(\text{yondelis})}(\tau_l) = (10.48 * 82.81)/113.77 = 7.63$. This value would be the FCF for the first quarter. According to Grabowski et al (2002), on the average the peak sales is reached the ninth year after launching the product. Note that a unique $C(t)$ equation defined in (5) is the one that we will implement here for all the compounds with an estimate for the drift parameter α equals 0.3.[21] This coefficient value will be the same for

[20] $1,214.65 = [(1,537.90/7 + 1,534.47/7 + 799.22/3 + 799.22/3)/4] * 5$.

[21] Given some data from Yondelis and imposing that the peak sales is obtained at the

all the compounds since we had no enough information for the rest. Finally, an starting value $C(0)$ for the simulations will also be necessary. Each initial value is computed by applying the formula $C(\tau_p)\exp(-\alpha\tau_p)$, see the last column in Table 3.

Since the risk premium η is 0.06, that corresponds to a beta value of 1.3 for Zeltia, then α^* in (5) equals 0.24. The annual volatility parameter ϕ in (5) is 0.38 which is the sample standard deviation based on daily returns of Zeltia for the period January to April in year 2003. Following Schwartz (2004), we set a negative small correlation between the stochastic processes for cost and cash flows such as -0.10. This value will be increasing in absolute value as we move to more advanced phases in R&D. This behavior is based on the idea that more successful projects take a shorter time to develop, so their costs are lower and their cash flows are higher. The difference in absolute value that we consider between any two consecutive correlations, for instance take the correlation between FCF and costs of phase I and the correlation between FCF and costs of phase II, will be 0.01.

Finally, once the patent expires the sales will become to decrease because of the generic entrance. According to some analysts' reports, we set a drop of 30%, 20%, 15%, 15%, 10% and 10% respectively for the first 6 years after the patent expiration.

5.4 Catastrophic events

The probability of a compound to reach the next phase is 2%, 65.48%, 42.71%, 72.63% and 80%[22] respectively in preclinical, I, II, III and approval

end of the first quarter of the ninth year, i.e. $\tau_p - \tau_l = 8.25$ years, we obtain the amount of 0.3 according to the formula: $\ln\left[C^{(\text{yondelis})}(\tau_p)/C^{(\text{yondelis})}(\tau_l)\right]/(\tau_p - \tau_l)$.

[22] These probabilities come from Sweeny (2002) and some analysts' reports.

phase.[23] Note that these empirical success probabilities, denoted as $\widetilde{P}_s$ where s is the phase, take into account the two different type of failures as shown in subsection 4.2, i.e. both the catastrophic events and the optimality of the abandonment option. So, $1-\widetilde{P}_s$ might be an overestimate of the unknown Poisson probability of failure due to the occurrence of catastrophic events at phase s. The true probability of success at phase s, labeled as P_s, can be computed in terms of the time to the first catastrophic event, $\mathbf{T_c}$, that is

$$P\left(\mathbf{T_c} > T_s\right) = \exp(-\lambda_s T_s) \tag{12}$$

where T_s represents the time, in years, to complete the ongoing phase[24] s and λ_s denotes the respective Poisson intensity parameter. In short, $P_s = \widetilde{P}_s + \epsilon_s$ where ϵ_s represents the error at phase s. Here, we will calibrate a different value of λ_s per both stage and compound. The steps for the calibration are the following:

1. Take as starting value for λ_s the one obtained by plugging both the corresponding T_s and half of the total probability of failure $1-\widetilde{P}_s$, as a guess,[25] for the ongoing phase into (12). For example, the Aplidine product is at the beginning of phase II, so $T_{II} = 2$ years, $1-\widetilde{P}_{II} = 1-0.4271 = 0.5729$, $P\left(\mathbf{T_c} < T_{II}\right)$ is equal to $(1-\widetilde{P}_{II})/2$ and taking $1-P_s$ where P_s is equation (12), then λ_{II} will be equal to 0.1688. Now, we can already start with the simulations.

2. Once the simulations are run for the valuation of Aplidine, we will

[23] Those compounds which are not set at the beginning of the phase, their probabilities will be corrected by a linear adjustment.

[24] See subsection 5.1.

[25] Since we do not know a priori how to split the probability of failure into the two parts, we will guess as a starting probability of failure for catastrophic events half of the total probability.

obtain the optimal number of abandonments, henceforth N_a, as a percentage of total paths, that is $(N_a/N_p)\,\%$.

3. Compute λ_{II} again according to (12) but now the probability of failure $P\left(\mathbf{T_c} < T_{II}\right)$ will be adjusted, i.e. $0.5729 - (N_a/N_p)$.

4. This procedure is repeated several times till the convergence is achieved, that is, stop once a very small difference between two consecutive values of Aplidine is obtained. Finally, we estimate a value for the intensity of Aplidine at phase II of 0.4157 and so, the probability of failure due to catastrophic events will be equal to 0.5645. So, the total probability of failure $1 - \widetilde{P}_{II}$ can be divided into 0.5645 and 0.0083, where the last corresponds to the optimal ratio of abandonments N_a/N_p at phase II.

5. For running the simulation to valuate Aplidine at phase II in step 1, we also need the intensity values for the remaining phases to completion, i.e. the ones corresponding to both phase III and approval. Hence, at the same time we take an initial value for λ_{II} we also repeat the procedure at step 1 for the other two. Once we have computed our first valuation of Aplidine, we will really adjust all the probabilites of failure for all the remaining phases and obtain new values of λ_{II}, λ_{III} and λ_{ap}. Once the convergence is achieved, the final values of λ_{III} and λ_{ap} will be 0.1187 and 0.1411 respectively.

5.5 Other parameters

1. It will be assumed for simplicity a constant real interest rate, denoted as r. Since the internal rate of return, denoted as i, for the 10-year German bond is 3.73% at May 30, 2003 and given the inflation target,

denoted as π^e, established by the European Central Bank of 2%, then $r = \ln\left[(1+i)\,/\,(1+\pi^e)\right]$ equals 1.68%.

2. PharmaMar has in cash the amount of €120 million that we will have to add to the total value of the compounds for the valuation of PharmaMar.

3. In each compound we use $60,000$ simulations with quarterly steps, that is $\Delta = 1/4$.

6 Simulation results

Using both the data and parameter values described in the last section, the value of PharmaMar with the abandonment flexibility is €1,883.35 million, €1,879.04 million without flexibility and consequently, €4.31 million would be the abandonment option value. Table 4 exhibits the values with and without flexibility and the option value for every compound (both clinical and preclinical ones) in PharmaMar. Note that there are two columns of values. For the moment, we will only look at column 1, labeled as "model 1". Two expected features can be concluded: first, the higher values correspond to the clinical compounds where Yondelis reaches the highest one and second, the higher abandonment option values correspond to those compounds in preclinical phase. If we exclude the cash statement from PharmaMar value in Table 4, the ratio of the total value with flexibility of clinical (preclinical) compounds to PharmaMar value is 80.44% (19.56%), the ratio of the total option value of all compounds to PharmaMar value is 0.24% and finally, the ratio of the total option value of clinical (preclinical) compounds to total clinical (preclinical) compound value is 0.04% (1.09%). As we mentioned, assuming a GBM for the whole stage 1 could lead to an overvaluation of the

project and so a negligible value for the abandonment option as it is shown. These results will change by considering a different behavior for the drug's life cycle as we will present in the next section, to be precise in subsection 7.1. Note that the abandonment option is higher, as we expected, for those projects being at preclinical than at clinical trials.

Table 5 shows in detail the abandonments, as a percentage of the total paths, corresponding to each remaining phase for each compound. For the clinical compounds, the optimal exercise for abandonment is carried out at phase III. The reason is that this phase shows investment rates higher than phases I or II. Meanwhile, for the preclinical compounds, excepting preclinical 1, the optimal abandonment occurs at this phase since the highest investment rate correspond to this one. Note that the optimal abandonment for the preclinical 1 compound takes place at phase III, this occurs because it is the one closest to end this stage, in concrete one year to go to the next phase, so it will resemble a clinical compound early at phase I. The average of the abandoned percentages for the clinical compounds is equal to 4.26 while it is 16.65 for the preclinical ones.

Finally, suppose a compound starting at the preclinical phase and so, an average lifetime of 3.5 years, as shown in subsection 5.2. Note that this compound does not really belong to PharmaMar. Indeed, it is an example with the idea of showing the impact on its valuation of how important is the abandonment flexibility early in the preclinical phase since neither of the five preclinical compounds in the moment of the valuation were at the beginning of this phase. It is shown in Table 5.2b, labeled as "preclinical 6" for Model 1, that the value with flexibility is €21.18 million, €18.10 million without flexibility and so, an option value, the largest, of €3.08 million. Its

corresponding percentage of abandonments is 29.56% while 23.43% would represent the highest one for the compound preclinical 5 among all the ones in PharmaMar. Note that preclinical 5 has a remaining lifetime of 3 years, that is the nearest to the beginning of the preclinical phase.

7 Sensitivity analysis

In this section, we will perform an exhaustive sensitivity analysis in order to assess the robustness of the valuation obtained in the previous section. First, we will start by considering a dynamics for the free cash flow different from our benchmark model, or model 1, and second, we will study the sensitivity of our valuation to changes in the parameters that govern the expected cost to completion equation, the free cash flow one and so forth.

7.1 An alternative life cycle pattern

As we know our benchmark model assumes a GBM specification for the FCF at stage 1 as we can see in subsection 3.2.1. Though this process is very tractable, the expected FCF would grow at a constant rate at perpetuity and it might overvalue the project. So, we could think that once the peak sales date, τ_p, has been attained, it would make no sense to let the FCF grow at the same level occurred before τ_p till the patent expiration T. Because of this, we will hint at alternative candidates for the FCF dynamics. To be precise, we will replace the GBM dynamics with a simple random walk process with no drift as a possible candidate for the period going from the peak sales date to the patent expiration date.[26] It means that, the FCF

[26] Other plausible candidates, also holding the period from τ_p to T, could be: (1) a GBM but now with a lower growth rate, (2) a constant FCF equals the FCF in the peak sales, i.e. $C_1(\tau_p)$, or (3) an Ornstein-Uhlenbeck (OU) process reverting to $C_1(\tau_p)$. We obtained the valuation of PharmaMar under (3) and the results were very similar to the ones under

behavior in stage 1, $C_1(t)$, will be the same as (5) for $t \leq \tau_p$ while

$$dC_1(t) = \phi dz^{\dagger}(t); \quad \tau_p \leq t \leq T$$

where $dz^{\dagger}(t)$ is an increment of a Wiener process and to simplify, we will assume that both the real and the risk-neutral measures are the same.[27] This new behavior for the stage 1 of the FCF dynamics will be labeled as "model 2".

Looking at model 2 in Table 4, the value of PharmaMar with flexibility (without flexibility) is €1,217.91 million (€1,201.41 million) and hence, €16.50 million would be the abandonment option value. Note that both a lower valuation of PharmaMar and a larger abandonment option value are forseeable results under model 2 as we discussed in the previous section. We can also conclude from Table 5 that both the percentages of abandoned paths and the implied option values in each compound are always larger under model 2 and specifically, for the preclinical compounds. Finally, if we take the compound "preclinical 6", we can appreciate the importance of the flexibility given by the abandonment option. If we value the project without considering the implied abandonment flexibility, the contribution of this compound to the total valuation would be negative and thus, the project would be worthless. It would make no sense to continue the R&D for this product while if we make a correct valuation, and consequently take into account the flexibility, its added value to the total amount would be positive. Also note that, the value of the project without flexibility is negative under model 2 while it is positive under model 1 due to its possible overvaluation

the random walk process. To shorten, we have decided not to incorporate alternative life cycle cases in the paper.

[27] We will also assume that $dz_c^*(t)\, dz^{\dagger}(t) = 0$ and $dz_s(t)\, dz^{\dagger}(t) = \rho_{sc} dt$. Note that ρ_{sc} is the same correlation as in (7).

discussed previously.

To conclude, we believe that model 2 is more realistic than model 1 since the last one would tend to overestimate the true values. This impression could also be held by checking the price that Zeltia shares were trading around May 2003. Given model 2, the PharmaMar contribution to each share of Zeltia[28] is €6.07. If we take a value of €1.5, according to analysts,[29] for the non-core assets per one share of Zeltia then a target price of one share of Zeltia would be €7.57 at the beginning of June, 2003. The closing price for Zeltia that date was trading at €7.75 and the average (median) price for this month was about €7.51 (€7.48) which is very close to our target price. It would be interesting to compare our target price for Zeltia with the ones assessed by some financial analysts. Table 6 exhibits the target price of Zeltia given by different analysts. To each analyst, we will only select among the different valuations of Zeltia through time the one nearest to the date the end of May 2003. It is shown that there is no consensus about the price because of the high uncertainty in valuating PharmaMar since there is barely uncertainty about the valuation of Zeltia's non-core assets per share assumed before. The range of the target prices is large, it goes from a minimum price of €3.80 to a maximum of €19.00. The average price is equal to €7.95 while the median is €7.53. Note that our target price of €7.57 approaches to the median which is a more robust statistics than the mean. The last column in Table 6 displays the closing price of Zeltia that was traded at each date in order to compare with its theoretical price.

[28] There are 200.7 million of outstanding shares of Zeltia.

[29] See the Spanish financial newspaper "Expansión" at date 07/03/03.

7.2 Change of parameters

We will only consider model 2 to carry out the sensitivity analysis.[30] Table 7 exhibits the effect of changing a certain parameter while keeping the rest as in section 5. It is shown that the changes in values move in the right direction as predicted.

When analyzing the impact of changing the volatility of either the investment cost volatility, σ_s, or the free cash flow one, ϕ, the result will be same: an increase (decrease) in volatility makes a larger (smaller) value of both the project and the option to abandon, as expected.

If we increase (decrease) the drift of the FCF, α^*, we obtain a higher (smaller) value of the project under either flexibility or without flexibility and a smaller (higher) option value to abandon. A similar behavior occurs to the size of the FCF measured through a percentage of sales: an increase of FCF would be similar as an increase in α^*.

It is also shown that a higher real interest rate drives to a higher option value to abandon. The same holds for the investment costs. If we consider the data from a standard pharmaceutical firm instead of a biotech one as our case, see section 5.2, the option value goes from €16.5 million to €57.37 million.

A shorter length of the patent life, also drives a higher option value. This parameter might be a control variable by a regulator. Note that a decrease in one year drives to an increase in the option value, going from €16.5 million to €20.48 million, and the value of the project is smaller.

[30] To abbreviate the paper we have selected one model, in concrete model 2 since it is more realistic than model 1 (see section 6).

Finally, considering a negative correlation between the investment cost at any phase and the cash flows, as a starting value for the initial valuation, then a higher absolute value makes a lower option value to abandon.

8 Conclusions

This paper is about a real case for the valuation of an early stage biotech company. This assessment is based on the real options approach and considers uncertainty in the cost to completion of the project, uncertainty in the cash flows once the drug is launched and the possibility of catastrophic events. It is also allowed the flexibility of abandonment that can only exercised at any time during the R&D period till the project is completed. We implement here a short extension of the model by Schwartz (2004). To be precise, the life cycle of the drug is modeled by considering a different and more realistic behavior for the evolution of the FCF, different from the GBM, once the peak sales is reached till the patent expiration, we will also allow for the possibility of the generic entrance once the patent expires, different expected costs to completion dynamics are considered here, that is one equation to each compound; a different probability of catastrophic event depending on the phase and so on. The real case we study here is the PharmaMar company where currently no drug is marketed yet. It consists of a portfolio of patents for oncological drugs. The portfolio contains compounds being at either I or II phase trials and other compounds from earlier stages, preclinical testing. It is shown that the abandonment value is higher for those compounds being in preclinical trials than those in clinical ones. Finally, the value of the firm is computed as a sum of the parts or R&D projects where we assume to simplify that they are independent.

Appendix

Here, we compute several quantiles, k_p, corresponding to the process $K_s(t)$ conditional on $K_{s,0}$ (see Table 2) per phase for each compound from PharmaMar. The following quantities are expressed in real million euros in the year 2003.

Table A.1: Quantiles obtained from the clinical compounds

Product	Yond	Yond	Aplid	Kah	Kah	Kah	ES	ES
Phase	II	III	II	I	II	III	I	II
$K_{s,0}$	9.28	40.58	18.55	0.99	7.95	17.39	1.99	7.95
p	k_p	k_p	k_p	k_p	k_p	k_p	k_p	k_p
10%	3.59	18.34	7.17	0.41	3.07	7.86	0.82	3.07
20%	4.45	22.19	8.89	0.50	3.81	9.51	1.00	3.81
30%	5.24	25.68	10.48	0.58	4.49	11.00	1.17	4.49
40%	6.09	29.27	12.17	0.67	5.21	12.54	1.35	5.22
50%	7.05	33.25	14.09	0.77	6.04	14.25	1.56	6.04
60%	8.22	37.99	16.42	0.90	7.04	16.28	1.80	7.04
70%	9.77	44.09	19.53	1.06	8.40	18.90	2.12	8.37
80%	12.11	52.99	24.21	1.29	10.38	22.71	2.60	10.38
90%	16.72	69.61	33.43	1.76	14.33	29.83	3.53	14.33

Yond=Yondelis; Aplid=Aplidine; Kah=Kahalalide-F; ES=ES-285

Table A.2: Quantiles obtained from the preclinical compounds

Product	Pre1	Pre1	Pre1	Pre1	Pre2	Pre3	Pre4	Pre5
Phase	prec	I	II	III	prec	prec	prec	prec
$K_{s,0}$	16.52	3.31	13.25	28.99	28.92	41.31	49.57	57.84
p	k_p	k_p	k_p	k_p	k_p	k_p	k_p	k_p
10%	6.45	1.35	5.12	13.10	11.29	16.13	19.36	22.59
20%	7.98	1.67	6.35	15.85	13.97	19.96	23.95	27.94
30%	9.40	1.95	7.49	18.35	16.46	23.52	28.22	32.92
40%	10.90	2.25	8.69	20.91	19.09	27.26	32.72	38.17
50%	12.61	2.59	10.06	23.75	22.07	31.52	37.83	44.14
60%	14.68	3.00	11.73	27.14	25.70	36.72	44.06	51.41
70%	17.43	3.53	13.95	31.50	30.52	43.59	52.31	61.03
80%	21.57	4.33	17.29	37.85	37.77	53.95	64.73	75.53
90%	29.69	5.87	23.88	49.73	51.98	74.25	89.10	103.97

Pre1=Preclinical 1; ... ; Pre5=Preclinical 5.

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Table 1. Allocation of R&D costs (% of total R&D costs)

Discovery	**10.00**
Synthesis and Extraction	10.00
Preclinical Testing	**28.05**
Biological Screening and Pharmacological Testing	14.20
Toxicology and Safety Testing	4.50
pharmaceutical Dosage Formulation and Stability	7.30
Regulatory Review (IND)	2.05
Clinical trials	**61.95**
Phases I, II and III	29.10
Phase IV	11.70
Process Development for Manufacturing and Quality Control	8.30
Regulatory Review (NDA)	2.05
Bioavailability	1.80
Other	9.00
Total	**100.00**

Source: Sweeny (2002).

Table 2. Expected cost per phase $K_{s,0}$ (€ 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-F		0.99	7.95	17.39	0.89
ES-285		1.99	7.95	17.39	0.89
Preclinical 1	16.52	3.31	13.25	28.99	1.48
Preclinical 2	28.92	3.31	13.25	28.99	1.48
Preclinical 3	41.31	3.31	13.25	28.99	1.48
Preclinical 4	49.57	3.31	13.25	28.99	1.48
Preclinical 5	57.84	3.31	13.25	28.99	1.48

Note: *prec* (*ap*) denotes the preclinical (approval) phase.

Table 3. Data to model FCF dynamics (€ million 2003)

	peak sales	peak FCF	initial FCF
Yondelis	1,537.90	82.81	1.59
Aplidine	1,534.47	82.63	1.18
Kahalalide-F	799.22	43.04	0.49
ES-285	799.22	43.04	0.39
Preclinical 1	1,214.65	65.41	0.44
Preclinical 2	1,214.65	65.41	0.38
Preclinical 3	1,214.65	65.41	0.33
Preclinical 4	1,214.65	65.41	0.28
Preclinical 5	1,214.65	65.41	0.24

Note: peak sales are per year while FCF are per quarter.

Table 4. Valuation of PharmaMar (€ million, 2003)

		Model 1	Model 2
Value with option			
	Yondelis	679.21	436.52
	Aplidine	442.65	283.01
	Kahalalide-F	166.86	106.20
	ES-285	129.78	81.87
	Preclinical 1	112.60	65.57
	Preclinical 2	85.93	48.27
	Preclinical 3	65.71	35.50
	Preclinical 4	48.26	25.11
	Preclinical 5	32.35	15.86
	Cash	120	120
	PharmaMar	1,883.35	1,217.91
Value without option			
	Yondelis	679.11	436.36
	Aplidine	442.48	282.79
	Kahalalide-F	166.74	106.06
	ES-285	129.61	81.69
	Preclinical 1	112.24	65.04
	Preclinical 2	85.45	47.10
	Preclinical 3	64.90	32.87
	Preclinical 4	47.19	20.82
	Preclinical 5	31.31	8.70
	Cash	120	120
	PharmaMar	1,879.04	1,201.41
Option value			
	Yondelis	0.11	0.16
	Aplidine	0.16	0.21
	Kahalalide-F	0.12	0.14
	ES-285	0.17	0.18
	Preclinical 1	0.36	0.53
	Preclinical 2	0.48	1.18
	Preclinical 3	0.82	2.64
	Preclinical 4	1.06	4.29
	Preclinical 5	1.04	7.17
	PharmaMar	4.31	16.50

Table 5.1. Abandoned paths (%): Clinical products

	Model 1	Model 2
Yondelis		
Abandoned paths: phase II	0.04	0.09
Abandoned paths: phase III	1.13	1.42
Abandoned paths: approval	0.56	0.44
Total of abandoned paths	1.73	1.95
Value with option	679.21	436.52
Value without option	679.11	436.36
Option value	0.11	0.16
Aplidine		
Abandoned paths: phase II	0.83	1.15
Abandoned paths: phase III	1.69	2.02
Abandoned paths: approval	0.93	0.58
Total of abandoned paths	3.46	3.74
Value with option	442.65	283.01
Value without option	442.48	282.79
Option value	0.16	0.21
Kahalalide-F		
Abandoned paths: phase I	0.04	0.04
Abandoned paths: phase II	1.71	2.01
Abandoned paths: phase III	2.35	2.47
Abandoned paths: approval	0.75	0.50
Total of abandoned paths	4.85	5.02
Value with option	166.86	106.20
Value without option	166.74	106.06
Option value	0.12	0.14
ES-285		
Abandoned paths: phase I	0.42	0.43
Abandoned paths: phase II	2.65	2.99
Abandoned paths: phase III	2.93	3.11
Abandoned paths: approval	1.03	0.34
Total of abandoned paths	7.02	6.86
Value with option	129.78	81.87
Value without option	129.61	81.69
Option value	0.17	0.18

Note: values are given in real million euros (year 2003).

Table 5.2a. Abandoned paths (%): Preclinical 1,2,3

	Model 1	Model 2
Preclinical 1		
Abandoned paths: preclinical	1.70	2.06
Abandoned paths: phase I	0.61	1.00
Abandoned paths: phase II	2.70	3.48
Abandoned paths: phase III	3.58	4.08
Abandoned paths: approval	1.97	1.20
Total of abandoned paths	10.55	11.82
Value with option	112.60	65.57
Value without option	112.24	65.04
Option value	0.36	0.53
Preclinical 2		
Abandoned paths: preclinical	3.58	6.23
Abandoned paths: phase I	0.60	0.80
Abandoned paths: phase II	2.55	3.33
Abandoned paths: phase III	3.55	3.88
Abandoned paths: approval	1.83	1.17
Total of abandoned paths	12.10	15.41
Value with option	85.93	48.27
Value without option	85.45	47.10
Option value	0.48	1.18
Preclinical 3		
Abandoned paths: preclinical	7.84	13.43
Abandoned paths: phase I	0.65	0.74
Abandoned paths: phase II	2.53	2.87
Abandoned paths: phase III	3.46	3.74
Abandoned paths: approval	1.84	1.57
Total of abandoned paths	16.31	22.35
Value with option	65.71	35.50
Value without option	64.90	32.87
Option value	0.82	2.64

Note: values are given in real million euros (year 2003).

Table 5.2b. Abandoned paths (%): Preclinical 4,5,6

	Model 1	Model 2
Preclinical 4		
Abandoned paths: preclinical	12.17	20.23
Abandoned paths: phase I	0.94	0.65
Abandoned paths: phase II	2.69	2.60
Abandoned paths: phase III	3.31	3.86
Abandoned paths: approval	1.74	1.92
Total of abandoned paths	20.85	29.27
Value with option	48.26	25.11
Value without option	47.19	20.82
Option value	1.06	4.29
Preclinical 5		
Abandoned paths: preclinical	15.94	28.62
Abandoned paths: phase I	0.99	0.54
Abandoned paths: phase II	2.59	2.21
Abandoned paths: phase III	2.75	2.86
Abandoned paths: approval	1.17	0.95
Total of abandoned paths	23.43	35.18
Value with option	32.35	15.86
Value without option	31.31	8.70
Option value	1.04	7.17
Preclinical 6		
Abandoned paths: preclinical	23.87	38.54
Abandoned paths: phase I	0.58	0.48
Abandoned paths: phase II	1.92	1.83
Abandoned paths: phase III	2.31	2.42
Abandoned paths: approval	0.88	0.66
Total of abandoned paths	29.56	43.93
Value with option	21.18	9.12
Value without option	18.10	-2.10
Option value	3.08	11.22

Note: values are given in real million euros (year 2003).

Table 6. Zeltia valuation (in euros)

Home	date	target price	actual price
UBS Warburg	05/19/03	4.00	7.35
Renta 4	05/14/03	5.60	7.49
Dresdner KW	04/29/03	9.20	7.13
Credit Lyonnais	04/28/03	7.53	7.21
InverCaixa	04/28/03	4.90	7.21
Ibersecurities	04/22/03	7.80	7.20
CAI Cheuvreux	04/14/03	4.90	6.86
ING Barings	04/04/03	8.10	6.38
Espírito Santo B&M	03/31/03	10.75	6.11
BSCH	03/11/03	19.00	5.08
SSSB	03/06/03	3.80	5.49
Banesto Bolsa	02/27/03	4.60	5.42
Ahorro	02/27/03	6.10	5.42
Julius Bäer	01/20/03	13.00	6.00
BBVA	01/15/03	11.60	6.00
Urquijo	12/09/02	7.10	6.62
M&G Valores	11/28/02	7.20	6.90

Source: JCF Group and Zeltia.

Table 7.1. Sensitivity analysis (€ million, 2003)

Costs	**With option**	**Without option**	**Option value**
$\frac{2}{3}$ **of standard**	**1,217.91**	**1,201.41**	**16.50**
Standard	1,099.10	1,041.73	57.37
Cost volatility, σ_s	**With option**	**Without option**	**Option value**
$\sigma_s - 0.4\ \forall s$	1,146.23	1,131.88	14.35
$\sigma_s - 0.2\ \forall s$	1,178.61	1,163.56	15.05
$\sigma_s\ \ \forall s$	**1,217.91**	**1,201.41**	**16.50**
$\sigma_s + 0.2\ \forall s$	1,265.90	1,249.33	16.57
FCF volatility, ϕ	**With option**	**Without option**	**Option value**
0.28	1,208.83	1,194.77	14.07
0.33	1,213.68	1,198.40	15.28
0.38	**1,217.91**	**1,201.41**	**16.50**
0.43	1,220.81	1,203.46	17.35
0.48	1,221.00	1,202.32	18.68
Drift, α^*	**With option**	**Without option**	**Option value**
0.230	1,046.49	1,023.13	23.36
0.235	1,128.79	1,109.13	19.66
0.240	**1,217.91**	**1,201.41**	**16.50**
0.245	1,313.50	1,299.66	13.84
0.250	1,416.23	1,404.64	11.59
FCF (% of sales)	**With option**	**Without option**	**Option value**
23.45%	999.95	976.25	23.70
28.45%	1,108.60	1,088.98	19.62
33.45%	**1,217.91**	**1,201.41**	**16.50**
38.45%	1,327.04	1,312.96	14.08
43.45%	1,436.32	1,424.22	12.10

Table 7.2. Sensitivity analysis (€ million, 2003)

Competition	**With option**	**Without option**	**Option value**
4 years	1,146.95	1,128.46	18.48
6 years	**1,217.91**	**1,201.41**	**16.50**
8 years	1,367.40	1,353.92	13.48
Correlation, ρ	**With option**	**Without option**	**Option value**
-0.15	1,236.25	1,219.90	16.35
-0.10	**1,217.91**	**1,201.41**	**16.50**
-0.05	1,199.33	1,182.80	16.53
0.00	1,178.78	1,162.21	16.57
Real interest, r	**With option**	**Without option**	**Option value**
0.88	1,392.72	1,379.56	13.16
1.28	1,302.31	1,287.57	14.74
1.68	**1,217.91**	**1,201.41**	**16.50**
2.08	1,138.90	1,120.36	18.54
2.48	1,065.38	1,044.52	20.86
Patent expiration, T	**With option**	**Without option**	**Option value**
19 years	1,085.36	1,064.87	20.48
20 years	**1,217.91**	**1,201.41**	**16.50**
21 years	1,348.17	1,334.63	13.55

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