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Chapter 1

Introduction

The health system and the financing is one of the main economic and social problems of our time. Over the past years we have seen dramatic changes in treatment of diseases through new innovations in health sciences. The OECD Health Data 2011 from June 2011 provides comparable statistics on health and health systems across OECD countries. Table 1.1 shows the increase of total expenditures in health as percentage of the gross domestical product from 1960 to 2010. for a selected sample of 16 OECD countries. For Austria as an example we observe an increase in total expenditures from 4.3% in 1960 to 11% in 2009[1].

Besides several other reasons like demographic change the expenditures on pharmaceutical research and development increased in the last two decades dramatically which had a direct effect on the percentage of GDP spent on health care. We will point out in the ongoing chapters on pharmaceutical R&D reasons for the increase. This increase in expenditures and the overuse of pharmaceuticals in OECD countries led to an increase in spendings on pharmaceuticals within the last 50 years which can be seen in Table 1.2.

For this reason a discussion about the health care system and the health care costs has to consider these rising expenditures in pharmaceuticals. An important role plays the private industry and the patenting system which allows a monopoly market situation for a certain time.

In this thesis we want to take a closer look at the expenditures of pharmaceutical

[1]Note that for the year 2010 no data for Austria is available.

Table 1.1: Total expenditure on health, % gross domestic product (OECD (2011))

Country	1960	1970	1980	1990	2000	2009	2010
Austria	4.3	5.2	7.4	8.3	9.9	11.0	
Canada	5.4	6.9	7.0	8.9	8.8	11.4	11.3
Finland	3.8	5.5	6.3	7.7	7.2	9.2	8.9
France	3.8	5.4	7.0	8.4	10.1	11.8	
Germany		6.0	8.4	8.3	10.3	11.6	
Iceland	3.0	4.7	6.3	7.8	9.5	9.7	9.3
Ireland	3.7	5.1	8.2	6.1	6.1	9.5	
Japan	3.0	4.5	6.4	5.9	7.7		
Luxembourg		3.1	5.2	5.4	7.5	7.8	
New Zealand		5.2	5.8	6.8	7.6	10.3	
Norway	2.9	4.4	7.0	7.6	8.4	9.6	
Spain	1.5	3.5	5.3	6.5	7.2	9.5	
Sweden		6.8	8.9	8.2	8.2	10.0	
Switzerland	4.9	5.5	7.4	8.2	10.2	11.4	11.6
United Kingdom	3.9	4.5	5.6	5.9	7.0	9.8	
United States	5.1	7.1	9.0	12.4	13.7	17.4	

companies and present methods to validate research and development costs. The investment in R&D in the pharmaceutical industry is not comparable to other industries due to several reasons. Pharmaceutical companies have to invest a huge amount in an uncertain investment with no cash flows for a long time. A target molecule which is examined in labratory studies to have a certain effect on a target within a disease is patented right after the labratory research. To enter the market the drug has to be authorized which requires the drug to pass three different stages of clinical trials. This time of clinical trials requires huge investments without any cash flows.

All these facts have to be taken into account when analyzing the value of such an investment. The case of GlaxoSmithKline investing in a cooperation with the Austrian biotech company Apeiron is then taken to validate our models regarding the calculation of a project value.

Table 1.2: Total expenditure on pharmaceuticals and other medical non-durables, % total expenditure on health (OECD (2011))

Country	1960	1970	1980	1990	2000	2009
Austria				9,9	12,3	12,5
Canada	12,9	11,3	8,5	11,5	15,9	17
Finland	17,1	12,6	10,7	9,4	15,2	14,3
France	23,5	23,8	16	16,9	16,5	16,1
Germany		16,2	13,4	14,3	13,6	14,9
Iceland	18,5	17,1	15,9	13,5	14,5	15,7
Ireland			11	12,2	14,1	17,5
Japan			21,2	21,4	18,4	
Luxembourg		19,7	14,5	14,9	9,1	
New Zealand			11,9	13,8		9,2
Norway		7,8	8,7	7,2	9,5	7,3
Spain			21	17,8	21,3	18,9
Sweden		6,6	6,5	8	13,8	12,5
Switzerland				10,2	10,8	10,1
United Kingdom		14,7	12,8	13,5	14,2	
United States	16,1	12,1	8,7	8,8	11,3	12

The evaluation of pharmaceutical research and development projects in the future is a crucial thing which is directly related to prices. If the percentage of failed R&D attempts increases due to wrong evaluation at first the sucessful R&D projects or in other words the drugs that enter the market have to make up the loss. Therefore a better evaluaton technique as a decision making instrument wouldn't only help the pharmaceutical company to decide between different projects but would also in the best case lower the prices charged on drugs and by doing that the expenditures on pharmaceuticals.

The pharmaceutical R&D process differs substantially from R&D processes in other industries due to length and uncertainty. Therefore evaluating these investments is

quite complicated and the most commonly used net present value analysis shows a lot of weaknesses concerning managerial flexibility which has to be included in the analysis. For this reason the aim of this thesis was to formulate, implement and test new models for evaluating pharmaceutical research and development which are based on the real options approach. Based on the case of a milestone payment agreement between GlaxoSmithKline and Apeiron we implemented the single-stage Least Squares Monte Carlo model by Schwartz (2004) and tested it on real world data.

Compared to the implementation by Schwartz (2004) who implemented his model in Fortran our single-stage model was implemented in MATLAB, which decreased the running time as far as we know substantially.

Furthermore we present in this thesis a new multi-stage model proposed as an extension by Schwartz (2004) in his Appendix which was not implemented and tested so far. The multi-stage model takes into account all four different research and development stages separately by using different durations, costs and probabilities of failure. We implemented the multi-stage model again in MATLAB using the same real data as for the single-stage model. We will present a comparison of the results of the two models and describe the usage of our new multi-stage model as a decision making instrument for pharmaceutical research an development investments.

This thesis is structured as follows. The first chapter gives an overview over real options theory starting with general option theory and describing different methods for calculating project values. The second chapter gives a literature overview and discussion on the estimation of research and development costs. We use results provided by various studies of DiMasi et al. (1991, 1995); DiMasi (2000, 2001); DiMasi et al. (2003) and compare them to the results from Public Citizen (2001). This is especially interesting since Public Citizen (2001) criticizes DiMasi and the Tuft Center. We will present the data used, the methodology and the results of both and afterwards review the main ideas and especially the data and methodology used. The describition of the general process of drug development is needed to understand how costs accrue in the R&D phase.

Chapter three describes the Monte Carlo simulation and the least squares estimation in general and develops the Least Squares Monte Carlo model for the single stage process following Schwartz (2004). Furthermore we try to give explanations why we have chosen the Least Squares Monte Carlo simulation over other real option approaches and why the Least Squares Monte Carlo simulation delivers better results than the net present value analysis which is most commonly used by companies.

Before the results will be presented the input parameters are discussed in chapter four by presenting the business profile of GlaxoSmithKline and in detail discuss the case of GlaxoSmithKline and Apeiron. Chapter 5 then combines the last two chapters by using the input data out of the case of GSK Austria and Apeiron and the single-stage model presented in chapter three.

Chapter 2

Real Options

2.1 Introduction

The term *real option* was used first in 1977 by Stewart Myers in his paper *Determinants of Coporate Borrowing*. The term referred to the option pricing theory we will present in the next section and discussed the application of option pricing for the valuation of non-financial investments which Stewart Myers called 'real'. These investments include according to Myers (1977) learning mechanisms and managerial flexibility such as the multi-stage pharmaceutical research development process we will discuss in this thesis. The most common approach to value research and development projects is the net present value approach (NPV), which basically discounts the expected cash flows at a certain discount rate which is chosen as to reflect the riskiness of a project (Newton et al. (2004))[1]. A limitation of the assumption of a discount rate reflecting the riskiness of a project is the acceptance of managerial inflexibility within the project (Copeland and Antikarov (2005), Newton et al. (2004)). We can therefore say according to Ross (1995) by including uncertainty and irreversibility in our analysis, the NPV rule is often wrong and option theory delivers better results.

Let us assume that the investment on a project lasts for 5 years and cash flows are realized as soon as investments are finished and research and development reached the

[1]We will present in Chapter Results a NPV analysis based on our case to compare it to our Least Squares Monte Carlo Simulation.

target of entering the market with a new product. The net present value approach does not include the option to abandon the investement after a certain time period, therefore it assumes according to Copeland and Antikarov (2005) that the project will proceed as planned, regardless what happens in the future. Under some circumstances these assumption can make sense and deliver valuable results, but since we are focusing on pharmaceutical research and development a better method to valuate project has to be found. We will go in to further detail in the next chapter by examining the costs and risks of pharmaceutical development.

An option exists whenever a decision maker or manager has the right, but not the obligation to perform a certain act . As for financial options, the holder of an option is given the right but again not the obligation to buy or sell a financial asset at a contracted price. The real option approach by Myers (1977) extends this approach to the situation where firms have similar rights with regard to real or non-financial assets. The real option approach works if two things happen: uncertainty concerning future cash flows and flexibility of the management to respond to this uncertainty.
Since the most influential early works of Myers (1977), Myers and Majluf (1984) and Kester (1984) two streams of research have emerged: investment decision and their economic performance implications.
Option pricing offers on the other side a way to include managerial flexibility in the validation of a project. Therefore we want to present in the ongoing sections the real option approach which developed from the mathematical options approaches by Black and Scholes (1973) and Merton (1973). These works inspired a rapid development on option pricing methods and will be therefore discussed in the next section.

2.2 Option Pricing

As mentioned before Black-Scholes modell proposed in 1973 by Fisher Black, Myron Scholes and Robert Merton is regarded as the breakthrough in mathematical option pricing[2] Following Black and Scholes (1973) there are six factors affecting the prices of a option. These factors are presented in the Black-Scholes formula used to calculate the value of an European option using the risk neutrality assumption.

$$C = S_0 N(d_1) - K e^{-rT} N(d_2) \tag{2.1}$$

where

$$d_1 = \frac{ln(S_0/K) + (r + \sigma^2/2)T}{\sigma\sqrt{T}}$$

$$d_2 = d_1 - \sigma\sqrt{T}$$

In the Black Scholes formula $N(d)$ is the cumulative normal probability density function, S_0 is the current stock price, K the strike price, T the time to expiration, σ standard deviation period (concerning the rate of return on stock) and r the risk free rate. The dividends expected during the life of the option are named as d_i.
Samuelson (1965) modeled an underlying stock price wih an expected return of α and discounted option values at exercise back to the pricing date with some rate β. The Black-Scholes formula follows these assumptions but with out taking into account α and β. Cox et al. (1979) therefore concluded that as long as the parameters α and β reflect the same risk aversion there is no effect on the option price. Considering an investor which is risk neutral, he would discount all cash flows at a risk free rate and therefore α and β would be both equal to the risk free rate. This is approach is known as the risk neutral approach to option pricing which we will discuss in further section since it

[2]Black, Scholes and Merton worked together on the modell. Fisher Black and Myron Scholes published together *The Pricing of Options and Corporate Liabilities* whereas Robert Merton published *Theory of Rational Option Pricing*. Myron Scholes and Robert Merton were received in 1997 the Nobel Prize in Economics. Fisher Black died in 1995.

opened the door to new option valuation techniques as the Monte Carlo method.
Following Hull (2009) there are several generalization to the Black-Scholes model which are useful for the further mathematical option pricing methods. Black and Scholes (1973) assume that the stock price follows a Geometric Brownian Motion with a constant volatility, which can be described as a measure of how much a stock is expected to move in the short-run. For the next important assumption we have to differentiate between European-style options and American-style options.

European-style options may be exercised only at a single time point in time or in other words may be only exercised at the expiry date of the option. American-style options on the other hand may be exercised at any point in time before the expiration of the option. The Black-Scholes model assumes European-style options. American-style options are more valuable than European-Style options due the higher managerial flexibility. According to Hull (2009) it can also be assumed that there are no dividends out of the option during the life of the derivate and that the risk free rate of interest, r, is constant and the same for all maturities. Furthermore it is assumed that there are no transaction costs or taxes due to the option.
As the Black-Scholes formula assumes that there are no dividends paid during its life following Copeland and Antikarov (2005) this is one of the main reasons why the Black-Scholes formula can't be used for real-options valuation. The other porblem with using the Black-Scholes formula for real option valuation is the fact that a real option can be seen like an American-style option whereas the Black-Scholes formula is has as a strong assumption European-style options (Copeland and Antikarov (2005)).
For this reason we have to take a deeper look at the definition of real options, different methods to valuate real options and other valuation techniques. Before that a general overview on options shall be given in the next section.

2.3 Put and Call Options

2.3.1 Call Options

A call option is a financial contract between two parties, the buyer and the seller of a option, which allows the buyer or investor to speculate in stocks that he doesn't own. The call option *gives the holder the right, but not the obiligation to buy the underlying asset by a certain date for a certain price* (De Weert (2006)). In the graphical illustration we see the strike price which is defined as the price at which the option can be exercised. For stock and index options these strike prices are commonly fixed in the contract. Assuming a hypothetical profit, if the price of the underlying instrument lies below the strike price, the option is called *out of money*. On the other hand if the underlying exceeds the strike price it is called *in the money* and *at the money* for a strike price equal to the underlying.

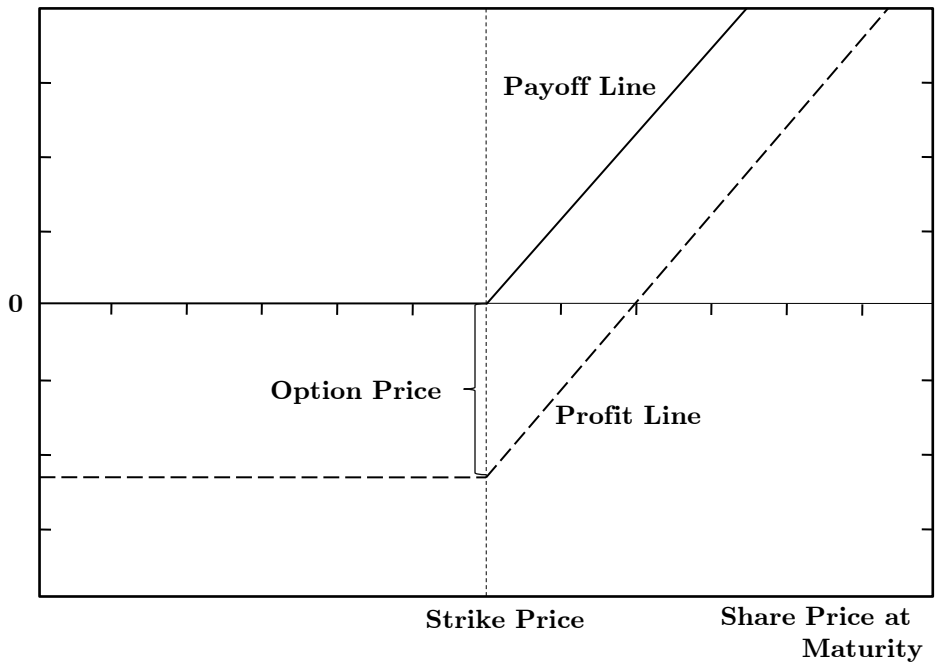

Figure 2.1: Payoff of a European Call option

If we don't take into account transaction costs the 'at the money point' can be seen as the break-even point. For *in the money* options we can think of an example considering a call option with a strike price €5.80 and a underlying with a trade value of €6.20. If the option holder excercises now his option he is in the money with €0.40, which means he excercised his option €0.40 cheaper than the market price. The opposite is true for the *out of the money options*. These are options which will not produce a profit if it is exercised. Considering again an example if an option holder contracted at a strike price of €6.00 and the trade value now is €4.00 he would be out of money with €2.00 which means that he wouldn't excercise the option since he can buy the stock for €4.00 at the market. Summarized this means if you would excercise the option right now you would be 'out of money'.

2.3.2 Put Options

A put option is again a financial contract between the two parties, buyer and seller of the option. It gives the holder of the option a right (but not an obligation) to sell in contrary to the call option the underlying asset on a certain date for a contracted price (De Weert (2006)). In other words a seller of an option wants to protect for example his shares under a certain price. A contract with an investor is signed to buy this shares at the contracted price at a certain date. In return the option holder pays the buyer a fee, if the shares rise above the contracted value he does not have to sell and if the shares fall below he is protected. Therefore the holder looses in this case only the fee paid for the option. In the money is not defined as how much the value of the option falls below the excercise price.

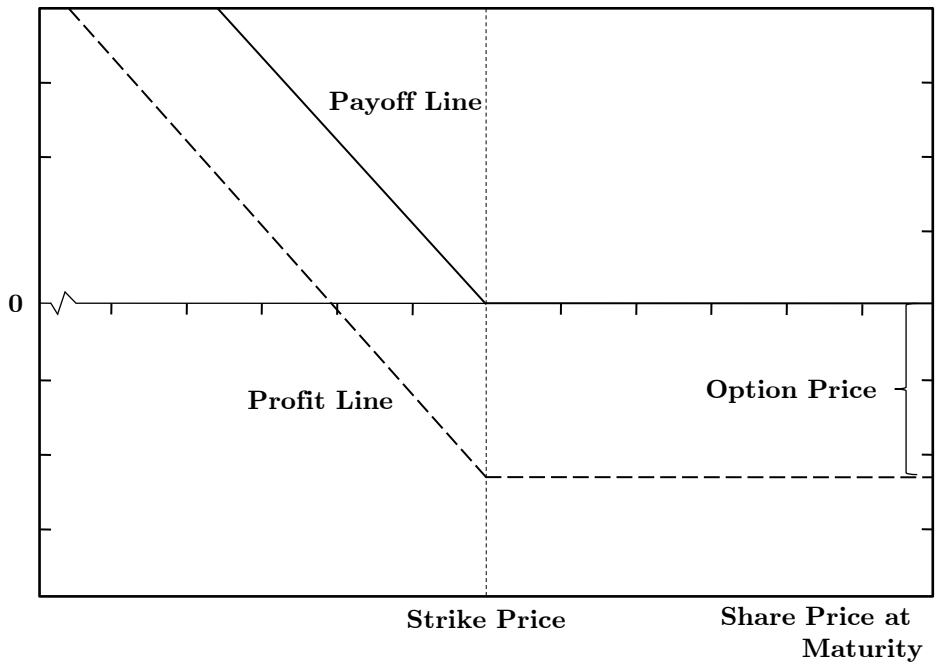

Figure 2.2: Payoff of a European Put option

If the option would be far beyond the excercise price it would be referred as be deep in the money. Generally speaking the option holder makes a profit if the price of the

underlying falls beyond the excercise price so he is compensated for the premium he paid before. This is again shown for a long European-style option in Figure 2.2. Note than the value of the underlying can't fall below the value of zero, therefore the value of the put option is said to be bounded.

2.4 Types of Real Options

The literature discusses several different types of real options with slightly differences in the number of types. Brealey et al. (2008) define four main types of real options with (1) a option to expand if the investment suceeds, (2) the option to abandon a project, (3) the option to vary the mix of output and (4) the option to wait and learn before investing. We will focus in our closer describtion of types mainly on the summary of Trigeorgis (1996) and Trigeorgis (2001) discussing seven different types of real options. Trigeorgis (1996) formulates four basic types of real options (1) options to defer, (2) options to contract/expand, (3) opton to abandon for salvage value and (4) option to switch use. Trigeorgis (1996) then ranks the real options depending on exclusiveness of ownership into proprietary options and shared options. Childs and Triantis (1999) mentions summarizes the types of real options on only three types: (1) options to grow, (2) contraction options and (3) flexibility options.

2.4.1 Option to defer

The description of this type of real option follows Trigeorgis (1996) and Trigeorgis (2001) and is also one of the above summarized real option types by Brealey et al. (2008) namely the option to wait and learn before investing. According to Copeland and Tufano (2004) this option is also called deferral call option. In this type of option the management or option holder is allowed to wait some time to see if ouput prices justify further investments. Therefore summarizing Brealey et al. (2008) and Copeland and Tufano (2004) the right to wait and learn before investion is the option to defer.
Generally this option is a call option but it can be either European-style or American-

style option. The usage of this project is mostly in natural-resource investment as Trigeorgis (1996) point out with the examples of constructing or building a plant or developing an oil or gas field.

2.4.2 Option to Expand and Option to Contract

An option to expand can be described as taking an option today may allow the option holder to consider and to take other projects in the future. Therefore it can be described as the right to increase the scale of production when the payoff of output is higher than the cost of increaisng the scale. The option to expand is also a call option.
On the other hand a the option to contract is the right to decrease the scale of production when the loss from producing at current scale is higher than the cost of reducing the scale. This is contrary to the option to expand a put option and can be used to decrease the loss. Both of the described options can be either American or European-style options.

2.4.3 Option to Abandon

If the cash flows don't meet expectations the options holder may sometimes abandon the investment. Since we will use this option for our mathematical project valuation in further chapters we will show an example of this option.
Consider a research and development process with different stages to pass before entering the market. Cash flows start as soon as the product enters the market put not before. Assuming an investment which does not pass one of the stages before entering the market the option holder is likely to abandon the option since further investments will not return expected cash flows with a high probability. A reason for abandoning the investment would be met as soon as the costs exceed future cash flows and the investment is not taken to allow future investments.
Summarized this means that that this option allows the option holder to save itself from further losses and can make therefore the project more valuable. It is equivalent to a put option and could be both European-style or American-style. According to Trigeorgis

(1996) even if this option is simple it is widely used in capital-intensive industries such as pharmaceutical industry.

2.4.4 Time-to-Build Option

Considering an investment which has several stages, the option holder has the right to abandon the project if new information within these stages is unfavourable. This is refered as an compound option which is an abandon option on an abandon option. Following what we described for the option to abandon this is extremly relevant for R&D intensive industries Trigeorgis (1996).

2.5 Real Option valuation research

In the following we want to give a short overview on valuation techniques discussed in the literature which had an impact on this thesis. Hartmann and Hassan (2006) discuss in their paper the application of real options analysis for pharmaceutical R&D project valuation. They present empirical results out of a survey which asked for the use of real options analysis within the project valuation of pharmaceutical companies. Elmquist and Le Masson (2009) present a evaluation framework for building innovative capabilities and Cortazar et al. (2001) present a real options model for the optimal exploration investments under uncertainty.

Another recent paper was published by Cassimon et al. (2011) who incorporate technical risk in compound real option models to value a pharmaceutical R&D licensing opportunity. The same idea is pointed out by Pennings and Sereno (2011) who evaluate pharmaceutical R&D unter technical and economic uncertainty. Jacob and Kwak (2003) give an insight into innovative techniques to evaluate pharmaceutical R&D projects and Perlitz et al. (1999) discussed in general the real options valuation as a R&D project evaluation tool. Considering the valuation of exploration and production asssets, Dias (2004) gives a general overview of real options models.

We will present in this thesis a technique to value one project, Van Bekkum et al. (2009)

discuss the perspective of real option on R&D portfolio diversification. Especially interesting concerning our case was the paper Brouthers and Dikova (2010) focusing on acquisitions and real options as the greenfield alternative.

2.6 Simple Valuation Methods

2.6.1 Net Present Value

We have discussed together with GlaxoSmithKline Austria the parameters for the case. We proposed the parameters used by Schwartz (2004) and they were slightly changed by GSK Austria to fit our case better.

The method we have focused on in this thesis, the Least Squares Monte Carlo simulation, is commonly not used in reality. Therefore we want to present the common model to evaluate investment, namely the net present value method.

Since we assume a maximum investment rate which is equal to the completion costs for each stage the investment rates can be described as in Table 2.1:

Table 2.1: Input Parameters for NPV Analysis

Period	Costs of Completion	Time in $Phase_j$	Investment Rate
Phase I	10	2	5
Phase II	35	2	17.5
Phase III	75	3	37.5
Approval	20	3	10

The cash flow rate, the terminal cash flow multiple and the real risk adjustable discount rate are taken from Schwartz (2004).

Table 2.2: Assumed Input Parameters for NPV Analysis (Schwartz (2004))

Cash Flow Rate	20
Terminal Cash Flow Multiple	5
Real Risk Adjustable Discount Rate	10%

As for the whole case we assume a period of 20 years which is divided into 10 years of research and development and 10 years of patent protection which equals a monopolistic situation. As a period of time we consider the year 2011 as the start of research and development with an end date in year 2031. Since we face cash flows only after the 10 years of research and development are finished we first calculate the discounted cashflows in between 2021 and 2030.

Table 2.3: Discounted Cashflows

Time	2021	2022	2023	2024	2025	2025	2026	2027	2028	2029
Cash Flows	20	20	20	20	20	20	20	20	20	20
Values	18.18	16.52	15.03	13.66	12.41	11.29	10.26	9.33	8.48	38.55

According to the table above the net present value at 2021 is calculated as the sum of all present values for each year between 2021 to 2030. For our case the net present value of the project at 2021 is 153.73 millon.

In the next step we include the costs for Phase I, Phase II, Phase III and Approval. These are weighted by transition probabilities which are taken from DiMasi et al. (2003) and then discounted to the basis year 2011.

Table 2.4: NPV Calculation

Period	Probability	Investment Rate	Weighted Investment Rate	Discounted Investment Rate
Phase I	0.71	-5	-3.55	-3.55
Phase II	0.314	-17.5	-5.495	-4.54
Phase III	0.215	-37.5	-8.0625	-6.05
Approval	0.2	-10	-2	-1.36
2021 NPV	0.2	153.73	30.74	11.85

If we sum up the net present value at 2021 which is again discounted with the discounted investment rates 2011-2021 the net present value is calculated as -3.66. A negative NPV would mean that the project would substract value from the firm. Therefore the decision making based on the NPV is not to start the project[3]

We have chosen a quite high discount rate with 10% and came to the presented results. If we assume a real risk adjustable discount rate of 3% the NPV becomes nearly 5 million dollars. This shows that the assumptions we make in the concept of NPV are not sufficient and the problem is that projects are often underestimated. The problem hereby is that the NPV underestimates the flexibility of the project and therefore underestimates the project at all.

The purpose of this NPV calculation was to show that there is a need for a more accurate modell of investment evaluation, which will be presented with the Least Squares Monte Carlo Simulation.

[3]Note that the NPV is very much dependent on the real risk adjustable discount rate.

Chapter 3

Costs of Research and Development

Through the discussion process with GlaxoSmithKline we came to the conclusion that there is a need in this thesis to present in detail the research and development process and its underlying costs. In the first section of this chapter the research and development process is discussed. The purpose of this section is to give a deeper insight into the R&D process and to give an understanding that the investment in pharmaceutical R&D differs substantial from other investments. The last part of the following section deals with the patent protection system in the EU and points out some reasons why a patent protection can be increased. Grabowski and Vernon (1994) point out that the patent protections have a significant effect on the expected cash flows, therefore it is necessary to discuss patent protections for a valid modell.

Section two provides insights into the estimation of costs of pharmaceutical research and development. GlaxoSmithKline as most other companies as well as the scientific community rely mostly on the research by DiMasi et al. (2003). We use results provided by various studies of DiMasi et al. (1991), DiMasi et al. (1995), DiMasi (2000), DiMasi (2001) and DiMasi et al. (2003) and compare them to the results from Public Citizen (2001) which comes to totally different results. We will present the data used, the methodology and the results of both and afterwards review the main ideas and especially the data and methodology used. DiMasi et al. (1991) and OTA (1993) came to their results either by basing on a case study for a specific drug, by ignoring the possibility of failure or using aggregate data. Since these estimations are important for our further

analysis it is crucial to discuss them in further detail.

3.1 Research and Development

In this section we want to present the research and development process and the cost structure of this process.
First we take a brief look at the research and development process and the different phases. The trials begin with laboratory trials. Scientists define a target in a certain disease and search for a molecule which has an impact due to this target. After this process the scientists are able to patent a candidate for an innovative drug. The next step is to verify the positive impact of this candidate. The research and development process has changed in the last years. The drug ADALT©from Bayer (used for diseases concerning the coronary arteries) for example took the chemist Friedrich Bossert 16 years in a trial and error principle to find the substance *nifedipine* (Mahlich (2006)). Nowadays this process is done by High Throughput Screening roboters. Due to Computer Aided Drug Design the time used for this process has been optimized in the last years, so the question is: why do costs rise? Therefore the first part of this section gives a brief overview over the structure of the clinical trials and should help to understand why costs for R&D rise within the last years:

3.1.1 Phase I

Phase I of the clinical trials is the first time of testing the new drug on humans. In this first phase a relatively small group of volunteers is formed. This phase deals mostly with pharmacokinetics and pharmacovigilance. Pharmacokinetics describes the tolerability of a drug and how the organism reacts about the substance. Pharmacovigilance describes the safety of the study drug. If scientists are aware of the risks the group of probands consists of people affected with this certain disease.

3.1.2 Phase II

When Phase I is completed the trials go on to Phase II. In this phase the results from Phase I have to be proven on a larger group sample. In general the size of the group lies between 20 and 300 patients. People involved in this study are volunteers and in some cases get paid for their participation. It is also the first time that the group of volunteers is divided in two groups to prove the positive results of a substance in comparison to a placebo.

3.1.3 Phase III

The groups of patients involved in Phase III consist of 300-3000 persons, depending on the type of disease and medical condition which is studied. This group of patients is then divided into two separate groups: one group gets the substance which scientists want to test and the other group gets a placebo. Because of the group size of patients, the long duration compared to the other phases and the two different data sets (one with placebo and one with the real substance), Phase III trials are the most expensive and time-consuming trials within the whole process.

3.1.4 Phase IV

In the clinical trials Phase IV is also described as the Post Marketing Surveillance Trial. Trials in Phase IV are made after the authorization of the drug and are therefore mostly for marketing reasons and for improvement of the drugs. If there are any harmful effects discovered in Phase IV trials this may cause that the drug is no longer sold.

3.1.5 Entry of drugs in phases

To understand the difficulties and the costs in R&D it is important to know how large the percentage is which enters one of the four phases. This percentage is shown in Figure 3.1. Obviously the percentage of entering phase I is 100%, but it is very interesting

that only 71 percent pass even the first phase and enter the second phase. For the cost analyses the percentage of drugs entering the market is the most interesting one. The Congressional Budget Office published the number of 21.5 percent of drugs which entered the first phase entered also the market (CBO (2006)).

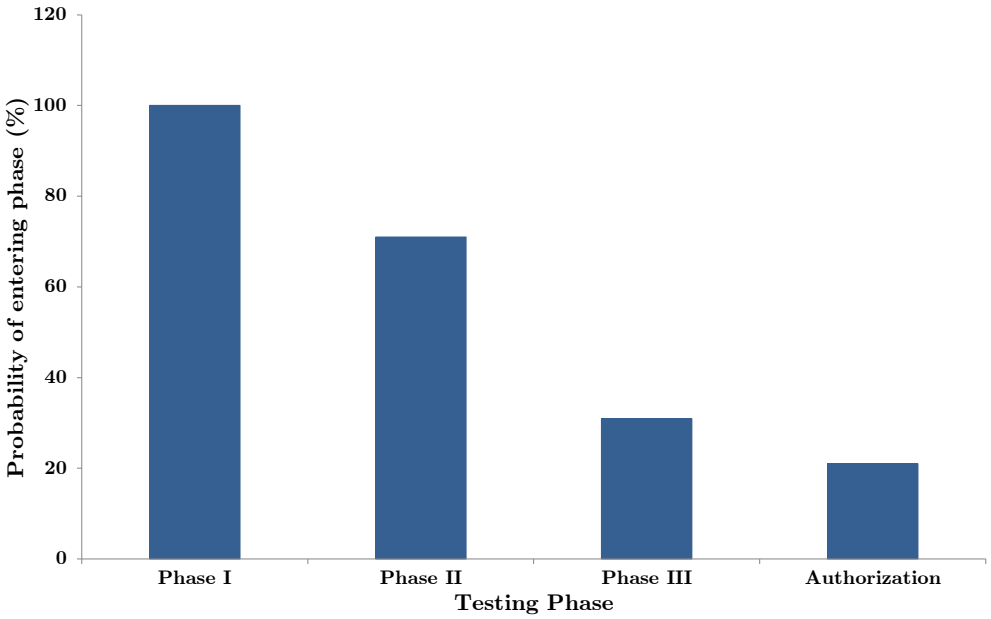

Figure 3.1: Entry of drugs in phases (DiMasi et al. (2003))

3.1.6 Patent Protection

Like most other products pharmaceuticals enjoy patent protection for 20 years. However, there are striking differences between drugs and other innovative products. In other industries products apply for a patent shortly before market entry. Pharmaceutical researchers and companies patent their drug long before it enters the market. They are patented as intellectual property of the inventor. Between patenting and availability of the drug to patients an average of 11.8 years elapses, which are essential for all stages of the investigations (DiMasi et al. (2003)). If you take the patent protection, which

applies to all industries equally, one can expect an average of eight years of patent life for an innovative pharmaceutical product (DiMasi et al. (2003)). For this reason, it is possible for the patentee to apply for additional protection (Supplementary Protection Certificate, SPC). This additional protection extends the patent term by up to 5 years. In addition to this protection option, there are other legal provisions that can be exploited by pharmaceutical companies:

3.1.7 Data Exclusivity

In addition to the patent rules there is also a so-called data exclusivity throughout the EU. For all submissions from 30 October 2005 on it holds that studies that were used for the new drugs can be used at the earliest after 10 years as a basis for the approval of a generic product.

After 10 years, it is possible for generic companies to use in the approval process the same studies that were already prepared for the approval of the original drug. With this new law inventor and patent holder can assume that their studies are protected for 10 years. Only after 10 years it is allowed that generic companies bring drugs on the market ('8 +2' rule).

Pharmaceutical companies, which act as proprietor of the drug found, are allowed to operate as a monopolist for 10 years and amortise the high research and development costs[1]. If it is possible for the holder of the authorization to use the drug for other indications and treatment methods, the protection of 10 years can be extended to 11 years (8 +2 +1' rule).

Special features in European patent law:

- *Roche - Bolar - Provision:* The preparation of documents for follow-up or generic products trials and studies of the patented drug may already be made during the

[1]Note that we assume innovative products which fall under a monopoly status after entering the market.

patent. This is not a special feature, but the European version of the Roche-Bolar amendment in the USA.

- *Paediatric drugs:* This clause exists since January 2007 in the European pharmaceutical law. The clause indicates that all new drugs in the EU must be tested on the application for children. If it turns out that new, patented drugs are suitable for children, additional protection for 6 months is allowed. After the expiry of the patent, data exclusivity can be obtained for an additional year if new pediatric data is submitted within the first 8 years of data exclusivity.

- *Orphan Drugs:* The patent holders of pharmaceuticals, which can be used to treat a rare disease (in the EU: less than 230.000 patients per year or 5 per 10.000 inhabitants), can request an orphan drug status at the EMA (European Medicines Agency). Orphan drugs enjoy market exclusivity under certain conditions to their approval. That is, after the initial approval of an Orphan Drug the EMA may not further approve applications for approval for a drug for this indication or issue a registration in this indication. In certain cases, the market exclusivity can be reduced to six years (Official Journal of the European Communities, 1999).

It is also clear that we face on both sides, the demand and the supply side, factors which are costs drivers. Seiter (2005) describes these costs drivers in '*HNP Brief #7-Pharmaceuticals: Cost containment, Pricing, Reimbursement*'. What we have presented in the last pages about patent rights shows that investing in R&D in pharmaceuticals and entering the market is costly and not that easy at all. On one hand it could be very difficult to access the market or on the other hand the existing market could be simply too small for more companies. These barriers in entering the market could drive up the price for a new drug. What we will see in the following pages is that even if they are critising each other both the studie by DiMasi et al. (DiMasi et al. (1991), DiMasi et al. (1995), DiMasi (2000), DiMasi (2001) and DiMasi et al. (2003)) and the Public Citizen (2001) report estimate a high number for R&D costs for pharmaceuticals. Therefore companies producing drugs will point out every clinical advantage of a new drug over

an old one even if it is marginal (Seiter, 2005). This is a cost driver on the supply side since the purpose is to shift the demand to the newer and in most cases more costly products.

On the demand side we also face cost drivers but in contrast to the supply side we face cost drivers through the volume of drugs which are bought and demographic changes. Health systems have to cope with a demographic - aging. Since treatments, hygiene and the quality of life became better and better over the years the demographic situation in OECD countries has changed dramatically. The volume of drugs sold is driven by this aging population and by the spread of diseases like HIV and malaria in developing countries (Seiter, 2005). Another cost driver on demand side is the physicians. The marketing efforts of companies selling drugs are huge and therefore physicians are guided to prescribe drugs with very little clinical advantages and higher costs. What has a huge impact on the demand side is the information asymmetry. Information asymmetry is given if one party has better information than the other party. For example in most cases the doctor knows more about the health status of the patient than the patient himself. This information asymmetry could lead to an acquisition of treatments and drugs without really knowing about the efficiency of the new treatment.

3.2 Costs of Research and Development

Together with Grabowski and Hansen, DiMasi has published since the early 90s a lot of papers concerning R&D costs for pharmaceuticals. The methodology hasn't changed a lot from the year 2003 paper by DiMasi et al. and the first paper in 1991. Afterwards this methodology and the data used by DiMasi et al. (2003) is discussed with the help of the 2001 Public Citizen (2001) paper on "*Rx R&D Myths: The Case Against The Drug Industry's R&D 'Scare Card'*". This paper criticizes the methodology used by DiMasi et al. (1995) and calculates R&D costs without using opportunity costs. In the last section we want to concentrate on a critical review of both of these econometric studies with the help of the Ernst&Young LLP *Pharmaceutical Industry R&D Costs:*

Key Findings about the Citizen Report.

3.2.1 R&D Costs by DiMasi et al

Joseph A. DiMasi, Ronald W. Hansen and Henry Grabowski examined in their 2003 study "*The price of innovation: new estimates of drug development costs*" the R&D costs for a new drug. For their study they took a random sample of 68 drugs from a survey of 10 pharmaceutical firms (DiMasi et al. (2003)). With these data they estimated the average pre-tax costs of a new drug. As these three authors are the leading experts in the estimation of R&D costs, three of their papers serve are presented in more detail in this thesis. In the study from DiMasi et al. (2003) costs for R&D were estimated at 802 million dollars for a new drug. In comparison to the market entries in the 1980s the total capitalized costs grew with a yearly growth rate of 7.4% (DiMasi et al. (2003)) above general price inflation. The main reason for this increase of R&D costs is associated with the size and number of clinical trials, which grew constant since the 1990s (DiMasi et al. (2003)). The spending in R&D in the last 25 years increased nearly to 50%. The main part of this increase took place in the early 1980s. Since then the R&D expenditures increased constantly by 19 percent. In the following abstracts we take a deeper look at the data and try to figure out a concrete image of R&D costs.

3.2.2 Data

Before discussing the structure of costs of the R&D process we should take a brief look at the data which was used int the paper by DiMasi et al. (2003). For the study of DiMasi et al. (2003) 10 multinational firms provided data about their new drug R&D costs. If taking the pharmaceutical sales as a measure of a firm's size, four of the survey firms are top 10 companies, another four are among the next 10 largest firms, and the remaining two are outside the top 20 (PJB Publications (2000))[2] For this sample of private firms it is not clear, whether the fact that the basic development was performed in government or

[2]Please note that all the companies in this sample are private firms. Universities or public research labs are not included in this sample.

academic labs has any effects on the results. DiMasi et al. (2003) use for answering this question the National Institutes of Health Report (2000) which comes to the conclusion, that of 47 FDA-approved drugs that had reached at least US 500 million in US sales in 1999, the government had direct or indirect use or ownership patent rights to only four of them (NIH (2000)). This can be confirmed by the Tufts CSDD database, which shows that out of 284 new drugs approved in the United States from 1990 to 1999, 93,3% where originated by industrial sector. The firms which are presented in the survey account for 42% of pharmaceutical R&D expenditures. From the 68 drugs which were investigated in the process, 61 are small molecule chemical entities, four are recombinant proteins, two are monoclonal antibodies, and one is a vaccine DiMasi et al. (2003).

3.2.3 Methodology

The expected costs of a research and development process are not easy to measure. To understand the model which was used the equation in DiMasi et al. (2003) for expected costs in the clinical period should be presented. In all of the three phases in clinical trial there is a certain probability that the drug will enter the phase. We define c as the costs in R&D for a randomly chosen drug. The expected costs therefore are a combination of the probabilities of entering a certain phase and the population mean costs for drugs that enter phases IIII,

$$c = E(c) = p_I \mu_{I|e} + p_{II} \mu_{II|e} + + p_{III} \mu_{III|e} + + p_A \mu_{A|e}$$

where p_I , p_{II} and p_{III} are the probabilities that a randomly selected entity will enter phases I, II or III and p_A stands for the probability that a long term animal testing will be conducted. μs stand for the population mean costs for drugs that enter phases IIII, and specifically $\mu_{A|e}$ stands for long-term animal testing.

3.2.4 Duration and structure of the developing phase

Table 3 is divided in three sections: in the first section we see the average duration of the preclinical phase. In the preclinical phase scientists search for molecules which have

some impact on the symptoms of a disease.

Table 3.1: Average Duration of an R&D Process (DiMasi et al. (2003))

Preclinical phase	Clinical Trials and Authorization	Total
4.3 Years	7.5 Years	11.8 Years

The process of finding the substance for the target takes place in the laboratory. This is one of the reasons why the time used for this process is relatively short compared to the other phases in the R&D process. The time estimated by DiMasi et al. (2003) for the preclinical phase is 4.3 years. The estimation for the clinical trials phase, which can be seen in Table 3, points out that in average 7.5 years are spent in this phase. As mentioned before since the late 1990s clinical trials became more complex. The pharmaceutical firms changed from producing drugs for acute diseases to drugs for chronic diseases. A chronic disease lasts for a long time so the studies had to be extended to capture significant results concerning the effects of the drug (most of the recent studies take up to 2-3 years in Phase III). Also the marketing authorization of a new drug has become more difficult due to new laws in several countries. As a result the group size of patients in a study increased. Summarized, this leads to a total development period of 11.8 years. Table 4 shows the cost analysis from DiMasi et al. (2003) and assigns them to the different stages in R&D.

Table 3.2: Cost Estimations (DiMasi et al. (2003))

	Preclinical phase	Clinical Trials and Authorization	Total
Direct costs	121	282	203
Opportunity costs	214	185	399
Total costs	335	467	802

In new estimations also opportunity costs are part of the total costs. Opportunity costs describe costs which occur when choosing one alternative but therefore forgoing another. Following the arguments by DiMasi et al. (2003) from an economic point of view

it is not sufficient to take only direct costs into account as not every drug can be placed on the market. Therefore the development and research costs for these fails appear as opportunity costs in the calculation. Opportunity costs exist in every industrial sector but in the pharmaceutical industry they are extremely relevant as the capital is tied for a long time due to the long research and development duration (DiMasi et al. (2003)). The calculated costs include both direct and opportunity costs thus increasing costs can also imply an increasing number of failures (DiMasi et al. (2003)). Figure 3.1 showed the percentage of drugs in the specific development phases. It is understood that every single drug goes through phase one. As it can easily be seen the number of drugs which go on to phase two declines by almost a third and in phase three the number of drugs is as small as 30% of the original number. Only about 21.5% are admitted for the last developing phase, the marketing authorization procedure.

3.2.5 The average R&D costs

With the summarized data in Figure 3.2 we can see an increase in the costs between the years 1976 and 2000. The costs have been sextupled up to 802 million dollars in the year 2000. Within 20 years the expenditures have changed dramatically. The first estimation from Hansen (1979) arrives at the conclusion that a total amount of 138 million dollars is needed for the R&D process of a new drug[3]. There is a constant increase from 1979 to 2000 with an estimated amount of 319 million dollars in 1988 and 445 million dollars in 1992. The reason for the rapid increase between 1992 and 2000 could be the change in the strategy of large pharmaceutical firms. Large pharmaceutical companies have turned their attention from acute towards chronic diseases. The consequence of this switch is that the time spent for clinical trials increased which then leads to higher costs in the R&D process. Acute diseases require a rather short time in clinical trials because their active pharmaceutical ingredient has to achieve a punctual effect. On the other hand drugs for chronic diseases have to prove their value over a long time. For that reason the clinical trials have to last over a long time to assure that the failure in testing the

[3]This estimation includes as always the opportunity costs generated by failed attempts, Figure 3.2

substance is minimized.

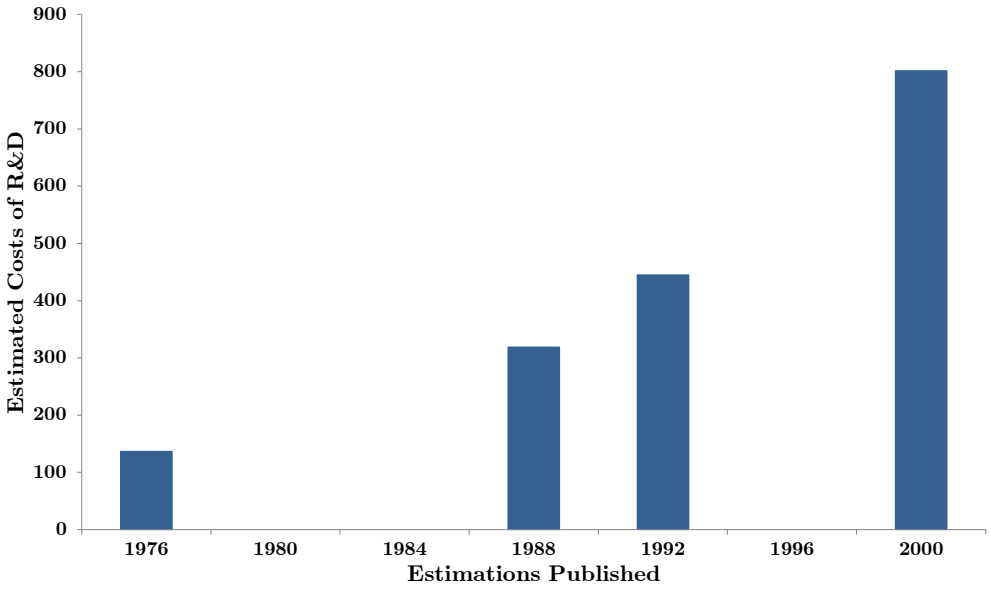

Figure 3.2: Average R&D costs (Hansen (1979), DiMasi et al. (1991) and DiMasi et al. (2003))

3.2.6 Structure of the costs

After we have seen the time required for research and development in the last sections, we now look at the cost structure in these explicit years. The years are chosen as a comparison of the studies which were made in those years (Hansen (1979), DiMasi et al. (1991) and DiMasi et al. (2003)). First we look at the pure, inflation adjusted data. These costs include the pre-clinical, the clinical and the total costs. Within the years from 1979 and 2000 the structure of the costs in R&D phases has changed dramatically. Figure 3.3 shows how the money is spent between preclinical and clinical phase.

Not only the total amount of money spent in R&D has increased but also the distribu-

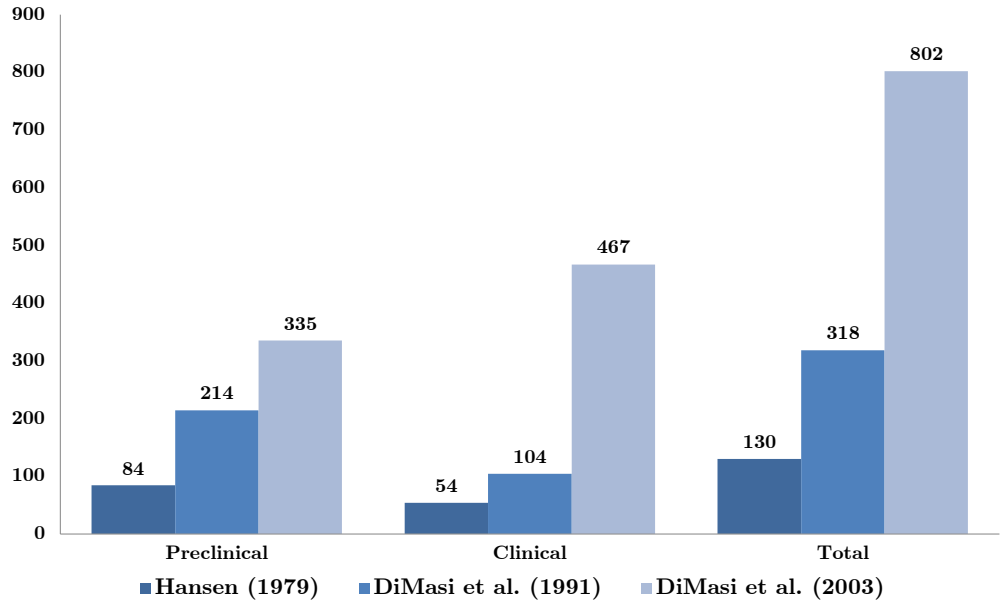

Figure 3.3: Structure of the costs in R&D phases

tion has changed. Table 3.3 compares the capitalized costs with the "out-of-pocket"-costs of the three studies from Hansen (1979), DiMasi (2001), and DiMasi et al. (2003).

Table 3.3: Annual growth rates in order to 'out of pockets' costs (Hansen (1979), DiMasi (2001), and DiMasi et al. (2003))

Period	Out-of-Pocket		
	Preclinical(%)	Clinical(%)	Total(%)
1970-1980	7.8	6.1	13.9
1980-1990	2.3	11.8	14.1

The time periods are limited to 10 years, thus the cost of bringing drugs onto the market in the 1970's are described by the study of Hansen (1979), the costs of the 1980's are from DiMasi et al. (1991) and the costs of the 1990's originate from DiMasi et al.

Table 3.4: Annual growth rates in order to capitalized costs (Hansen (1979), DiMasi (2001), and DiMasi et al. (2003))

Period	Capitalized Preclinical(%)	Clinical(%)	Total(%)
1970-1980	10.6	7.3	17.9
1980-1990	3.5	12.2	15.7

(2003). The total "out of pocket"-costs of the period 1970-1980 are 13.9%, thus they are almost identical to the "out-of-pocket"-costs of the period 1980-1990 which are 14.1%. Hence we should draw our attention to the costs divided into the specific phases of the developing procedure rather than to the total costs. Therefore we take the study of DiMasi et al. (2003) into consideration which divides costs for the preclinical phase and the clinical phase. As it can be seen during the years 1970-1980 the "out-of-pocket"-costs were rather uniformly distributed between preclinical and clinical phase. The costs in the clinical phase will increase more and more as the time of study increases and therefore the costs of this phase rise. The number of drugs in the first phase of development which were admitted to the market declined to 10% in the last few years (DiMasi et al. (2003)).

3.2.7 Reasons for increase in R&D costs

As we have seen in the last paragraphs one reason for the increase in R&D is the turn in production from drugs for acute to drugs for chronic diseases. The study of DiMasi et al. (2003) comes to the conclusion that the trials and studies in the R&D process for chronic disease must generate more data and take longer to show long-term benefit in patients. This is one of the main reasons for the increase in R&D expenditures over the last years. In summary the study of DiMasi et al. (2003) comes to a list of reasons for the increase in drug development costs over the last years:

- Increase of failed attempts in the R&D process (in the state of clinical trials).
- Regulations, which ask for a longer and larger clinical trials.

- The increase of clinical trials itself[4].
- The attention is more and more turned to producing drugs for chronic diseases[5].
- The introduction of new methods in the R&D process and the restructuring of the production process involve new costs. When a new method is introduced it entails some run-in period.

Additionally, studies found that only one in every 5000-10000 molecules screened in the laboratory makes it to the market DiMasi (2001). The increase in R&D costs was shown by Figure 3.2. It shows the increase from 137 million dollars in 1976 published by Hansen (1979) up to 802 million dollars in 2000 published by DiMasi et al. (2003). The other data are taken from the paper DiMasi et al. (1991).

3.3 Public Citizen

The Public Citizen (2001) report criticizes that the studies by DiMasi et al and the arguments made by the Pharmaceutical Research and Manufacturers of America (PhRMA) about the cost situation of R&D do not display the reality. Their analysis suggests that the risk which is faced for research and development of new drugs isn't that high due to the fact that the industry gets subsidized a lot and taxes on profits are very low (Public Citizen, 2001).

3.3.1 Data

The Public Citizen (2001)report uses data from the PhRMA which is divided in two categories:

1. "domestic" data which describes all expenditures by companies (both American and foreign) in the U.S. and

[4]Also trials which are made to differentiate the product of one firm from the product of another firm are considered here.

[5]This assumption only holds for large pharmaceutical firms. Small firms search for a niche therefore it's supposable that they produce drugs for acute diseases.

2. "abroad" expenditures, which describe expenditures by U.S. companies abroad (Public Citizen (2001)).

For the analysis data concerning the market entries of drugs are taken from the FDA. The problem here is that the FDA reports the number of drugs entering a certain market without any connection to where the expenditures on R&D were done.

3.3.2 Methodology

The Public Citizen (2001) report used a simple model to estimate R&D costs. They used the data provided by the PhRMA on the expenditures in R&D and divided it by the amount of drugs entering the market. In comparison to DiMasi et al they didn't use the opportunity cost of capital with the idea to show the actual expenditures for R&D. This major difference in the analysis of R&D costs compared to DiMasi et al will be discussed later.

3.3.3 The average R&D costs

In the following results derived from the Public Citizen (2001) report are shown. For the results 7 year periods are taken which should simulate the time between R&D expenditure (in other words the duration of the different phases we have discussed at the beginning) and the market entry of a certain drug on the market. Then these data are compared to the number of drugs entering the market reported by the FDA. Using the example by the Public Citizen (2001) report from 1988 through 1994 PhRMA reported 69.7 billion of total R&D expenditures which corresponds to 88 billion dollars inflation adjusted in 2000. Then the average over these 7 years is taken which yields 12.5 billion per year.

This is compared to the number of approved drugs by the FDA from 1994-2000. Since the FDA has approved 667 new drugs in this time frame 95.3 approved drugs are calculated for each year (Public Citizen, 2001).

The strategy of the authors is to look at the after-tax R&D expenditures per new drug.

They argue that R&D is taxed in the U.S. with a factor of 0.6 for each dollar spent, which yields to 71 million dollars after tax expenditures derived out of 107.6 million dollars pre-tax R&D expenditures.

Looking at Table 3.5 provided by the Public Citizen (2001) report for the Average R&D Cost per New Approved Drug during the 1990s we see that with the help of the data provided by PhRMA and the FDA pre-tax and after-tax expenditures per drug are calculated for 7 year R&D time periods between 1984 and 1994. Compared to the cost structure seen in DiMasi et al. (1991), DiMasi et al. (1995), DiMasi (2001) DiMasi et al. (2003) and Hansen (1979) the expenditure is not anywhere as low as the numbers by the Public Citizen (2001) report[6]. The Public Citizen (2001) report argues that DiMasi et al. (1991) in their studies used data on the most expensive entities for R&D, namely the new chemical entities (NCE's). To be comparable to these studies the Public Citizen (2001) report tested their methodology on NCE's data. Table 7 shows that for new molecular or chemical entities the R&D expenditure doubles also in the Public Citizen (2001) report but is still lower than the results by DiMasi et al. (1991).

Important to notice is that the Public Citizen (2001)report argues that NCE's are only a part of R&D and the analysis of them is not that important as the studies by DiMasi et al suggest. As discussed before DiMasi et al. (1991), DiMasi et al. (1995), DiMasi (2000), DiMasi (2001) and DiMasi et al. (2003) used for their data NCE's to derive the total R&D expenditure.

3.4 Conclusion

We have presented two methods for estimating the R&D costs for drugs. Now we want to discuss the differences between these two methods. As mentioned before the Public Citizen (2001) report does not include the opportunity costs of capital. The study by Ernst&Young LLP (2001) confirms DiMasi et al. (2003) who described the R&D process as highly risky. The economic theory describes opportunity costs as the opportunities one would have by using the money spent for other investments. Especially in sectors where we are confronted with high risk investments it is necessary for an analysis to include these opportunity costs in the analysis since the decision maker decides in this

[6]Note that the argument includes inflation adjusted expenditures

Table 3.5: Average R&D Cost per New Drug Approved During the 1990s ($ in millions, all in year 2000)

7-Year R&D Period	Average Annual R&D Spending	7-Year NDA Period	Average Annual NDA's Approved	Pre-Tax R&D Spending per New Drug	After-Tax R&D Spending per New Drug
1988-1994	10255.3	1994-2000	95.3	107.6	71
1987-1993	9387.8	1993-1999	91.3	102.8	67.9
1986-1992	8473.3	1992-1998	92.4	91.7	60.5
1985-1991	7613	1991-1997	88.6	86	56.7
1984-1990	6887.1	1990-1996	80.4	85.6	56.5

Table 3.6: Average R&D Cost per New Molecular Entity During the 1990s ($ in millions, all in year 2000)

7-Year R&D Period	Average Annual R&D Spending	7-Year NME Period	Average Annual NME's Approved	Pre-Tax R&D Spending per NME	After-Tax R&D Spending per NME
1988-1994	7588.9	1994-2000	33.4	227.02	149.8
1987-1993	6947	1993-1999	33.1	209.61	138.3
1986-1992	6270.2	1992-1998	31.9	196.82	129.9
1985-1991	5633.6	1991-1997	31.9	176.84	116.7
1984-1990	5096.4	1990-1996	29.6	172.34	113.7

situation for a higher risk investment and against one with a lower probability of failing. We think that the use of opportunity costs as a decision making instrument to decide whether or not investing in a certain investment is a standard procedure. Our critiques on the DiMasi et al studies focus on the direct inclusion of these opportunity costs into the overall R&D expenditure estimations. We described that DiMasi et al. (2003) calculated out-of-pocket costs of 403 million dollars and the opportunity costs of 399 million dollars and by summing them up DiMasi et al. (2003) came to the result of 802 million dollars pre-approval costs. It has to be clarified if opportunity costs are the costs for an alternative direct investment or if they consider the case where one spends 10.000 dollars now on R&D with a high risk and waits for ten or more years until he gets anything out from this.

Comparing the methodology used by DiMasi et al with the methodology used by the Public Citizen (2001)we came to the conclusion that the model used by the Public Citizen (2001)is more or less a rough calculation of how costs for the R&D process look like. Since we agree with the Ernst&Young LLP (2001) study that the R&D process in drugs is highly risky, including probabilities of entering different phases in the model makes more sense than simply dividing the expenditures by the number of drugs entering the market. Therefore calculating the expected costs by incorporating the transition probabilities will lead to a more significant result than dividing sales by the number of drug entries.

Both Ernst&Young LLP (2001) and the OTA (1993) study conclude that the data used by DiMasi et al. (2003) shows a substantial consistency between aggregate R&D spending estimates and cash outlays per NCE estimated by DiMasi (Ernst&Young LLP (2001)). After the review of the data used by DiMasi et al and Public Citizen (2001)we found shortcomings in both studies. By going through the paper by DiMasi et al. (2003) and especially the data section we did not find any information about the drugs which were chosen for this study. The data used in the study consists of ten multinational pharmaceutical firms. Four companies in the data set are top 10 companies, another four are among the next 10 largest firms, and the remaining two are outside the top 20.

We also know that from the 68 drugs reported: 61 are small molecule chemical entities, 4 are recombinant proteins, 2 are monoclonal antibodies and 1 is a vaccine. What we don't know is why these drugs were reported from the pharmaceutical companies. Since we don't know why the firms reported these drugs and how the process of reporting took place, we cannot follow the Ernst&Young LLP (2001) report.

The usage of new chemical entities in the data was described by the Public Citizen (2001)report as a shortcoming of the data used by DiMasi et al. (1991). To our opinion new chemical entities may cause a large increase in public health. As we have described in the beginning new chemical entities have to pass several phases before they are allowed to enter the market. This NCE has never been tested on therapeutic efficiency on humans before. We have also described that a generic medicament is allowed after some time to use the study on clinical trials and enters the market without arranging own clinical trials. But the main question is if the study wants to estimate the average overall R&D costs in the pharmaceutical industry or not. We have mentioned several reasons why NCE's are different from other drugs. If the interest would be an average R&D expenditure estimation it would be not sufficient to include only those, even if their impact is higher to public health (which cannot be proven in this paper).
We have shown that another huge difference between the two estimations is which type of results they used. DiMasi et al used pre-tax estimations whereas the Public Citizen (2001)used after-tax estimations. Considering after-tax estimations leads to lower R&D costs since the Public Citizen (2001)report used the highest corporate tax rate and concluded that the R&D process of drugs is subsidized. We have looked through various scientific papers considering the R&D costs for drugs and found that almost all considered pre-tax estimations. The reason is that taxing the R&D process with the highest corporate tax does not include the financial profile of the business. Another point is that tax deductibility in this case has nothing to do with a subsidy for R&D in this sector. It has the purpose of not double taxing and therefore deducting expenses like R&D and salaries which accrue to other entities that pay income tax (Ernst&Young LLP (2001)). By using after-tax estimations one would tax the R&D process twice and

it is obvious that this is not the same as subsidizing the R&D process.

As far as we have studied existing literature, reviews and data we came to the conclusion that Public Citizen (2001)highlights some difficulties and shortcomings when estimating the costs on R&D in the pharmaceutical industry. But we believe that the estimations which were done by Public Citizen (2001)were made explicitly with the idea that the costs by DiMasi et al. (1991) were overestimated. Since many of the arguments used by DiMasi et al. (2003) and Public Citizen (2001) do not stand up to close scrutiny we cannot agree with the study by Ernst&Young LLP (2001) and therefore cannot consider the studies by DiMasi et al as an estimation for R&D costs. As described, the shortcomings of DiMasi et al. (2003) are the incorporation of opportunity costs and the data set used. The shortcomings of Public Citizen (2001) are in our opinion the after-tax results used, the methodology and also the used data set.

We conclude that the assumptions ade by Schwartz (2004) based on DiMasi et al. (2003) as well as the assumptions by GlaxoSmithKline follow the results of our analysis.

Chapter 4

Monte Carlo Simulation

In this chapter we want to present the Least Squares Monte Carlo algorithm (LSM) used by Schwartz (2004). Schwartz (2004) introduced his model as a one stage process. The assumption hereby is that the whole research and development process is not divided into different phases and assumed to be a one stage process. Schwartz (2004) has implemented his one stage process to value the R&D process of a pharmaceutical company in Fortran. In this thesis we want to implement the model presented by Schwartz (2004) in MATLAB and change the input parameters to fit the case of GlaxoSmithKline and Apeiron to value their milestone payment agreement. Schwartz (2004) proposed in the Appendix an extension to this problem to more accurately fit the R&D process. This multi-stage model will be presented and implemented in the next chapters.

4.1 Introduction

The project valuation method underlying the LSM algorithm following Longstaff and Schwartz (2001) is based on the general option pricing theory of Black and Scholes (1973), Merton (1973), Harrison and Kreps (1979), Harrison and Pliska (1981) and Heath et al. (1992) we have presented before. A multifactor Gauss Markov implementation of the proposed valuation method by Heath et al. (1992) is presented in Brace and Musiela (1994).

The pricing of financial options in generally by simulations is discussed frequently in

literature in the last years. Bossaerts (1989) discussed in a early contribution this way of valuing options by simulations. Boyle et al. (1997), Broadie and Glasserman (1998), Tsitsiklis and Van Roy (1999), Joshi et al. (2007) and Barone-Adesi et al. (2008) used simulations for valuing real options and had therefore an impact on this thesis as their suggestions concerning simulations were implemented in our model.
In the last years a lot of papers were published improving the valuation method by Schwartz (2004). An impact on this thesis had the recent works by Rasmussen (2002), Stentoft (2004), Wang and Hwang (2007), Cortelezzi and Villani (2009), Golec et al. (2010), Cuervo-Cazurra and Annique Un (2010) and Cassimon et al. (2011) which focused on solution methods to solve the real options valuation problem for R&D projects.

4.2 Least Squares Monte Carlo Algorithm

Least Squares describe an approach to approximate solutions for overdetermined or inexactly specified systems of equations. The purpose of the least squares approach is not to solve the equations directly but rather minimize the sum of squares of the residuals. Longstaff and Schwartz (2001) introduce $C(\omega, s; t, T)$ which describes the path of cash flows which are generated by the option with ω being a sample path. This function is conditional on the option not being excercised at or prior to point in time t and the optionholder is following the optimal stopping strategy for all s, $t < s$. The least squares are used to approximate the conditional expectation function for each point in time recursively, $t_{K-1}, t_{K-2}, ..., t$. The induition behind that is that $C(\omega, s; t_k, T)$ can differ from $C(\omega, s; t_{k+1}, T)$ since it may be optimal to stop a t_{k+1} and with this changing all subsequent cash flows in a realized path. Following Longstaff and Schwartz (2001) the value of continuation $F(\omega; t_k)$ can be expressed as

$$F(\omega; t_k) = E_Q\left[\sum_{j=k+1}^{K} exp\left(-\int_{t_k}^{r_j} r(\omega, s)ds\right) C(\omega, s; t_k, T)|\mathcal{F}_{t_k}\right] \tag{4.1}$$

Longstaff and Schwartz (2001) assume that the functional for Equation 4.1 can be expressed as a linear combination of measureable basis functions. These basis functions

are a set of polynomials. The model by Schwartz (2004) which we will use as a basis for our model does not explicitely clearify which polynomials as basis functions were used. Longstaff and Schwartz (2001) use Laguerre polynomials but also point out that others like Legendre or Chebyshev can be used.

4.2.1 Total Cost to Completion (K)

Following Schwartz (2004) this parameter refers to the total costs of completion. In agreement with GlaxoSmithKline we have set this parameter K at €223 million. These costs are defined as the total costs spend by GlaxoSmithKline within the milestone payment. The total costs to completion will decrease over time. Since we include following Schwartz (2004) investment uncertainty K follows a stochastic process. A stochastic process describes compared to a discrete process that there may be an inital starting point but with ongoing different possibilities of the process.

4.2.2 Cash Flow Rate (C)

The cash flow rate can be described as the cash flows that would be received per year if the project which is valued would be completed . Therefore if the project is completed, this means in our case that the research and development is completed, the cash flows are realised. These two different cash flows can be described as anticipated cash flows and realized cash flows. We defined for our case study a quarterly cash flow rate of €12.5 million. As we have described for K the cash flow rate follows also a stochastic process by the same behaviour.

4.2.3 Maximum Investment Rate (I) and Terminal Cash Flow Multiple (M)

Furthermore a maximum rate of investment I per year has to be defined for our case. Following Schwartz (2004) and DiMasi (2001) the average duration of a research and development process and therefore the investment period is 10 years and since the total

cost to completion at the starting point for GlaxoSmithKline are €223 million which equals €22.3 million of maximum investment rate. We consider in this case that the pharmaceutical company enters the market with its new drug and is protected by patent laws. This means that we do not consider drugs entering the market which are not protected by patent laws. We have described in the last chapters the reasons for patent protection. If a drug is under patent protection the cash flows for the patent holder are decreased significantly after the expiration of the patent due to the entry of generic drugs (Grabowski and Vernon (1992)). Schwartz (2004) included this fact in his paper by assuming that the terminal value of the project is five times terminal cash flow rate which equals the terminal cash flow multiple M to be 5.

4.2.4 Annual Probability of Failure (λ)

We have shown in the chapter on research and development cost estimation that there is a certain probabilty of failure for each project during the period of investment. Following Schwartz and Moon (2000) such events are called catastrophic events and could be unknown sideeffects of a drug or another company getting the patent for a certain molecule. A Poisson probability due to Ross (2003) satisfies the conditions that the number of successes in two disjoint time intervals is independent and the probability of a success during a small time interval is proportional to the entire length of the time interval. Therefore the Poisson probability with parameter λ can be used to describe the per unit of time probability of failure since with a defined unit time of one year. At the point in time were the project fails its value will jump to zero (Schwartz (2004)).

To run the simulaton following Schwartz (2004) further parameters have to be defined. The time step size Δt is described as the time whenever the option holder, in our case GlaxoSmithKline, can abandon to exercise the option. This means that GlaxoSmithKline can stop the payment and the project under certain circumstances every quarter of a year. Furthermore the time until the expiration is also taken from Schwartz (2004)

by 20 years [1]. Including the time step size this yields to a matrix with n paths (the number of possibilities derived by the simulation) and 80 points in time leading to a $n \times 80$ matrix.

4.2.5 Investment Cost Uncertainty

As we have mentioned before following Schwartz (2004) that the expected cost to completion is a dynamic parameter and can be therefore described by a controlled diffusion process[2]

$$dK = -Idt + \sigma(IK)^{\frac{1}{2}}dz \tag{4.2}$$

Since K has been defined as the total costs to completion dK equals the change in total costs to completion. I is again the investment rate and dt the time step size per year. Following Schwartz (2004) dz is an increment to a Gauss Wiener process[3] which is assumed to be uncorrelated with the market portfolio and σ the cost uncertainty.
The function can be described by the first term $-Idt$ which is the control of the diffusion process. This should reflect what we have said about the cost to completion. The estimated remaining costs to completion decrease as the investment proceeds.
Pindyck (1993) described the technical uncertainty, which is in our case $\sigma(IK)^{\frac{1}{2}}dz$, as the physical difficulty of completing the project and therefore can only be resolved by investing in the project. This definition of Pindyck (1993) has been used by Longstaff

[1] This assumption by Schwartz (2004) follows the estimations by DiMasi (2001). We have shown that the calculated value varied in the paper by DiMasi et al. (2003) but we take for our model also a 20 years of patent protection.

[2] Note that this controlled diffusion process is based on the work by Pindyck (1993) and following Schwartz (2004) any other process can be used without major changes in the analysis

[3] Following Merton (1998) a Gaussian process is a stochastic process $\{X_t; t \in T\}$ for which any linear functional applied to the sample function X_t will result normally distribution. The Wiener-process is named after Norbert Wiener. One of the most best known examples of the Wiener process is the Brownian motion. The Wiener process is described as a continuous stochastic process $W(t)$ for all $t \geq 0$ with $W(0) = 0$. The increment $W(t) - W(s)$ is then Gaussian with a mean of 0 and variance $t - s$ for $0 \leq s < t$ (Merton (1998)).

and Schwartz (2001) to describe the uncertainty in their least squares approach which is the basis for the model by Schwartz (2004). Therefore this definition is also used in this thesis.

According to Pindyck (1993), the cost uncertainty σ, can be inferred from a simple analytical expression which relates the variance of the projects total cost and the volatility parameter σ assuming that cost and cash flow processes are uncorrelated and the variance of cost to completion follows the following expression

$$Var(K) = \frac{\sigma^2 K^2}{2 - \sigma^2} \tag{4.3}$$

4.2.6 Cash Flow Uncertainty

Follwing Schwartz (2004) the dynamics of the net cash flow rate can be described by a Geometric Brownian motion:

$$dC = \alpha C dt + \phi C dw \tag{4.4}$$

Where again dw is an increment to a Gauss Wiener process which is correlated with the market portfolio. It may also be correlated with the uncertainty in the expected cost to completion of the project. The parameter α is defined as the cash flow drift or in other words the rate of inflation, whereas η is the risk premium associated with the cash flow process and ϕ defines the cash flow uncertainty.

Schwartz (2004) argues that for our purposes the risk neutral or risk adjusted process will be used

$$dC = (\alpha - \eta) C dt + \phi C dw \tag{4.5}$$

The risk premium associated with cash flow process η depends on the probability of a successful completion of the project, β, the return of the market, r_m and the risk free

rate, r:

$$\eta = \beta(r_m - r) \tag{4.6}$$

If we define $(\alpha - \eta) = \alpha^*$ where α^* as the risk adjusted drift we can reformulate the equation as

$$dC = \alpha^* C dt + \phi C dw \tag{4.7}$$

As mentioned before the cash flows are received by the option holder after the investment has been completed. The cash flows we receive in the simulations before the end of the investement are cash flows that would be received if the investment would be completed.

4.2.7 Value of the Project

We have two possibilities, either the paths in which the investment is completed or paths in which the investment is not completed.

Paths in which the investment is completed

For each path and discrete point in time two possible outcomes can be described. One outcome s that the investment is completed and the other is that the investment is still progressing. The value of the project is a function of realized cash flows and time. We calculate following Schwartz (2004) cash flows backwards from the end of the patent protection NT as a function of the terminal cash flow multiple and the cashflows of the point in time. Therefore at the expiration date of the patent, the value of the project is calculated as

$$W(i, NT) = M \cdot C(i, NT) \tag{4.8}$$

It is important to mention that this boundary condition holds if the project wasn't abandoned before. From this on we calculate the project value for those periods where

the investment is completed backwards starting with $W(i, NT)$. The following function is calculate until the stopping criterion is reached which is the discrete point in time where costs of completion are larger than 0.

$$W(i,j) = exp(-r\Delta t)W(i,j+1) + C(i,j)\Delta t \tag{4.9}$$

In the implemented simulation this procedure is looped until the period where research and development is not completed.

4.2.8 Paths in which the investment is not completed

For the case that the investment is not completed and an optimal abandonment is possible, the expected value of continuation is estimated following Schwartz (2004) by regressing the discounted value of the project $W(i,j) = exp(-(r+\lambda)\Delta t)W(i,j+1)$ onto a set of basis functions at point j in time. According to Schwartz (2004) the value received by this is the best unbiased estimator for the conditional expected value. The rule derived from this equation says that for all those paths for which the received value is smaller than the additional investment which has to be made in period j, the optimal strategic choice of the option holder is to abandon and therefore the investment rate I is set to $W(i,j) = 0$. For all those paths were the calculated value is larger than the additional investment, the value of the project is calculated as

$$W(i,j) = W(i,j)' - I\Delta t \tag{4.10}$$

This role back algorithm works by rolling back in time and searches for every discrete point in time or decision node if the decision criteria are met. According to Schwartz (2004) we have implemented the value of the project starting at time zero and moving forward until the expiration of the patent.

4.3 Solution Procedure

According to Schwartz (2004) we focus in the simulation of total cost of completion and expected cash flows not on continously points but rather on discrete points in time.

The argument is that a real option can only by exercised at a discrete point in time. Following Schwartz (2004) this assumption would made perfectly sense for analysing RD projects. The equation we have described for total cost of completion and expected cash flows have to be adapted to fullfill this assumption:

$$K(t+\Delta t) = K(t) - I\Delta t + \sigma(IK)^{\frac{1}{2}}(\Delta t)^{\frac{1}{2}}\epsilon_1 \tag{4.11}$$

$$C(t+\Delta t) = C(t) - exp((\alpha^* - 0.5\phi^2)\Delta t + \phi(\Delta t)^{\frac{1}{2}}\epsilon_2) \tag{4.12}$$

The parameters ϵ_1 and ϵ_2 are standard normal variates with correlation ρ. Standard normal variates can be derived by a Z transformation and will be obtained in the simulation by $\epsilon_1 = x_1$ and $\epsilon_2 = \rho x_1 + x_2\sqrt{1-\rho^2}$. The independent random drawings from a standardized normal distribution x_1 and x_2 are generated by a random function of MATLAB and then used to calculate ϵ_1 and ϵ_2. Moreno et al. (2001) examined the impacts of different basis functions on option prices and came to the conclusion that it can be not proved which basis function provide the best regression results. Schwartz (2004) has not clearly mentioned which basis functions he uses for his implementation of the algorithm. Schwartz (2004) mentions that he uses polynomials wth nine terms as bass functions. According to Longstaff and Schwartz (2001) the types of basis functions used include the Hermite, Legendre, Chebyshev, Gegenbauer and Jacobi polynmials. We present solutions using Legendre polynomials as basis functions for our coefficients. To compare our results generated with Legendre polynomials we used also Chebyshev polynomials for our one-stage model.

4.4 Legendre polynomials

For our implementation we have chosen the Legendre polynomials and used them as basis functions. The Legendre polynomials are solutions to

$$\frac{d}{dx}[(1-x^2)\frac{d}{dx}P_n(x)] + n(n+1)P_n(x) = 0$$

Figure 4.1 shows a plot in MATLAB of the first Legendre polynomials.

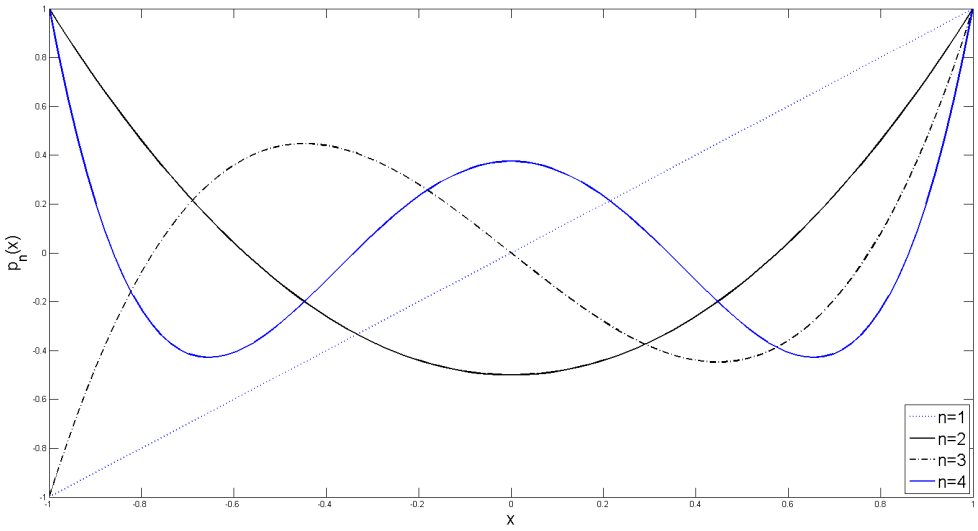

Figure 4.1: Legendre Polynomials

$$P_0(x) = 1$$
$$P_1(x) = x$$
$$P_2(x) = \frac{1}{2}(3x^2 - 1)$$
$$P_3(x) = \frac{1}{2}(5x^3 - 3x)$$
$$P_4(x) = \frac{1}{8}(35x^4 - 30x^2 + 3)$$
$$P_5(x) = \frac{1}{8}(63x^5 - 70x^3 +^5 x)$$

The reason why we need these polynomials is that we connect the polynomials with the cash flow variable, the total cost variable, the income and cost variable. According to Schwartz (2004) if there are state variables, the set of basis functions should include them. The overall function is derived by ordering the Legendre three and four polynomial

to the cash flow variable and the five and six Legendre polynomial to the total cost variable. The second Legendre polynomial is described as the product of income and cost variable. Therefore we can describe the overall function as:

$$W^* = 1 + L_{II}(C \cdot K) + L_{III}(C) + L_{IV}(C) + L_V(K) + L_{VI}(K) \tag{4.13}$$

where L is the Legendre polynomial numbered from $II - VI$ since $L_I = 1$.

According to Schwartz (2004) our model does not take into account to delay the investment and to restart the project when after it stopped. Therefore it only takes into account the abandonment as mentioned previously. The argument Schwartz (2004) uses to not consider the restart of the project in the field of research and development is that cash flows will reduce to expiration of the patent. In our model this is included by the fact that if the value of a project equals 0, it will stay at the value 0 until the expiration of the patent.

4.5 Chebyshev polynomials

As mentioned we tried different polynomials for our one-stage model. In the following we present the Chebyshev polynomials for which we will also present solutions to the one-stage model in the forthcoming chapter. Chebyshev polynomials are used in many parts of numerical analysis.

For an integer value of $n \geq 0$ following function defines the Chebyshev polynomials

$$T_n(x) = cos(ncos^{-1}x)$$

with $-1 \leq x \leq 1$

Consider $x = cos(\theta)$ with $0 \leq \theta \leq \pi$ then $T_n(x) = cos(n\theta)$.

For $n = 0$

$$T_0(x) = cos(0 \cdot \theta) = 1$$

$n = 1$

$$T_1(x) = cos(\theta) = x$$

$n = 2$

$$T_2(x) = cos(2\theta) = 2cos^2(\theta) - 1 = 2x^2 - 1$$

After we have shown how the first three polynomials are derived we show in the following the first five polynomials which we will use in our one-stage model:

$$\begin{aligned} T_0(x) &= 1 \\ T_1(x) &= x \\ T_2(x) &= (2x^2 - 1) \\ T_3(x) &= (4x^3 - 3x) \\ T_4(x) &= (8x^4 - 8x^2 + 1) \\ T_5(x) &= (16x^5 - 20x^3 +^5 x) \end{aligned}$$

Chapter 5

GlaxoSmithKline and the Case

We the last section we have presented the Least Squares Monte Carlo simulation and we have described why we choose this method to evaluate the case study. Before we start to present our input data and results the case study will be presented.

5.1 Business Profile

GlaxoSmithKline (GSK) is one of the world's largest research-based pharmaceutical companies that discovers, develops, manufactures and markets human health products (GlaxoSmithKline (2011)). According to the Fortune 500 report 2010 GlaxoSmithKline is the fourth largest pharmaceutical company worldwide concerning total revenues. Table 5.1 (Fortune (2011)) shows the total revenues in USD billions and the change in percentage from 2008 to 2009.

Table 5.1: Largest Pharmaceutical Companies 2010 (Fortune (2011))

Rank	Company	Total Revenues	Change 09/08
1	Johnson&Johnson	61.90	-2.9
2	Pfizer	50.01	3.5
3	Roche	47.35	7.5
4	**GlaxoSmithKline**	45.83	16.5
5	Novartis	44.27	6.8
6	Sanofi-Aventis	41.99	6.3
7	AstraZeneca	32.81	3.8
8	Abott Laboratories	30.76	4.2
9	Merck & Co.	27.43	15.0
10	Bayer HealthCare	22.30	3.8
11	Eli Lilly	21.84	7.2
12	Bristol-Myers Squibb	18.81	6.2

It is an innovative company that produces branded products only, which it has developed itself. The company has two main divisions, pharmaceuticals and consumer healthcare.

Figure 5.1: Logo of GlaxoSmithKline (GlaxoSmithKline (2011))

The mission statement of GlaxoSmithKline is to *improve the quality of human life by enabling people to do more, feel better and live longer* (GlaxoSmithKline (2011)). GlaxoSmithKline states that the company values can be described through:

- Respect for people
- Patient focused
- Transparency
- Integrity

The focus of GlaxoSmithKline is to be the company in the pharmaceutical industry with the highest ethical standards and corporate responsibility principles (GlaxoSmithKline (2011)). Due to this (GlaxoSmithKline (2011)) defines three key aspects which have to hold for their R&D:

- GlaxoSmithKline may explore and apply new technologies and will constructively engage stakeholders on any concerns that may arise.
- GlaxoSmithKline will ensure that our products are subject to rigorous scientific evaluation and testing for safety, effectiveness and quality
- GlaxoSmithKline will comply with or exceed all regulations and legal standards applicable to the research and development of our products

Figure 5.2: Statement of GlaxoSmithKline (GlaxoSmithKline (2011))

The consumer healthcare businesses of GSK consist of over-the-counter (OTC) medicines, oral care products, such as the toothpaste brands Aquafresh, Macleans and Sensodyne, and nutritional healthcare drinks (GlaxoSmithKline (2011)). The pharmaceuticals division is the largest part of GlaxoSmithKline's businesses and can be divided into prescription drugs and vaccines. The headquarters of GSK are located in the UK, with additional operational headquarters in the USA. This report deals with the pharmaceuticals division only.
GlaxoSmithKline conducts R&D at more than 20 sites and employs 15,000 employees in R&D (GlaxoSmithKline (2011)). The principal facilities are located in UK, USA,

Japan, Italy and Belgium, and minor R&D sites are located in Canada, France and Spain. All R&D for vaccines is carried out in Belgium. GSK is involved in many different R&D partnerships with academic institutions, biotechnology companies and other pharmaceutical companies. The company has a leading position in genetics and in new drug discovery technologies.

GlaxoSmithKline employs 44,000 people in sales and has the largest sales force in the pharmaceutical industry (GlaxoSmithKline (2011)). It has various co-marketing and co-promotion agreements with other pharmaceutical companies. GlaxoSmithKline is a leader in the four therapeutic areas mentioned above and in vaccines. Worldwide, it had a market share of over 20% for respiratory treatments, a share of approximately 13% for antiinfectives and close to 10% of central nervous system drugs (GlaxoSmithKline (2011)).

Following the Annual Report 2010 GlaxoSmithKline has global pharmaceutical sales of over 22 billion pound and also the largest share in several therapeutic areas, including the vaccine and over-the-counter products (OTC).

5.1.1 Strategic Focus

In the Annual Report 2010 GlaxoSmithKline formulated three strategic priorities for the future:

- **Grow a diversified global business** - Diversification of business to create a more balanced product portfolio and move away from a reliance on traditional markets is a strategic focus of GlaxoSmithKline. Therefore GlaxoSmithKline invests in emerging markets like Japan, in products like vaccines and consumer healthcare business.

- **Deliver more products of value** - The aim of GlaxoSmithKline is to sustain an industry-leading pipeline of products, ensuring that they demonstrate value for healthcare providers. The R&D strategy of GlaxoSmithKline is built around focusing on the best science, diversifying through externalisation of research, and

improving the returns on investment.

- **Simplify the operating model** - GSK is a large and complex organisation. A transformation of the operating model to assure a reduction of complexity leading to improve efficiency and reduce costs is also a strategic focus of GSK.

- Concerning sustainability GlaxoSmithKline is strongly committed to social and environmental responsibility - this fact is reflected in R&D, the production processes and the products.

5.2 The Case

[1] In the pharmaceutical industry, it is a common practice, that pharmaceutical companies integrate biotech companies by mergers & acquisition to gain a higher innovative capability. As already mentioned, GlaxoSmithKline pursues also another strategy. The company participates in biotech companies by milestone payments. The following overview of the press releases from 2008 to 2010 concerning cooperation between Austrian biotech companies and GlaxoSmithKline tries to illustrate the approach of GlaxoSmithKline.

In October 2008, GSK Biological and AFFiRiS concluded the highest endowed contract in the Austrian biotech industry until then (AFFiRiS (2011)). In fact, GSK Biological paid up to €430 millions plus royalties for exclusive licensing rights to AFFiRiS. AFFiRiS GmbH produces vaccines against Alzheimer's, atherosclerosis and other diseases with urgent medical needs. The company possesses several patents and has its domicile in Vienna. Subject of the contract between GSK and AFFiRiS are several vaccines against Alzheimer's. Two of the vaccines are already in the clinical phase I.

GSK pays €22.5 millions up-front, further payments will be paid with the progress of the vaccine development (AFFiRiS (2011)).

[1] The informations in this section rely mostly on interviews with the management of GlaxoSmithKline Austria.

In 2009, GSK and Amgen resolved a cooperation in which the companies will share the commercialization of Amgen's monoclonal antibody *denosumab*. The drug prevents and treats different bone diseases (osteoporosis, bone metastases, bone density due to Cancer therapy and bone erosion due to rheumatoid arthritis). The intention of this cooperation is assure a global and rapid availableness of the drug once it is allowed in the different countries. While Amgen commercializes the American and European market, GSK will register and distribute *denosumab* in countries in which Amgen does not have a commercial presence.
Amgen, which is the biggest biotech company in the world, is convinced that the supply in cooperation with GSK is far more effective, than if they would do it on their own (Amgen (2011)). In financial terms, the agreement between the GSK and Amgen, schedules an initial payment and further commercial milestone payments to Amgen in the amount of € 120 million, as well as the payment of ongoing royalties (Amgen (2011)).

In December 2009, GSK Biologicals and Intercell formed a strategic alliance to develop and commercialise innovative needle-free patch-based vaccines (Intercell (2009)). The agreement will include Intercell's candidate vaccine for travellers' diarrhoea (Phase III) and an investigational single application pandemic influenza vaccine (Phase II), as well as other potential future patch vaccines. In terms of the agreement, GSK will make an up-front cash contribution of € 33.6 million, in addition to an equity investment of up to € 84 million through a staggered shareholding purchase option of up to 5% in Intercell (Intercell (2009)).

In February 2010, GSK announced another cooperation with an Austrian biotech company, Apeiron Biologics AG. GlaxoSmithKline paid € 12.5 million up-front and milestone payments amounting to € 236 million were arranged (Apeiron (2010)). In return, GSK obtained the exclusive rights on the project 'APN01'. APN01 (recombinant human angiotensin converting enzyme 2) is a biopharmaceutical against the acute respiratory distress syndrome and is currently in the phase I development(Apeiron (2010)).

The cooperations with AFFiRiS, Intercell and Apeiron are just three of 15 global cooperations with biotech companies that were concluded in the last years (GlaxoSmithKline (2011)). Just these three deals comprehend payments of €783.6 million - €70 million were paid up-front. In October 2009 AFFiRiS received the first milestone payment in the amount of €10 millions after the successful completion of the phase I.

According to Evelyn Schödl, General Manager of GSK Austria, one of the main goals of GSK is to *grow a diversified global business*. For this reason, they do not want to rely only on their own R&D department, but they seek cooperation with external partners in science. These technology transfer agreements benefit GSK by giving them access to new markets. Accordingly, the central business development team is searching worldwide for talent, ideas, technologies and new drugs away from their own research.

Together with GlaxoSmithKline Austria and Apeiron we focused in this thesis on the case of their milestone agreement and tried to implement a project evaluation model based on their agreement.

Chapter 6

Results

This chapter is divided into two sections: the first sections describes the conclusions made by several interviews with management of GlaxoSmithKline and analysts from the BAWAG P.S.K. The second section shows the computational results derived from the Least Squares Monte Carlo simulation. In the conclusion chapter we will compare the computational results with the findings of the qualitative research.

We made several interviews with the management of GlaxoSmithKline, Apeiron and analysts from BAWAG P.S.K. We especially want to point out the interviews with Dr. Ronald Pichler, External Affairs Director GSK Austria, and Dr. Edwin Glassner, Analyst at the Risk Analytics&Modelling Department at BAWAG P.S.K. These interviews had a deep impact on this thesis since the need for a a R&D project valuation method was pointed out by the management of GlaxoSmithKline Austria.
After conducting several interviews concerning the milestone agreement fo GlaxoSmithKline with Apeiron we focused on specifying parameters with the help of the parameters defined in Schwartz (2004) and the results by DiMasi (2001); DiMasi et al. (2003). We have described in the Introduction how this thesis developed from the qualitative approach to implementing and interpreting the quantitative modell. After we have shown the results for the one-stage model and the extension to a multi-stage model we will integrate again in the conclusion our qualitative results.

6.1 Computational Results

Before we discuss the results derived by the Least Squares Monte Carlo simulation we summarize the parameters we used. In discussion with GlaxoSmithKline Austria some parameters were changed in comparison to Schwartz (2004) to better fit the case.

Table 6.1: Parameters Used in the Simulation

Parameters	Value
Total Cost to Completion	€223 million
Maximum Investment Rate	€25 million per year
Cost Uncertainty	0.5
Cash Flow Rate	€50 million per year
Cash Flow Uncertainty	0.35
Cash Flow Drift	0.02
Terminal Cash Flow Multiple	5
Annual Probability of Failure	0.1
Time to Expiration of the Patent	20 years[1]
Correlation between Costs and Cash Flows	-0.1
Risk Premium Associated with Cash Flows	0.036
Risk-free Rate of Interest	0.05
Time Step Size in Simulations	0.25 year
Number of Simulations	60000

The Least Squares Monte Carlo simulation was implemented in MATLAB. All experiments were conducted on a AMD Phenom(tm) II X4 955 processor with 3.2 GHz. In the following we want to present a convergence analysis and a computational time for the different number of paths[2].

[2]For our computational experiments the random seeds number is chosen as 0.

6.1.1 Computational Time

For the computational time we see that it is steadily increasing with an end value of 944.04 seconds or 15.73 minutes for our case study number of paths 60.000. We approximated a function fitting the computational time received from the experiments with

$$F(x) = 2.44 \times 10^{-7} x^2 \tag{6.1}$$

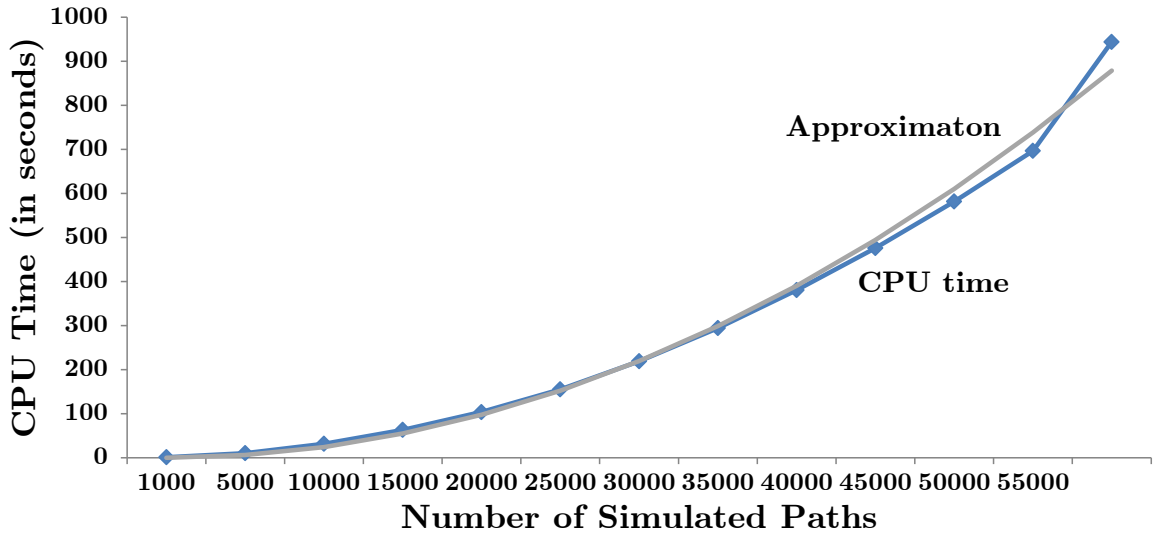

Figure 6.1: Computational Time

Both the approximation function and the function received by our computation experiments are plotted in Figure. A computational time of 15.73 minutes can be seen as not too long by considering that the result is two 60000×80 matrizes for both the cost to completion and the expected cash flows needed for the calculation of the projects value. As we will see in the convergence analysis already a sample of 35000 paths delivers us very good results with a deviation of 2 % of the result received by a simulation with

60000 paths. The computational time reduces in the case of 35000 paths to 3.64 minutes, therefore considering this computational time a practical use of this model can be seen.

6.1.2 Convergence Analysis

Before we will go into further detail we present a convergence analysis. We calculated the project value for 1000-60000 paths for the random seed number of 0 and compared it to the final project value which is calculated by

$$PV = \frac{\sum_{i=0}^{4} PV_i}{n} \forall i = 0, ..., 4 \tag{6.2}$$

where PV_i is the project value for each random seed number from 0 to 4 and n is the total number of random seeds.

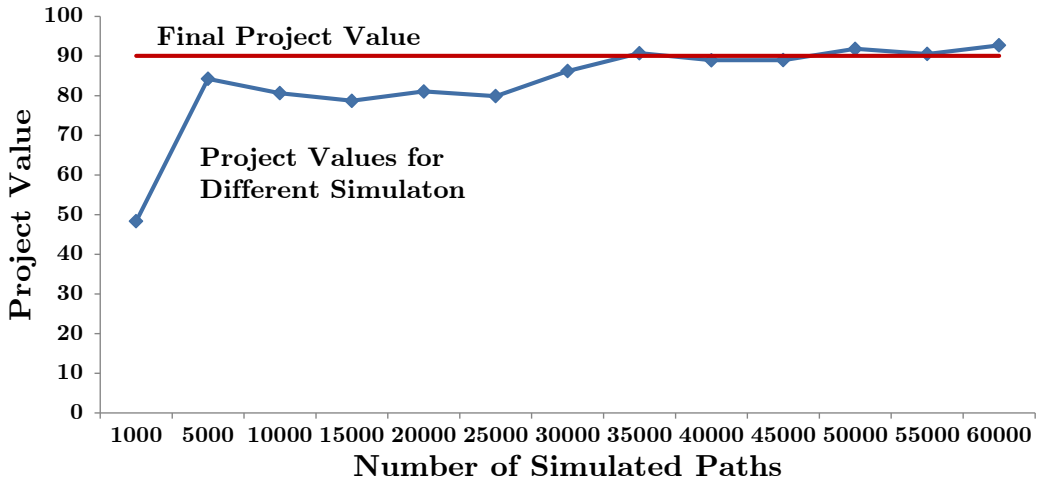

Figure 6.2: Convergence Analysis

The convergence analysis shows that by increasing the number of paths the calculated project value converges around the calculated final project value. This apparent trend of convergence shows that the assumptions we made in front were correct and that the final project value is validated[3].

[3]For further remarks see the convergence proof by Schwartz (2004).

6.2 Project Value Results

In the last section we have presented the convergence analysis which examined the convergence of different number of paths for the random seed number zero concerning the total project value. As we have shown in the last section the overall project value is derived as $PV = \frac{\sum_{i=0}^{4} PV_i}{n}$. The seed of random numbers is implemented by the MATLAB function **randn('state',j)** which returns normally distributed random numbers for each j state. The results are presented in Table 6.2 with a path number for each seed number:

Table 6.2: Project Value for the Single-Stage Model

Seed of Random Numbers	0	1	2	3	4
Project Value (million €)	92.6876	90.2786	94.2085	87.5583	90.0434

The average out of these project values is then €90.95528 million which is our final value of the project.

6.2.1 Cost to Completion and Cash Flow Analysis

Figure 6.3 shows a for a random sample of 50 paths the total cost of completion for each path. According to Figure 6.3 the total cost to completion decrease over time. Due to the generation of 50000 paths the total cost to completion start as described at the defined costs with a certain deviation which can be seen in Figure 6.3.
Our sample of 50 paths reflects the fact mentioned by Pindyck (1993) that the total cost of completion decrease with development and technical uncertainty processing. In Figure 6.4 we have plotted the behaviour concerning the expected cash flows for the 50 randomly chosen paths. The cash flow rate lies for most of these 50 sample paths between €2 to 10 million per quarter.

For Figure 6.5 we have randomly select one path out of the 60.000 paths simulated and plotted cost to completion and cashflows per quarter. Until the research and development

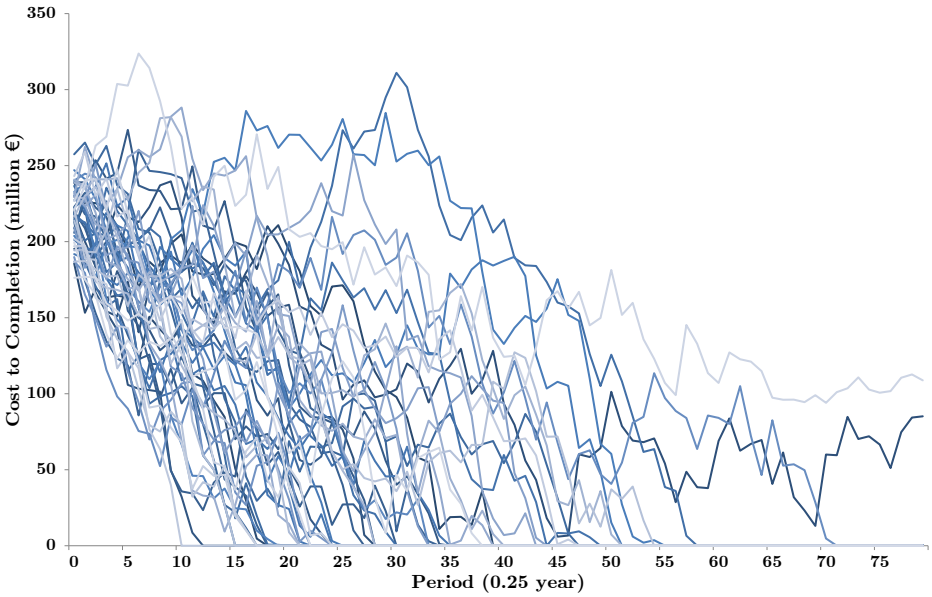

Figure 6.3: Total Cost to Completion

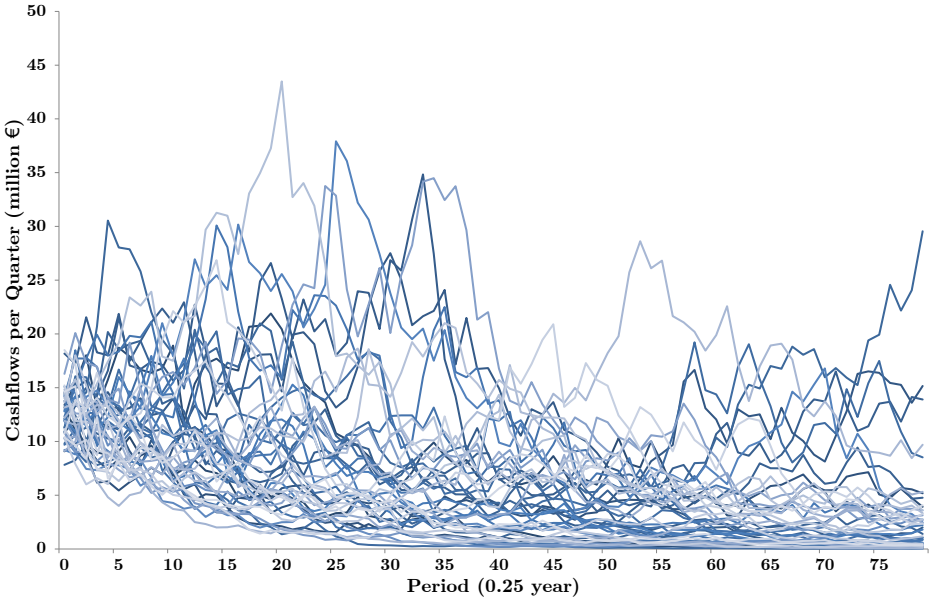

Figure 6.4: Expected Cash Flows

and therefore the investment is finished which can be seen in Figure 6.5 that the cost to completion are zero, the cash flows are anticipated. After approximately 4 years the investment is completed and the cash flows start. These cash flows are now realized cash flows and are plotted until the expiration of the patent after 20 years. Following Grabowski and Vernon (1994) the cash flows reduce dramatically after the expiration of the patent due to generic drugs entering the market. It would be far more complex to forecast future realized cash flows after the expiration of the patent since we have to estimate the probability of generic drugs entering the market, the new price and the number of competitors.

Furthermore we have described in the chapter on drug cost estimation that there are certain conditions when patent protection is increased by several years. We would have to consider also this possibility in our forecast. Therefore we focus in our case only on the patent protected time.

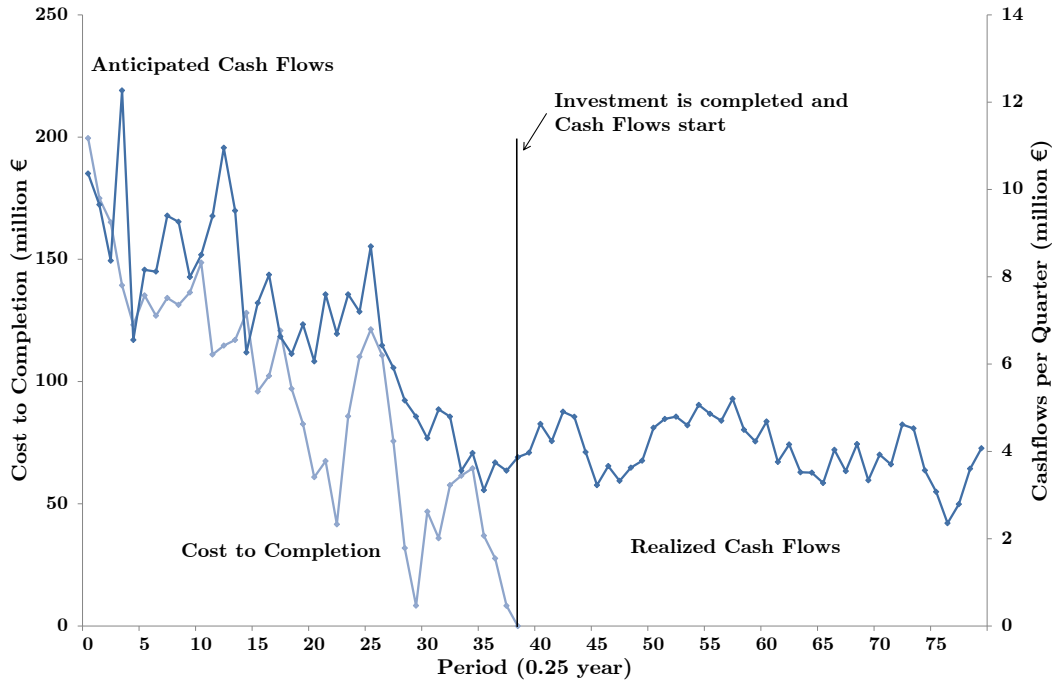

Figure 6.5: Sample Path Analysis

6.2.2 Sensitivity Analysis

In the following section a sensitivity analysis concerning some parameters will be presented. We want to examine the effects of a change in our parameters which helps us to control if our programm works accurately. Due to computational reasons the number of paths for this sensitivity analysis was reduced to 35000 paths.
The first sensitivity analysis concerns the cash flow uncertainty. For our case study we have set the cash flow uncertainty parameter to 0.35. Figure 6.6 shows what happens if we use different cash flow uncertainty parameters. By increasing the cash flow uncertainty parameter the project value increases. This result follows Schwartz (2004) with the reason that cash flow uncertainty increases the probability of good outcomes. On the other hand it also increases the probability of bad outcomes and by definition of the model also increases the probability of abandonment.
In other words this means that if the cash flow uncertainty is high the value of the project gets higher due to the option to abandon the project. We will see that by increasing the cost uncertainty the project value also increases, but the effects behave opposite. The result in our sensitivity analysis was that by increasing the cash flow uncertainty the percentage of paths which were abandoned, increased.
To understand why the project value increases consider an example: research and development would be finished after ten years but after two years costs are higher than expected cash flows. If the option holder has no possibility to stop the investment, he would loose a lot of money. Therefore the option where he has the possibility to abandon has a higher project value due to cost savings.

Before we examine different parameters for cost uncertainty we examine the correlation between costs and cash flows. The value of the project increases the higher the correlation between costs and cash flows gets. The reasoning for this is that a negative correlation implies that either costs are low and cash flows are high or costs are high and cash flows are low. This means that the received values are wider distributed. It is clear that a positive correlation corresponds to a higher probability that the project will be

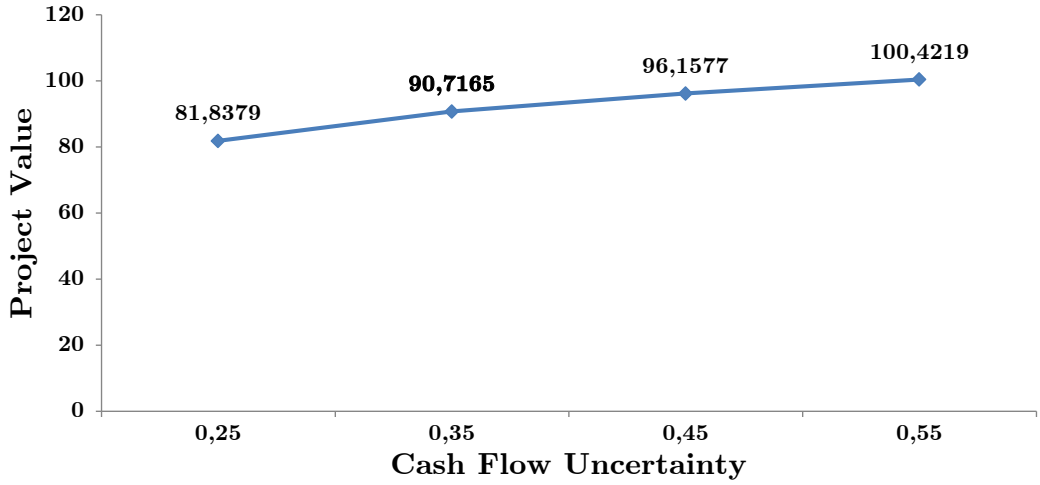

Figure 6.6: Sensitivity Analysis Cash Flow Uncertainty

abandoned. We considered in our sensitivity analysis for the correlation between costs and cash flows negative correlations from -0.15 to -0.05 and a correlation of 0 which means that there is actually no correlation. According to Figure 6.7 a clear trend can be seen: The closer the correlation gets to positive values the project value decreases due to the arguments presented before. It is clear that by increasig the cost uncertainty the value of the project increases. The probability of abandonment decreases with increasing the cost uncertainty. The assumption hereby is that according to Schwartz (2004) there is a higher learn effect by investing with more uncertainty. This is also shown by Figure 6.8. Varying the cost uncertainty between 0.3 and 0.6 leads to an increase in the project value from €70.7227 to €100.1114 million.

By increasing the expected costs to completion the project value decreases. As in the sensitivity analysis before we keep all other parameters constant and just increase the expected cost to completion from €180 million to our case study costs of €223 million. The project value decreases then from 151.51 to 90.71 which can be seen in figure 6.9.

According to our analysis shown in Figure 6.10 increasing the maximum rate of investment leads to an increase in project value. An increase in the maximum rate of

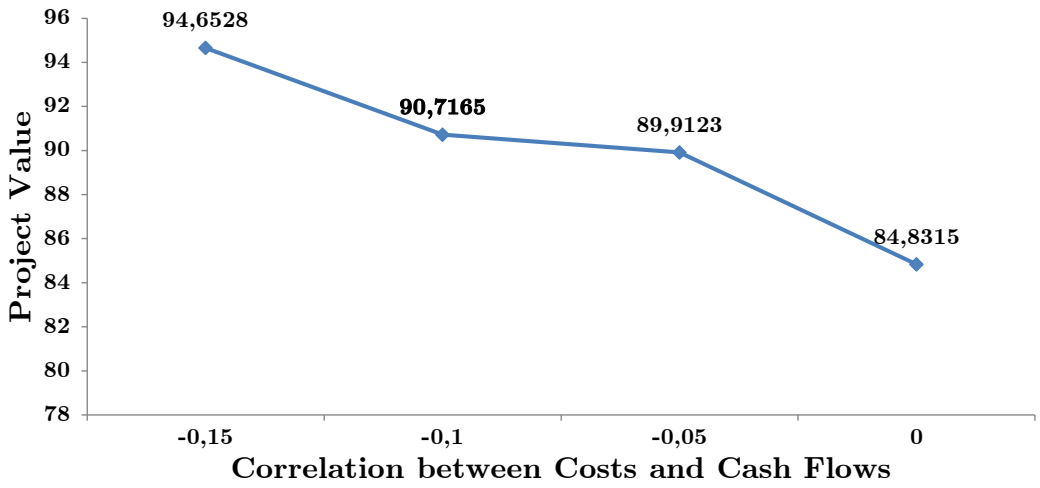

Figure 6.7: Sensitivity Analysis: Correlation between Costs and Cash Flows

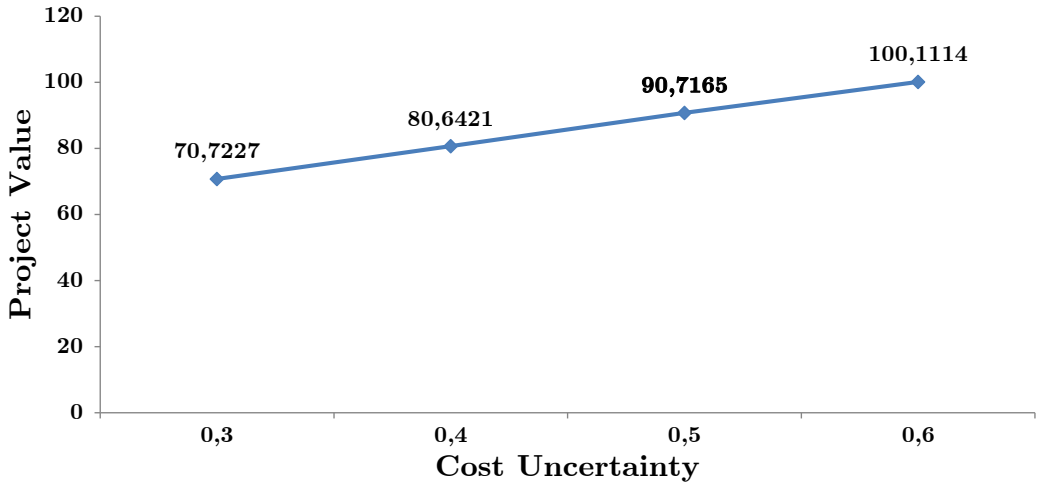

Figure 6.8: Sensitivity Analysis: Cost Uncertainty

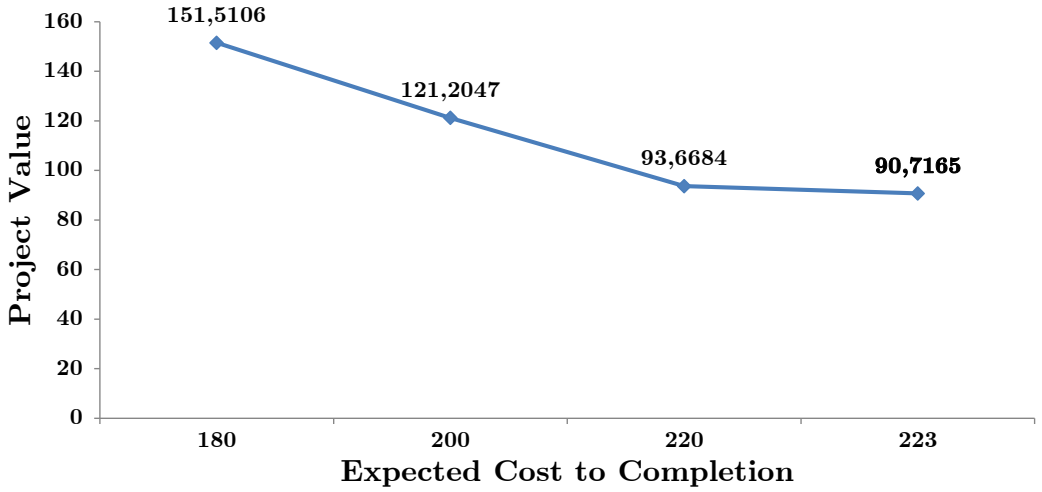

Figure 6.9: Sensitivity Analysis: Expected Cost to Completion

investment per year leads to an earlier finish of the research and development phase which then leads to a longer time of realized cash flows increasing the value of the project.

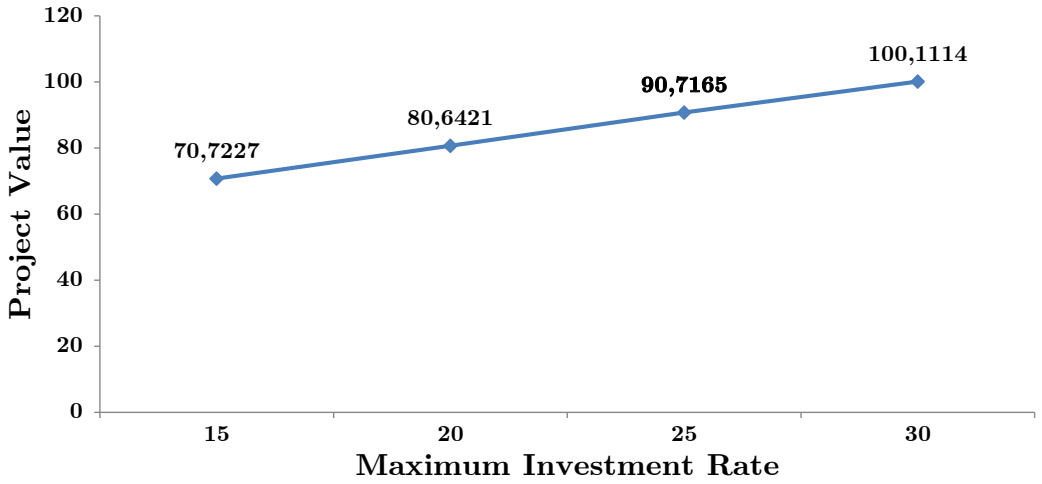

Figure 6.10: Sensitivity Analysis: Maximum Investment Rate

The next sensitivity analysis is done concerning the expiration of the patent. We have assumed according to Schwartz (2004) that the patent expires after 20 years. We have now run the simulation with a patent expiration of 18, 20, 22 and 24 years. Clearly as shown in Figure 6.11 the project value increases with the years of expiration of the patent increase.
Since the time for realized cash flows increases with an increase in expiration of the patent the value of the project increases keeping all other parameters constant.

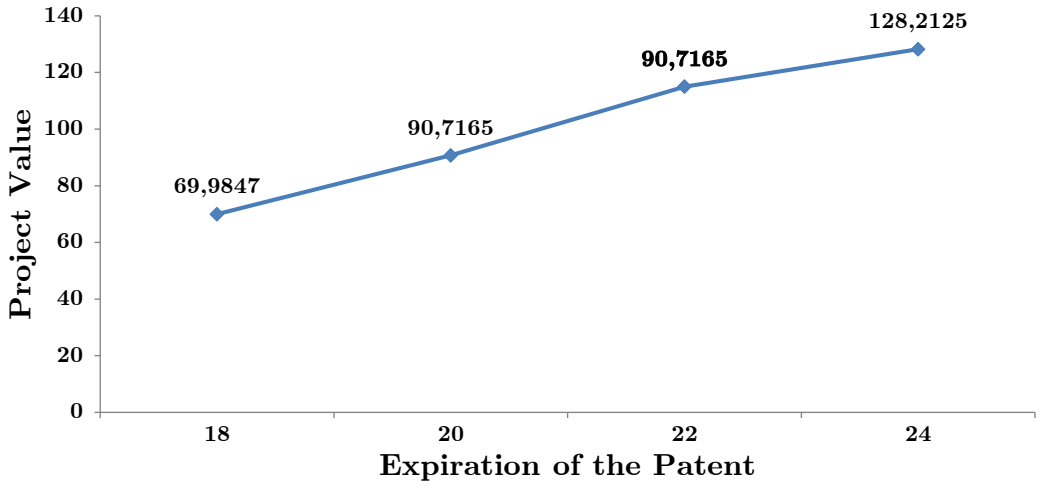

Figure 6.11: Sensitivity Analysis: Expiration of Patent

6.2.3 Project Value Results for Chebyshev Polynomials

The presented results were derived with the assumptions of Legendre polynomials as basis functions. In the following we want to compare the results derived to results we generated with Chebyshev polynomials as basis functions.

Table 6.3: Project Values with Chebyshev polynomials as basis functions

Seed of Random Numbers	0	1	2	3	4
Project Value (million €)	93.6102	90.7578	95.1899	88.3298	91.3333

The average calculated out of the project values of seed numbers is €91.8442 million. We see that compared to the average project value calculated with Legendre polynomials as basis function the difference is €0.88892 million. Figure 6.12 shows the difference for seed numbers $0, 1, 2, 3, 4$.

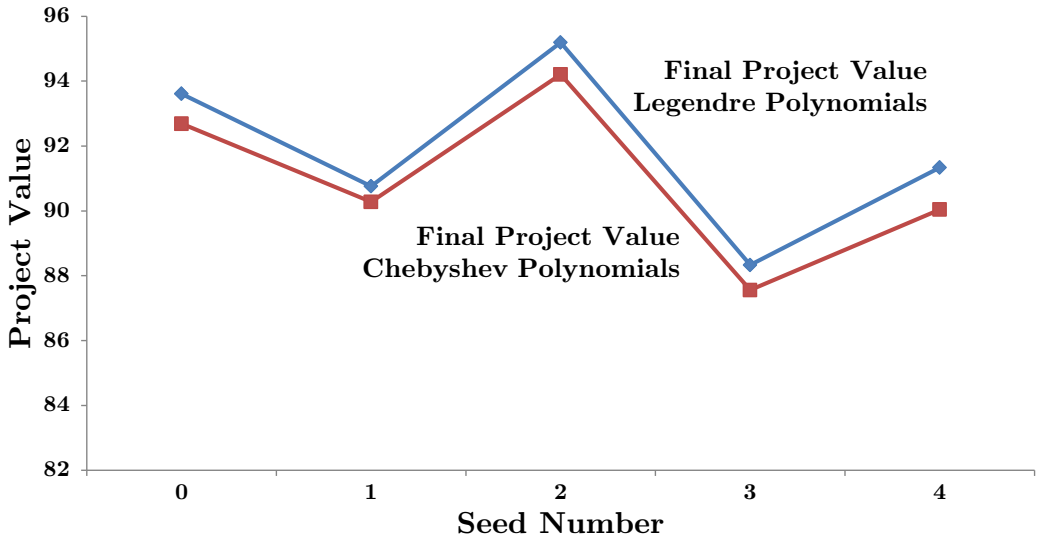

Figure 6.12: Comparison: Legendre and Chebyshev Polynomials

Chapter 7

Multi-stage Extension

We have presented results and sensitivity analysis for our case study based on the single-stage model by Schwartz (2004). Schwartz (2004) argued that there is a logically extension to his model to a multi-stage model. We have shown in the chapter on cost estimation of pharmaceuticals that there are different costs for every different phase of the research and development process. We therefore try in this chapter to extent this model to a multi-stage model which includes different probabilities of failure for each phase and different costs for each phase. The extension of the one-stage model was proposed by Schwartz (2004) and we tried to implement his extension fitting our case. For each phase, the expected costs are calculated seperately in MATLAB, therefore changing the equation for the dynamics of expected costs to

$$dK_j = -I_j dt + \sigma_j \sqrt{I_j K_j} dz_j \tag{7.1}$$

We change in this thesis several parameters in comparions to single-stage process:

1. Expected costs for all different phases, K_j
2. Expected time for all different phases T_j
3. Maximum investment rate for all different phases I_j
4. Probabilities of failure for all different phases λ_j

All other parameters which we have defined before remain constant for all phases.

7.1 New defined parameters

7.1.1 Total Cost to Completion (K_j)

In accordance with GlaxoSmithKline we agreed on a total costs to completion for each stage which together sum up to the total costs we used in the one-stage simulation of €223 million[1]. Table 7.1 shows the different costs for each stage:

Table 7.1: Cost to Completion per Phase

Stage	Phase I	Phase II	Phase III	Authorization
Costs to Completion	25	45	123	30

As discussed in the chapter on cost estimation in pharmaceutical research and development, the costs in phase III are due to the complexity of the stage far the highest. This complexity mostly arises by the large sample of patients needed for the different stages.

7.1.2 Expected Time to Completion (T_j)

We considered hereby the expected time to completion following Schwartz (2004) with 10 years to make our results between one-stage and multi-stage simulation comparable. This follows also the work by DiMasi (2001), Vernon (2005) and DiMasi et al. (2003) with certain variations in the time to completion around 10 years. Together with GlaxoSmithKline Austria we divided this total expected time of completion between the different stages. These completion times are shown in Table 7.2:

Again we assume Phase III to have the longest time to completion and Phase I the shortest according to DiMasi et al. (2003).

[1]Note that these are approximative costs and are used to test the multi-stage simulaton. Improvements shall be made for all input parameters in the future. The purpose of this thesis is to see if the simulation works and delivers good results.

Table 7.2: Time To Completion per Phase

Stage	Phase I	Phase II	Phase III	Authorization
Time to Completion	1.5	2.5	4	2

7.1.3 Maximum Investment Rate (I_j)

After we have defined the total cost to completion and the expected time to completion, the maximum investment rate can be calculated. The maximum investment rate is calculated by dividing the total cost to completion by the expected time to completion

$$\frac{K_j}{T_j} \ \forall j = 1, ..., 4$$

Table 7.3 presents the maximum investment rates for each phase.

Table 7.3: Maximum Investment Rate per Phase

Stage	Phase I	Phase II	Phase III	Authorization
Time to Completion	16.6	18	30.75	15

7.1.4 Probability of Failure (λ_j)

The probability of failure is calculated by using the proposed formula from Schwartz (2004).

$$e^{-\lambda T_j} = 1 - R \tag{7.2}$$

As discussed in the previous sections λ follows a Poisson probability function and describes the probability of failure. R is the rate of catastrophic events according to Schwartz (2004), but notice that $(1 - R)$ is not the real success rate since the a success rate has to includes failures due to catastrophic events but also the optimal excercise of

the abandonment option (Schwartz, 2004). We assumed that this rate in the single-stage simulation with 0.5, which is a reasonable assumption as we will see by calculating the overall probability out of each stage probabilities. Table 7.4 shows the rates $(1 - R)$ for all different phases:

Table 7.4: $(1 - R)$ per Phase

Stage	Phase I	Phase II	Phase III	Authorization
(1-R)	0.8	0.75	0.85	0.9

By taking the product of the $(1 - R)$ probabilities for each phase which equals 0.47 we see that a rate of 0.5 was a good approximation by Schwartz (2004) for the one-stage model. With these assumed input factors we can calculate the probability of failure, λ. Reformulating equation 7.2 leads to

$$\lambda = -\frac{ln(1 - R)}{T_j} \tag{7.3}$$

If we solve this new equation for all phases by including their different completion times T_j and the rates this leads us to the probabilities of failure presented in Table 7.5:

Table 7.5: Probability of Failure per Phase

Stage	Phase I	Phase II	Phase III	Authorization
λ	0.14	0.11	0.04	0.05

Before the results are presented in the next section and compared to the single-stage simulation, the other parameters used in the multi-stage simulation are presented. Note that these parameters have not changed to the single-stage simulation so the results are still compareable.

Table 7.6: Parameters Used in the Simulation

Parameters	Value
Cost Uncertainty	0.5
Cash Flow Rate	€50 million per year
Cash Flow Uncertainty	0.35
Cash Flow Drift	0.02
Terminal Cash Flow Multiple	5
Time to Expiration of the Patent	20 years
Correlation between Costs and Cash Flows	-0.1
Risk Premium Associated with Cash Flows	0.036
Risk-free Rate of Interest	0.05
Time Step Size in Simulations	0.25 year
Number of Simulations	60000

7.2 Results

The Least Squares Monte Carlo multi-stage simulation was implemented in MATLAB and all experiments were conducted on a AMD Phenom(tm) II X4 955 processor with 3.2 GHz. In the following we present a generated sample path and the results and running time for different seeds of random numbers. As shown in the Table 7.6 the number of paths simulated was chosen due to comparability reasons to the single-stage model at 60.000 paths.

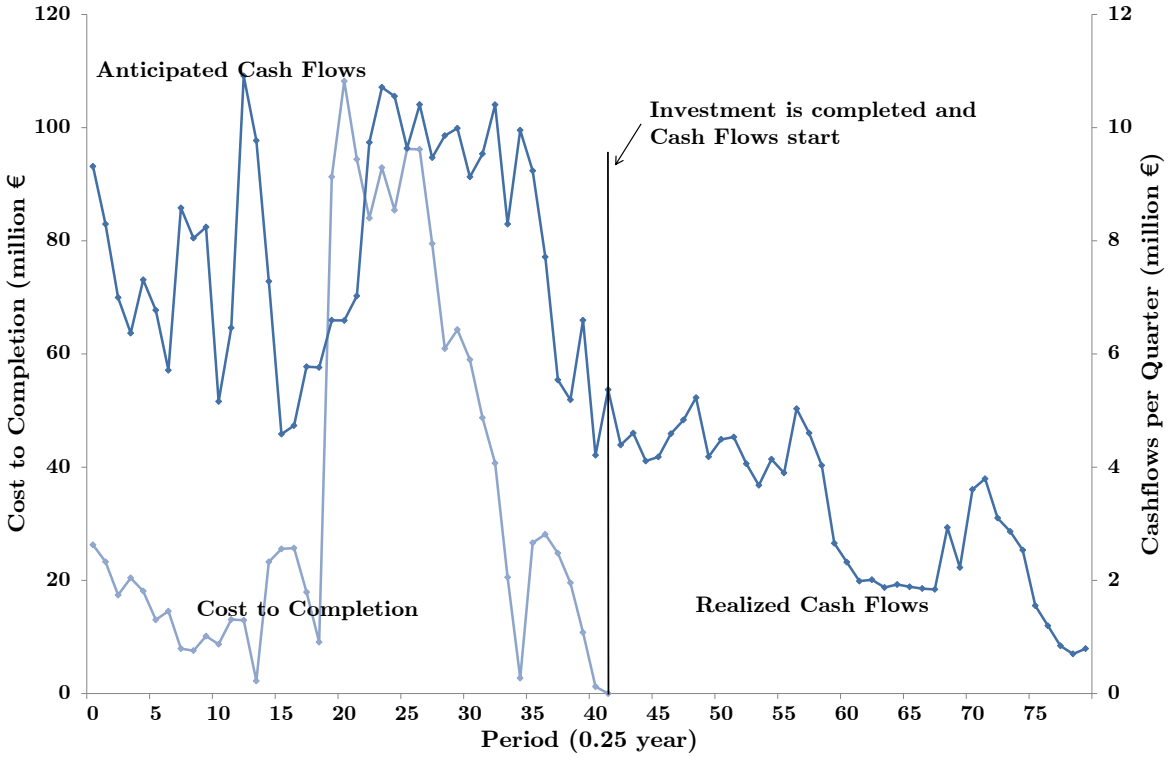

Figure 7.1: Sample Path for the multi-stage model

Compared to the sample path in the single-stage model the total cost to completion

vary over time since we defined different costs for the different stage[2]. We see from Figure 7.1 that approximately between 4 and 8 years is an increase in costs which is directly linked to Phase III of the R&D process. The investment is completed in period 41 which equals approximately 10 years. At point 0 in time assumed cash flows are around €9 million. At the expiration of the patent the cash flows equal approximately €0.8 million. Table 7.7 shows the calculated project values for diferent seed of random numbers and the running time in minutes. The average and therefore the final project value was calculated as €91.00492 million.

Table 7.7: Project Values per Phase

Seed of Random Numbers	0	1	2	3	4
Project Value (million €)	92.4008	90.1053	93.5402	87.6363	91.342
Running Time (*min*)	29.98	15.72	15.70	29.02	15.67

As the last part of this chapter we want to compare the results from the multi-stage model with the results from the single-stage model. As described in this chapter we changed the input parameters but its furth mentioning that the sum of the total cost of completion stay constant as well as the overall probability of failure did not change.

Table 7.8: Comparison PV Single-stage/Multi-stage

Seed of Random Numbers	0	1	2	3	4
Multi-stage model (million €)	92.4008	90.1053	93.5402	87.6363	91.342
Single-stage model (million €)	92.6876	90.2786	94.2085	87.5583	90.0434
Difference (total)	-0.2868	-0.6233	-0.6683	0.078	0.9386

We see from Table 7.8 that there is a certain difference between the project values

[2]Please note again that Figure 7.1 shows a randomly selected path and therefore might not represent a typical path

received from the single-stage model and the multi-stage model but it proves also that the assumption by Schwartz (2004) is reasonable that a single-stage model is a good approximation for the problem with a much lower running time. The overall average of the single-stage model was calculated with €90.955 million and the average of the multi-stage model as mentioned with €91.004 million.

Chapter 8

Conclusion

Investments on research and development in pharmaceutical companies are characterized by a high level of future uncertainty. In this thesis, we discussed the case of GlaxoSmithKline and Apeiron and tried to value the project with real option techniques. In the following we want to present the structure of our research and discuss problems and possible extensions to this thesis.

After we have defined the topic of this thesis, several interviews with GlaxoSmithKline, Apeiron and financial analysts were conducted. We came to the conclusion that there is a need for a new project valuaton technique and we agreed on implementing the Least Squares Monte Carlo simulation by Schwartz (2004). As presented in the chapter on our single-stage model which follows the model by Schwartz (2004) the different R&D phases were summarized as one stage. We discussed the results from the single-stage model again with GlaxoSmithKline and Apeiron and made some adjustments.

Schwartz (2004) proposed an extension to a multi-stage model in the Appendix but did not implemented it. We tried to extend our model following the proposed extension by Schwartz (2004) and implemented it in MATLAB. We came to the result that the single-stage model by Schwartz (2004) delivers very good results in acceptable computational time whereas the multistage model allows us to vary the parameters as for example the probability of failure for each phase.

For our case we assumed that the product of all probabilities of failure have to be equivalent to the probability of failure for the single-stage model. Therefore the difference

between both models concerning the final project value was rather small.

The Least Squares Monte-Carlo (LSM) models delivers different results from the standard net present value (NPV) analysis since it includes (managerial) flexibility allowing the model to stop the research process or in other words to abandon the option. The NPV analysis is widely used in practice but does not included those flexibilities. Therefore it mostly underestimates projects and yields to negative results.

For our case we also found out that the LSM model is superior to the Binomial Tree Model in R&D project valuation because the LSM model considers more uncertainties and therefore captures more features of real world R&D projects.

As the section on computational time showed the Least Squares Monte Carlo simulation approach as an extension by Schwartz (2004) delivers good results in acceptable computational time. We have to consider that this model can be just used to value R&D projects without competitive interactions. To some extend we tried to model competitive interactions by the probability of failure term which per definition included also the probability that another company entered the market with a similar product before research and development of the project was completed. Further research should be done in the future on including game theoretic concepts into the real options framework. Some research on the field of investment decisions in a real option and game theoretical framework has been done in the past years. We want to point out Krychowski and Quélin (2010) with a focus on pharmaceutical R&D and a *A Strategic R&D Investment with Flexible Development Time in Real Option Game Analysis* by Villani (2009).

Another limitation of our multi-stage approach is that the model can only be used in situations in which the duration of the cash flows depends on the duration of the whole project. In this situation only options to abandon are considered.

There are some improvements which we propose to implement in further research. We have compared Chebyshev and Legendre polynomials as basis functions but the robustness of the model concerning the basis functions should be tested on a broader variety of polynomials.

Furthermore the LSM model still can be extended to improve accuracy of the implemen-

tation. Cash flows from drug sales start very low at the introduction of a new drug, then grow to a maximum close to the expiration of the patent, and decrease substantially once the patent has expired (Grabowski and Vernon (1994)). In the future this assumptions should be taken into account.

The problem we face is that it is very difficult to forecast future sales after the expiration of the patent. During the duration of the patent we assume a monopoly situation therefore we only have to estimate the potential and the need of the product on the market and define a certain expected cash flows and a cash flow uncertainty. If we would now consider competition we would have to estimate the degree of competition and the resulting market share which has a direct impact on the sales and cash flows.

The last thing to mention is that we have implemented our model in MATLAB. The reason why we have chosen MATLAB over other programmes and languages is that MATLAB is a numerical computing environment which delivers (concerning our matrix manipulations and calculations) very good results and the implementation is in our opinion a lot faster compared to C++ for example. Nevertheless future research should try to implement the model using other languages as C++ which will have definitely a high effect on running time and probably on the quality of the results.

Summarizing, in this thesis we present two possible project evaluation models based on a real options approach. We implemented the single-stage model by Schwartz (2004) and also the proposed multi-stage extension and adapted the models to fit the case of GlaxoSmithKline and Apeiron. The obtained results show that the real options approach and in particular the Least Squares Monte Carlo simulation should be consulted as a decision making tool for project evaluation by companies in the future.

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Abstract

The main objective of this work is to formulate, implement and evaluate a pharmaceutical investment following the real options approach. After a presentation of different models the Least-Squares Monte Carlo model by Schwartz (2004) is presented and implemented. The input data for the model is based on the case of a milestone payments agreement between GlaxoSmithKline and the biotech company Apeiron. The data was collected and validated through interviews with the management of GlaxoSmithKline and Apeiron. After the implementation of the single-stage model, the results were again discussed with GlaxoSmithKline and Apeiron and the objectives for an extension of the model were set. The extended model considers the research and development phases as separate stages with different cost structures and probabilities of failure.

This thesis is structured as follows: After the introduction the second chapter gives an overview of the real options theory, starting with general characteristics of financial options. The third chapter provides an overview of the structure of the pharmaceutical research and development process and discusses various methods for estimating cost and duration. The fourth chapter describes the Monte Carlo simulation in general and develops the Least Squares Monte-Carlo model for the single-stage process. In addition, explanations as to why the Least-Squares Monte Carlo approach was chosen over other approaches and why it generates better results than the standard net present value analysis are presented.

Before the results of the single-stage model are presented in chapter six, the milestone payments agreement between GlaxoSmithKline and Apeiron is presented in chapter five. In chapter six the results of the single-stage model for the milestone payments agreement between GlaxoSmithKline and Apeiron are presented and discussed in terms of convergence and sensitivity analysis. Furthermore as in chapter seven, the implementation of various basis functions such as Legendre or Chebyshev polynomials is discussed.

Lastly, in chapter seven the extension of the model of Schwartz (2004) in a multi-stage model is introduced and the achieved results are compared with the results obtained from the single-stage model in chapter six.

The results, which are achieved by both the single-stage and the multi-stage model, display an improvement on net present value analysis if the underlying data is suitable.

Zusammenfassung

Diese Arbeit hat als Hauptziel ein Bewertungsmodell für eine pharmazeutischen Investition nach dem Ansatz der Realoptionen zu formulieren und zu implementieren. Nach einer Diskussion verschiedener Bewertungsmodelle wird eine Least-Squares Monte Carlo Simulation nach Schwartz (2004) vorgestellt und implementiert. Als Fallstudie dient die erfolgsbedingte Kooperation zwischen dem Pharmaunternehmen GlaxoSmithKline und dem Biotechunternehmen Apeiron. Die Daten wurden durch Interviews mit dem Management von GlaxoSmithKline und Apeiron erhoben und ausgewertet. Nach der Implementierung des einstufigen Modells wurden die Ergebnisse erstellt und mit GlaxoSmithKline und Apeiron besprochen. In der Folge wurden die Ziele für ein erweitertes Bewertungssystems festgelegt. Dieses erweiterte Modell betrachtet die Forschungs- und Entwicklungsphasen als getrennte Stufen. Es bildet daher die unterschiedlichen Kostenstrukturen und Ausfallswahrscheinlichkeiten zwischen den Phasen realistischer ab.
Diese Magisterarbeit ist wie folgt aufgebaut: Nach der Einleitung gibt das zweite Kapitel einen Überblick über die Realoptionen Theorie beginnend mit allgemeinen Charakteristika von Finanzoptionen. Das dritte Kapitel gibt einen Überblick über die Struktur des pharmazeutischen Forschungs- und Entwicklungsprozesses und diskutiert verschiedene Methoden zur Schätzung von Kosten und Dauer. Das vierte Kapitel beschreibt die Monte Carlo-Simulation im Allgemeinen und entwickelt das Least Squares Monte-Carlo Modell für den einstufigen Prozess. Darüber hinaus wird erläutert warum der Least-Squares Monte Carlo Ansatz gewählt wurde und dass dieser zu verlässlicheren Ergebnissen als die Net-Present Value Analyse führt.
In Kapitel fünf wird die Kooperation zwischen GlaxoSmithKline und Apeiron vorgestellt. Als Basis für dieses Kapitel dienten vor allem Interviews mit dem Management von GlaxoSmithKline Austria und Apeiron. In Kapitel sechs werden die Ergebnisse des einstufigen Modells für die erfolgsbedingte Kooperation zwischen GlaxoSmithKline und Apeiron dargelegt und anhand von Konvergenz- und Sensitivitätsanalysen diskutiert. Des Weiteren wird die Implementierung von verschiedenen Basisfunktionen wie Legendre oder Chebyshev Polynom erörtert. In Kapitel sieben wird die Erweiterung des Modells von Schwartz (2004) in ein mehrstufiges Modell vorgestellt.Die Resultate aus dem mehrstufigen Modell werden mit den Ergebnissen des einstufigen Modells verglichen.
Die Ergebnisse, welche sowohl durch das einstufige als auch durch das mehrstufige Model erreicht werden, stellen bei entsprechender Datenlage in jedem Fall eine Verbesserung zur gängigen Net-Present Value Analyse dar.

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