“Corporate Financing by Selling R&D Options”

Examined based on the Example of Research Conducting Biotechnology Companies

Zur Erlangung des akademischen Grades eines Doktors der Wirtschaftswissenschaften

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Preface

The origin of this study leads back to my initial master studies at the University of Karlsruhe where I attended my first lectures on finance and general financial option theory. Over the years my interest in this field of economics always remained high. When the financial situation of young biotechnology companies deteriorated significantly after the "Biotech Bubble" on the global stock markets in 2001 I asked myself how the value hidden inside the research projects of these young companies can be unlocked to potentially finance their operations. Finally, in early 2003 I approached the Fraunhofer Institute for Systems and Innovation Research (ISI) at Karlsruhe for an initial discussion on the idea of selling option rights on ongoing research projects as a financing tool for young biotechnology companies. The supportive feedback I received during this discussion from Professor Dr. Hariolf Grupp and Dr. Thomas Reiss finally encouraged me to investigate this topic in more detail and make it the subject of a doctorate thesis.

I want to thank Professor Dr. Hariolf Grupp for accepting me as an external doctorate candidate at the University of Karlsruhe and for taking on the role as the doctoral thesis supervisor. I not only want to thank him for his advice but also for his patience and understanding for my work situation during the entire process. Without his encouragement and understanding this work might have never been completed.

I also want to thank Prof. Dr.Marliese Uhrig-Homburg and Dr. Thomas Reiss for always friendly and supportive discussions, their valuable input and their willingness to act as additional reviewers of my thesis. At this point I also want to thank Dr. Sandra Dreyer, who was able to provide many key industry insights that helped improving the quality of this work. Her feedback as an industry expert also encouraged me to complete this study. In addition I want to thank Prof. Dr. Svetlozar Rachev and Prof. Dr. Georg Bol for the fair treatment and their participation in the final examination board.

Finally I want to thank my employer A.T.Kearney for giving me support and sufficient freedom to complete this study.

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Rüdiger Pleines

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Abbreviations

AADA	Association for Adult Development and Aging
AARP	Association for the Advancement of Retired Persons
ACRP	Association of Clinical Research Professionals
AE	Adverse Effects
AHC	Academic Health Center
AIDS	Acquired Immune Deficiency Syndrome
ANDA	Abbreviated New Drug Application
AV	Additional Value
BC	Best Case
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
bil.	Billion
BLA	Biological License Application
BMS	Bristol-Myers Squibb
BS	Black Scholes
CAGR	Compound Annual Growth Rate
CAPM	Capital Asset Pricing Model
CATD	Computer Assisted Trial Design
CBER	Center for Biologics Evaluation and Research
CBOE	Chicago Board Options Exchange
CDER	Center for Drug Evaluation and Research
CEDD	Center of Excellence for Drug Discovery
CEO	Chief Executive Officer
CFO	Chief Financial Officer
COO	Chief Operating Officer
CMR	Center for Medicines Research
CRA	Clinical Research Associate
CRC	Clinical Study Coordinator
CRF	Case Report Form
CRO	Contract Research Organizations
CSDD	Center for the Study of Drug Development
CTA	Clinical Trial Application
CTX	Clinical Trial Exemption
DAI	Deutsches Aktieninstitut
DAV	Drug Approval Value
DDD	Defined Drug Dose

DTB	Deutsche Terminbörse
e.g.	latin: exempli gratia (for example)
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EL	Execution Limit
EMEA	Evaluation of Medicines
EPD	Electronic Patient Diaries
et. al.	and others
EU	European Union
EUREX	European Exchange
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDM	Finite Difference Method
FIPCO	Fully Integrated Pharmaceutical Company
FMS	Flexible Manufacturing Systems
FR	Failure Rate
GAO	Government Accounting Office
GBM	Geometric Brownian Motion
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HMO	Health Management Organizations
HTS	High Throughput Screening
i.e.	latin: id est (that is / that means)
IMD	Incrementally Modified Drug
IMMED	International Marketed Medicines Database
IND	Investigational New Drug Application
IPO	Initial Public Offering
IRB	Institutional Review Board
IT	Information Technology
JV	Joint Venture
LOA	License Option Agreement
M&A	Merger and Acquisition
MATIF	Marche de Terme Internationel de France
MCA	Monte Carlo Analysis
MCO	Managed Care Organization

mil.	Million
MP	Market Potential
MPV	Market Present Value
NAS	New Active Substance
NCE	New Chemical Entity
NDA	New Drug Application or New Drug Approval
NDD	New Drug Delivery Systems and Formulations
NDS	New Drug Submission
NIH	National Institutes of Health
NME	New Molecular Entity
NMV	Net Margin Value
NPV	Net Present Value
NYSE	New York Stock Exchange
OECD	Organization of Co-operation and Development
OHRP	Office of Human Research Protections
OTA	Office of Technology Assessment
OTC	Over the Counter
p.	Page
PCR	Polymerase Chain Reaction
PDUFA	Prescription Drug User Fee Act
PEI	Paul-Ehrlich-Institut
PhRMA	Pharmaceutical Research and Manufacturers of America
PIPE	Private Investment in Public Equity
PLA	Product Licensing Application
PSUR	Periodic Safety Update Report
R&D	Research and Development
RCC	Research Conducting Company
RDLP	Research and Development Limited Partnership
RO	Real Option
ROI	Return on Investment
RRC	Resource Requiring Company
RTF	Refusal to File
SAE	Serious Adverse Effects
SBM	Standard Brownian Motion
SCE	Standardized Case Example
SCT	Society for Clinical Trials

SDE	Stochastic Differential Equation
SMO	Site Maintenance Organization
SNP	Single Nucleotide Polymorphism
SoCRA	Society of Clinical Research Associates
SOFFEX	Swiss Options and Financial Futures Exchange
SPC	Supplementary Protection Certificates
SWORD	Stock Warrant Off Balance Sheet Research and Development
TIFFE	Tokyo International Financial Exchange
TIND	Treatment Investigational New Drug
TLA	Technology License Agreement
TR	Technical Risk
TVM	Time Value of Money
UHTS	Ultra High Throughput Screening
US	United States
USA	United States of America
US$	United States Dollar
VC	Venture Capital
WACC	Weighted Average Cost of Capital
WBDC	Web Based Data Capture
WC	Worst Case
WHO	World Health Organization

PART I: Introduction & Theoretical Background

1 Introduction

"I think Big Pharma likes the high cost of drug development because it is a barrier to entry against smaller firms, particularly against biotechnology companies. Smaller firms get the drug in Phase I, maybe into Phase II, and because of the high cost of R&D must seek a partner to continue the development process. Big Pharma, if they really were against the high cost of drug development, would be on the Hill trying to get FDA to modify its drug approval standards." - Robert Oldham, CEO Cancer Therapeutics[1].

This quote concisely summarizes one of the key challenges young companies in the biotechnology industry are facing in the marketplace today. The high cost related to developing a new drug in combination with a lack of financial resources often prevents these companies from developing their own drug discoveries to a point where they can be launched on the market. Although various types of financing are available, they do not seem to be accessible to an extent that enables the young companies to pursue their projects independently over the long timeframe from base research to final drug approval. This ongoing problematic situation raises three key questions.

1. Does an innovative financing approach, such as selling option rights on ongoing drug development projects theoretically represent an appealing concept for young biotechnology companies to raise money to support their operations?
2. How receptive would the market be to such a concept and would it also be sufficiently attractive for big pharmaceutical companies to act as buyers of these option rights?
3. How much money can a young biotechnology company expect to raise if the concept proves theoretically attractive?

Despite the fact that financing has always been a critical issue in the biotechnology industry and option theory has now found its way into the valuation of drug development projects, the ideas have not merged yet. Until today, no comprehensive study for the practitioner can be found among scientific publications that directly deals with the questions stated above and therefore they are covered in this study.

1.1 Objective and Scope

With the underlying questions raised in the introduction section above being relatively broad, this first section frames the objective and scope of this work in more detail.

Objective

The objective of this study is to investigate the idea of selling option rights on ongoing drug development projects as a potential tool for young biotechnology companies to raise funds to

[1] See PAREXEL (2003, p. 10)

finance their operations. These option rights are referred to as the R&D option or the research option during the course of this study. The R&D option in this context grants the owner the right to acquire the unlimited, exclusive and royalty free rights on an ongoing drug development project at the time of final drug approval for a predetermined lump sum payment[2]. To frame the discussion about this broad topic, three aspects represent the main objectives of this study:

1. An investigation of the practical demand for an innovative financing tool like a R&D option for the biotechnology industry including an assessment of the receptiveness of big pharmaceutical companies for this concept as potential buyers of R&D options.
2. A description of the characteristics of a R&D option deal and how the underlying drug development project compares to financial and to other types of real options.
3. The development of a subjective valuation model to "ex ante" estimate the financing potential of a R&D option deal over the expected duration of a drug development project and to identify the key parameters that represent its main value drivers.

Each of these key objectives is related to an innovative aspect not to be found in scientific literature. Although there is a vast number of studies and reports describing the state of the biotechnology and pharmaceutical industry, none of these investigates whether a specific financing concept represents an appealing fund raising tool within the current environment. While reaching the second main objective the study extends an existing theoretical real option classification into a more pragmatic one and assesses for the first time the applicability of existing option valuation models on the specific problem of valuing an option on an ongoing drug development project. During the process of reaching the third major objective it is not only the entire subjective valuation approach itself, which builds on a double jump diffusion process, that is not described in this way in any other source. In addition, this study also intends to model technical failure risk of drug development projects in an innovative way as a time continuous default function not to be found in any other publication.

Because of the type of topic discussed, this study is mainly intended for the industry practitioner. To take the special requirements of this target audience into account the following points are considered when structuring this work.

- The industry environment is described in detail to demonstrate the practical relevance of this work.
- Key concepts around financing and option theory are summarized to an extent necessary to clarify the scientific context.
- All formulas are developed step-by-step with detailed explanations to gradually increase modeling complexity.

[2] The concept details and underlying assumptions are described in section 5.3.

- The various steps when building the valuation model are demonstrated using an exemplary drug development project for illustration purposes.
- Different alternatives are presented as to how a valuation step can be conducted although some are not pursued further (e.g. different types of distribution functions) to present advantages and drawbacks of each approach.
- Highly sophisticated mathematical concepts, such as complex partial differential equations, are avoided whenever possible.
- The final model and its preceding valuation steps can be evaluated using standard spreadsheet software.

The objective of this study is not to develop a closed form valuation formula that creates the opportunity to assign the one and only correct price to any R&D option. Instead, a subjective valuation approach is developed forcing management of companies evaluating a potential R&D option deal to discuss and think about the true value drivers of such a transaction. The knowledge gained from the discussion of these key value drivers can be considered as valuable from a managerial standpoint for negotiation purposes as the price range resulting from the model itself.

This study does not delve into the optimization of individual input parameters for the model because this issue is specific to every individual case and requires a comprehensive study on its own. However, the intent is to present a framework that enables the practitioner to assess the magnitude of the financing potential related to a R&D option and to be aware of the major risk factors when preparing or negotiating such a financing deal.

Scope

When discussing issues of the biotechnology industry one has to consider that the situation of a company in the global context not only depends on its own strategy, achievements, and development projects. It also depends on the regional environment in which a company operates. Generally, differentiation is made between the three regions North America, Europe and Asia-Pacific are distinguished from each other. Although these three regions are interlinked, they nevertheless reveal individual dynamics and trends for the developments in the biotechnology industry.

For the purpose of this study only the regions North America and Europe are considered and within these two regions the major markets USA and Germany. While the study's conceptual conclusions can be transferred to other countries and regions[3], industry trends and the current market environment are only discussed for these two countries because they represent good examples of a highly advanced market on one hand and a market in an early development

[3] There may be country specific laws or accounting standards that do prevent the use of a R&D option as a financing tool. These issues are not within the scope of this study.

stage on the other hand. This market discussion is necessary to determine market receptiveness for the R&D option as a financing tool.

After determining the regional scope of this work, a closer look is taken at the companies operating in the broad field of biotechnology. The term biotechnology itself can be explained as solving problems by using biological processes[4] but this can be done in various ways. A widely accepted classification of the biotechnology industry is the one that separates activities into four distinct fields. These fields are referred to as red, green, grey and white[5] biotechnology[6].

Red Biotechnology: Medical Applications

Red biotechnology includes all biotechnological activities applied to medical processes. Red biotechnology focuses on the human being with the main goal of finding innovative solutions to medical questions and problems. The most important objective is the development of innovative drugs to treat medical conditions or genetic defects affecting the human being, especially in cases where traditional pharmaceutical products do not exist or have proven inefficient.

Besides the main area of therapeutic drug development there are three other areas that fall under the definition of red biotechnology. These are diagnostic, drug delivery systems and tissue engineering.

Green Biotechnology: Agricultural and Food Applications

The term green biotechnology includes all biotechnological activities applied to agricultural plants and processes. This type of biotechnology mainly focuses on altering plants to adapt their individual characteristics in a targeted way. This can include an increasing resistance against fungi, bugs and other crop pests as well as against severe weather conditions. Another objective is to accelerate plant growth and the related reduction in crop cycle durations. Although biotechnologically altered plants are designed to require only a minimum of external pest- and fungicides, therefore reducing the amount of chemicals in the agricultural industry, green biotechnology is the most controversially discussed form of biotechnology.

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[4] The OECD defines biotechnology as "the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods, and services", Massey (2004, p. 1).

[5] In very specific cases the term blue biotechnology is used to describe the marine and aquatic applications of biotechnology. The use of this term is relatively rare and therefore it is not considered at this point.

[6] For a more detailed description of activities related to each of the biotechnology segments refer to Reiß and Koschatzky (1997, p. 1-8).

Grey Biotechnology: Environmental Applications

The area of grey biotechnology is not as clearly defined as the areas described above especially when it comes to the separation from the field of white biotechnology. Under the main definition of this part of the industry, grey biotechnology includes all activities that use biotechnological processes in environmental applications. This can include the alteration of microorganisms and plants to filter toxic substances from air, soil or water.[7] Another application often discussed in public media is the substitution of traditional fossil fuels with more environmentally friendly fuels based on biological, renewable energy sources[8].

White Biotechnology: Chemicals, Industrial Products and Cosmetics

Under white biotechnology one understands biotechnological approaches applied to industrial processes leading to more efficient products and less resource consuming production. Examples include organisms designed to produce certain chemicals, the alteration of enzymes for more efficient detergents, or the alteration of chemicals in cosmetics for an improved tolerance by the human skin. White biotechnology also allows the large scale production of biological products like vitamins or pulp for further processing.

From the four areas of biotechnology described, the red sector aggregates over 80% of all existing biotechnology companies and is therefore the largest segment. While the green biotechnology sector currently represents the second largest segment, white biotechnology is considered the one with the largest growth rates in the near future. Some sources predict that one third of the industrial production in certain areas could be produced using biotechnological processes in the future.[9]

This study focuses on the pharmaceutical relevance of biotechnological processes and therefore on the field of red biotechnology. Within this market segment of red biotechnology, the study focuses on the problems of "young research conducting biotechnology companies" or simply referred to as "young biotechnology companies". This type of company represents young companies that currently conduct research on one or more biotechnological drug development projects. At the same time these companies do not have an approved product to be sold in the marketplace and therefore neither report any notable profits nor do they generate a stable stream of revenues.

To complete the scoping of this work it needs to be added that contractual and legal issues related to the implementation of a R&D option deal are not discussed within the scope of this study. The same is true for the topic of agency theory[10], which is not discussed at this point

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[7] For a good overview on applications of the grey area of biotechnology one can refer to Reiß et al. (1995, p. 7).

[8] See also Heilmann (2005)

[9] Compare to Ernst&Young (2004b, p. 47)

[10] For a general discussion on agency theory see Ross (1973) and in the context of information flow see Marschak and Radner (1972).

but represents a valuable topic for further research because of the asymmetric information[11] distribution between a research conducting company and potential buyers of a R&D option. Other fields of interest entail questions regarding the treatment of a R&D option deal from an accounting[12] standpoint. In order to limit the scope of this study, these topics are left for future research.

1.2 Structure of the Study

The scope of this work requires the coverage of multiple fields of discussion and therefore the main body of this study is organized in three parts. Part one includes the first four chapters and contains the background information representing the theoretical base for this study. In an introductory chapter, the current situation of the pharmaceutical and biotechnological industry is described to create an understanding of the economical environment that builds the framework for this study. In this context the main problems of major players of the pharmaceutical industry are discussed. These major players can be considered potential partners of young biotechnology companies for the presented financing approach. For the biotechnology industry the chapter describes the historical development of the market approach and future perspectives of the industry. In addition, the requirements that have to be fulfilled for the industry to develop to its full potential are discussed. The findings of chapter one are referenced at a later stage when the general need for new financing strategies and market receptiveness towards the specific financing concept presented in this study are assessed.

The second chapter describes how the standard drug development process is structured. Besides a description of the individual process steps the entire drug development process is discussed along two dimensions, namely a time and a cost dimension. For the time component it is investigated how long it takes to complete the individual process steps for an average industry project. The defined standard development times serve as a reference for the quantitative part of the study. In addition, the cost structure of an average project is investigated relative to the identified standard development times to estimate the financing need of a company without stable cash inflows over the course of a standard project.

The third chapter introduces selected main concepts of financial option theory and the practical application of options as financial instruments. In addition, the main factors influencing the value of a basic financial call option are described. The remainder of this chapter deals with real options and how they are generally classified in scientific literature before a more practical real option classification scheme is introduced. This alternative concept separates different types of real options based on characteristics of real life business

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[11] For a general discussion on asymmetric information, corporate finance and investment refer to Hubbard (1990).

[12] A valuable discussion on accounting treatment of research and development itself can be found at Zhang (2002).

transactions. The alternative approach is used to compare the characteristics of real options in general and a drug development project in particular to basic financial options. This is done with the objective of assessing the applicability of existing option valuation methods on the valuation of real option problems.

The subsequent chapter four discusses the availability of different financing strategies for young biotechnology companies. In this context internal, external and additional industry specific financing methods are discussed with respect to availability and desirability in the specific business situation of these companies. This chapter concludes the first part of the study and serves as an assessment of the industry's need for new financing approaches.

Part two, containing chapters five and six, is related to the conceptual idea of a R&D option and the scientific context to which it refers. Chapter five is dedicated to the core idea of financing operations of young biotechnology companies by selling option rights on ongoing drug development projects. For this purpose the risk factors involved in drug development are discussed before introducing the actual financing concept. These main risk factors include the technological risk of project failure, uncertain market entry timing, unknown product lifetime, general market uncertainty and competition from substitute products. In this chapter assumptions are also made to define and frame the presented financing concept. In addition, theoretical advantages and disadvantages are described that the selling and buying side of a R&D option deal expose themselves to under this fund raising concept.

The following chapter six describes the scientific context relevant for this study. In this chapter option based valuation approaches for drug development projects are introduced and it is discussed to which extent they can be transferred to estimate the financing potential of an option with a drug development project as the underlying asset. The four main approaches are the tree based methods used at Shockley et al. (2003), Black-Scholes variations used by Banerjee (2003), compound option approaches as used at Gamba et al. (1999), Schäfer and Schässburger (2001) or at Cassimon et al. (2002, 2004) and simulation techniques used at Bratic et al. (1997) and Bode-Greuel and Greuel (2005).

At the end of part two the key question remains as to how much money can be raised through the introduced financing approach during the various stages of the drug development process. To answer this key question part three of the study, which contains the remaining chapters seven to ten, is dedicated to quantitatively assessing of the fund raising idea introduced. This part leads the practitioner through a step-by-step discussion with increasing conceptual complexity. This allows him to more easily follow the logic of the final valuation model and also to understand some of the challenges and problems that potentially become relevant when evaluating a R&D option.

As a first step of this assessment chapter seven discusses the financing potential of the R&D option in a simplified, idealistic market environment to introduce some of the price influencing factors that need to be considered. The simplified market environment is characterized by a known and constant market potential of a new drug and by an absence of competitive forces. The main innovation of this chapter is the consideration of technical failure risk of a drug development project as a monotonous decreasing continuous time

function over the entire R&D process. In addition, different distribution functions are discussed to model the risk of uncertain project duration. At the end of this chapter a pricing range is derived, which is dependent on the subjective price expectations of extreme types of investors. These extreme expectations set an upper and a lower limit to the potential price of a R&D option. To demonstrate the developed valuation approach an illustrative drug development project is defined and evaluated step by step during this chapter.

In chapter eight the approach is expanded into a more realistic view by considering price relevant input factors, which are neglected in the idealistic market view of chapter seven. Additional factors in this model are general market trends, unexpected variations in market trends, potential market expansions through new products and applications, influences from competitive forces and a general uncertainty in the initial market estimate for a new drug. To consider these additional factors, the previous assumption of a constant market potential is relaxed and the market potential of a new drug under development is modeled using a stochastic double-jump-diffusion process. During the second part of the chapter a valuation model is built around the stochastic market potential to determine the R&D option's pricing range. To demonstrate this approach the illustrative case example is expanded by additional factors and the model is solved using Monte-Carlo simulation techniques.

In the following chapter nine investigations are conducted to analyze the sensitivity of the developed valuation model in a realistic market environment to changes in its input parameters. The results of this sensitivity analysis are incorporated into an option sensitivity space. With the valuation approach being a subjective model with multiple estimated input parameters, this sensitivity space gives indications on the relative importance of precise estimations for these parameters. Based on the derived sensitivity space, comparisons are made for price changes caused by input parameter changes between the R&D option and a standard European call option.

Chapter ten concludes the study by summarizing the main results derived during the previous chapters. In addition, certain interesting topics related to this study are highlighted, which cannot be covered within the scope of this work but are recommended for future research activities. At this point it has to be noted that the simulations of the stochastic processes determining the market potential development of a new drug are completed using standard spreadsheet calculation software[13]. The discrete approximations of continuous valuation problems as well as the Monte Carlo simulations conducted in part III of this work are all solved using the same standard software tool. A detailed presentation of the programming efforts necessary to solve the valuation equations derived in this study would result in a technical manual not manageable within the scope of this work. To avoid an overload with technical details, readers interested in the structure and the detailed programming of the valuation file are kindly asked to contact the author directly.

[13] Microsoft® Office Excel 2003

1.3 Industry Background and Current Situation

To prepare the groundwork for this study on an innovative financing concept for young biotechnology companies, it is essential to create a general understanding of the industry environment these companies operate in. At the same time it is also necessary to take a closer look at the situation of large, research conducting pharmaceutical companies because these companies represent potential buyers of the R&D options investigated.

1.3.1 Situation of the Pharmaceutical Industry

After decades of scientific discoveries the pharmaceutical industry can look back on a period of corporate success stories. Since the end of the 1980s, the industry was able to develop a multitude of breakthrough products creating wealth and prosperity for the key industry players. This development has raised the expectations of the financial community and the general public on the future development of this industry. Today's industry finds itself in an environment that has significantly changed leaving the main industry players with a set of problems making it difficult to live up to the high market expectations.

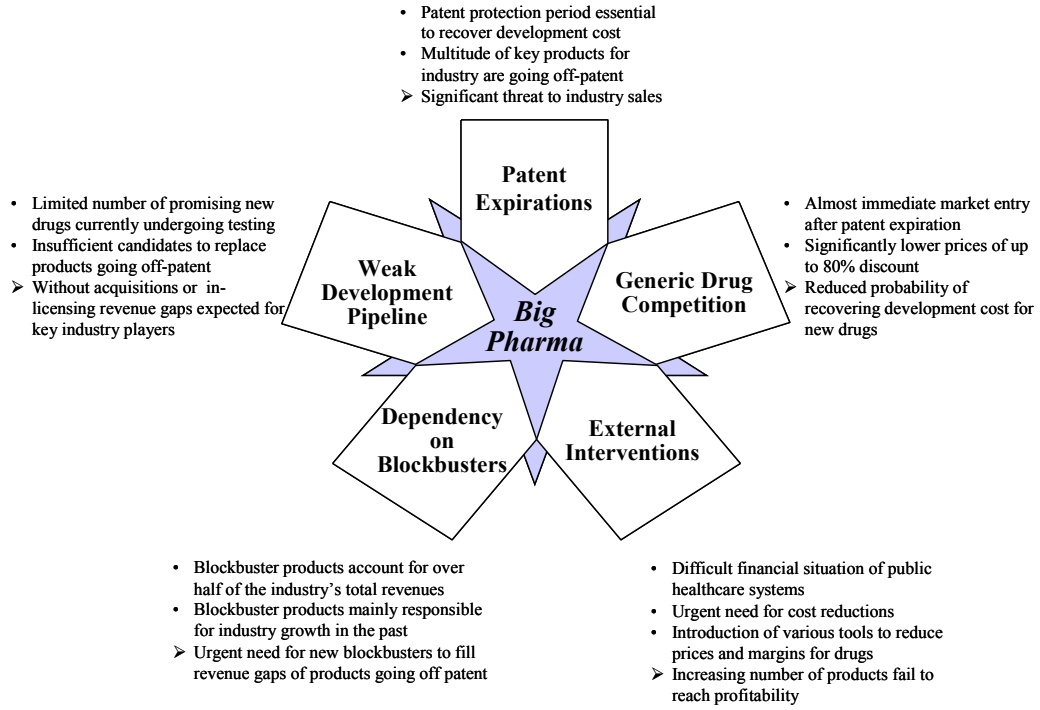

Figure 1.1: Main problem areas of the pharmaceutical industry

The problems for this industry can be reduced to a set of five main problems, namely the expiration of patents for successful products, the competition arising from the generic drug industry, price pressure from health care organizations, an urgent need for new blockbuster products, and development pipelines, which are short of promising new breakthrough

discoveries. Figure 1.1 summarizes these five main challenges large pharmaceutical companies face in the marketplace.[14]

Patent expirations

For research intensive industries it is essential to own patents on new discoveries because they protect them from direct competition[15] for a specific period of time. During the protection period the patent owner can use the absence of direct competition to recoup his R&D investment and also earn a profit exceeding the initial investment. Patents are therefore a necessary tool to initiate research activities.[16]

The problem the pharmaceutical industry is facing in this context is an increasing number of drugs losing their patent protection status in the near future. During the two-year period 1998/1999 the annual sales volume of products going off-patent in the US was worth around US$4.4 billion and tripled until 2001/2002 when over US$13.2 billion in annual sales went off-patent according to Mullins et al. (2003). Although these numbers appear large, the situation is expected to become worse. As shown in Figure 1.2, patent expirations in the US are going to increase to peak levels of over US$8 billion in sales volume per year. For the upcoming period from 2005 to 2008 a total of over US$31 billion in annual sales is expected to go off-patent. Hisey (2004) estimates the corresponding worldwide numbers are expected to reach over two times this amount or about US$72 billion between 2005 and 2008.

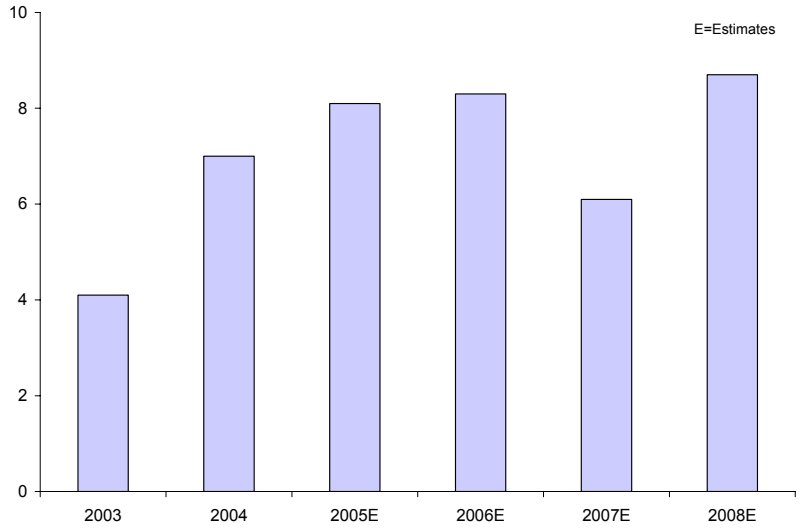

Figure 1.2: Pharmaceutical patent expirations US (2003-2008 in US$ bil.)[17]

[14] Compare also to Ruess and Salz (2002)

[15] It does not protect them from indirect competition where other companies sell different products with similar characteristics for the same medical indication.

[16] Chapter 5.1.3 discusses the importance of patents for the industry in more detail.

[17] Source: Teitelbaum et al. (2003) and Motheral et al. (2003)

There are ways to renew or extend the patent protection period if the patent for a product reaches the point of expiry and a company wants to further be protected against direct competition. Examples of how the initial patent protection period can be extended include the discovery of additional therapeutic uses or new application formats. However, in cases where this is not successful, the patent owner can apply for a Supplementary Protection Certificate (SPC) that officially extends the initial patent protection period. In cases where these two options are not given the company finds itself in a situation where investors expect them to find new products or business opportunities to make up for the resulting loss of revenues and profits. Patent protection terms, potential extensions and effective patent protection periods are discussed in more detail in section 5.1.3.

Generic Drug Competition

The second major problem for established pharmaceutical companies, which is closely related to the previously described one, is the increasing competition from generic drug manufacturers. This issue of increasing generic drug competition has two aspects to it, namely a time and a price component. In the past, generic drug competitors entered the market slowly over time after a brand name drug had gone off-patent. This gradual market entry allowed brand name drug manufacturers to generate sales after the end of the patent protection period that were only gradually reduced over time. This type of market entry has changed towards a "more rapid sales erosion by brand name products with recent patent expirations"[18].

There is a trend towards generic drugs entering the market faster and more successfully after patent expiration of a branded drug. In certain extreme cases, brand name products can lose the majority of their market share literally over night. Frank and Seiguer (2003) show that it took selected generic drugs about 60 months to acquire 80% market share ten years ago while this time period is reduced to only nine months for recent generic market entries. An example of this development is Eli Lilly's former blockbuster drug Prozac®, which generated revenues of more than US$2 billion in 1999. When its patent protection status expired in 2001, it lost 80% of its market share within two months[19]. Over the following months, this loss increased and stabilized at 94%[20]. Teitelbaum et al. (2003) show several more examples where generic drugs were able to gain over 80% market share within two months after patent expiration and over 90% after a six month period. Boles (2004) supports this trend by finding that sales volumes of drugs that have lost patent protection status can drop to 5% of the levels before the arrival of generic drug competitors.

The reason why manufacturers of generic drugs are quickly able to capture market share resides in their significant price advantage. During the patent protection period, large

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[18] According to Grabowski and Vernon (2000b, p. 106)

[19] Compare to Harris (2002)

[20] See Teitelbaum et al. (2003)

pharmaceutical companies have sufficient market power to price some selected products well above production cost due to the absence of direct competition. Since generic drug manufacturers do not have to finance expensive base research activities, they are able to price their products below their direct brand name competition. This cost advantage can range from 30% to 80%[21] and as more generic competitors enter the market, the more the price of a drug converges against actual production cost[22].

With the described rapid market entry and their price advantage, generic drug manufacturers were able to capture a large share of the total drug market. Danzon and Furukawa (2003) found that already back in 1999, 58% of all prescriptions in the US and 61% in Germany were filled with generic drugs. As a result from their lower prices compared to branded products, their share of the total sales volume was lower with 18% and 34% respectively. Other sources like Motheral et al. (2003) confirm this trend of increasing generic drug usage and expect it to continue.[23]

External Industry Interventions

Financial problems in governmental healthcare budgets and at large health care organizations promote the use of generic drugs. These entities expect savings from the faster availability of cheaper generic drug versions of branded products.[24] While this squeeze on price occurs after patent expiration, there is a second type of price pressure, which already takes place while a drug is still patent protected. Healthcare organizations in the US require pharmaceutical companies to enter drug rebate programs in order for their prescription drugs to be covered. Under the Medicaid program manufacturers of brand name drugs have to pay a rebate of either 15.1% of the average manufacturer price (AMP) or the difference between the AMP and the lowest price offered to non-federal purchasers, whichever amount is greater[25]. Additionally, more complex price reduction schemes have been introduced under the Medicare program. Although US companies often consider this a threat to profitability, Scherer (2004, p. 929) concludes in his study on price control that "the United States […] are considered to be the least aggressive among industrialized nations in imposing governmental price controls".

A similar development with tighter regulations can be observed in Germany where the federal health care system either establishes fixed prices for prescription drugs or requires rebates from the drug manufacturers to reduce cost. These rebates have recently been

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[21] Compare to Handelsblatt (2002a) or Frank and Seiguer (2003)

[22] According to Grabowski and Vernon (2000b, p. 106)

[23] Another form of competition not discussed here are alliances between small pharmaceutical companies attacking specific indications currently covered by large pharmaceutical companies. For recent trends on this topic see Hofmann (2003).

[24] See Handelsblatt (2002a)

[25] Compare to Peters (2004)

increased for patent protected prescription drugs from 6% to 16% with a significant negative impact on the revenues and profits of large pharmaceutical companies.[26]

An alternative way for health care organizations to reduce cost is the delisting of certain drugs or the switching of drugs from prescription drug status to over-the-counter (OTC) status. Whereas delisting negatively impacts total sales volume, switching increases competition between products and marketing cost for the manufacturer. Such actions can result in a delayed break-even of up to six years according to Giesecke (2001, p. 65).

For the pharmaceutical industry in Germany, increasing governmental interactions resulted in limited opportunities to increase prices and therefore, the average price development for pharmaceutical products is lagging behind overall increases in consumer prices[27]. In the US, big pharmaceutical companies are still able to enforce more aggressive pricing strategies that make drug prices increase faster than the general cost of living.[28]

Need for New Blockbuster Products

The pharmaceutical industry owes a large portion of its wealth and historical growth to large blockbuster drugs. BCG (2004b) found that industry growth over the last decade can almost exclusively be attributed to the market introduction of large blockbuster[29] drugs or to sales increases of existing blockbuster products. Historically, large pharmaceutical players focused on treatments for indications affecting a large number of patients to maximize the return on their R&D investment. This strategy proved very successful, especially during the 1990s. At that time the penetration of several high potential therapeutic areas like antibiotics, depression medications, cardiologic medications, gastrointestinal drugs, respiratory drugs or diabetes treatments led to an introduction rate of eight to ten new blockbuster products per year. These historical successes in combination with the previously described problem of expiring patents put pressure on the entire industry. To keep growing at a rate of 10% a year, the big industry players would need to introduce at least two to three new blockbuster drugs[30] a year, which is far from reality today.

With an increasing number of drugs for high potential therapeutic areas being introduced, there is less room for new blockbuster products because more competing products are sharing the same markets. As a result, big pharmaceutical companies are forced to either penetrate

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[26] See BPI (2004b, p. 48) and Fischer, Manfred (2004)

[27] Compare to BPI (2003b, p. 48)

[28] The extent to which general inflation is exceeded strongly depends on the research study considered. According to Dorschner (2005), the AARP reports drug prices increases twice as high as inflation while a PhRMA study shows that price increases are only slightly above overall inflation in the US.

[29] In this context blockbuster drugs are defined as drugs with an annual sales volume exceeding US$500 mil. in 2001 US$.

[30] According to R&M (2005)

new therapeutic areas with less competition[31] or to develop new drugs that are effective and competitive enough to replace blockbuster products in an established market. Both strategies are extremely resource intensive to pursue[32].

In their search for new blockbuster drugs the industry started increasing their spending on research and development as shown in Figure 1.3. Between 1992 and 2003, R&D expenditures increased at a compound annual growth rate (CAGR) of 6.2%. Based on the latest PAREXEL (2003) industry outlook this trend is expected to continue and global R&D expenditures are expected to exceed US$57 billion in 2006.

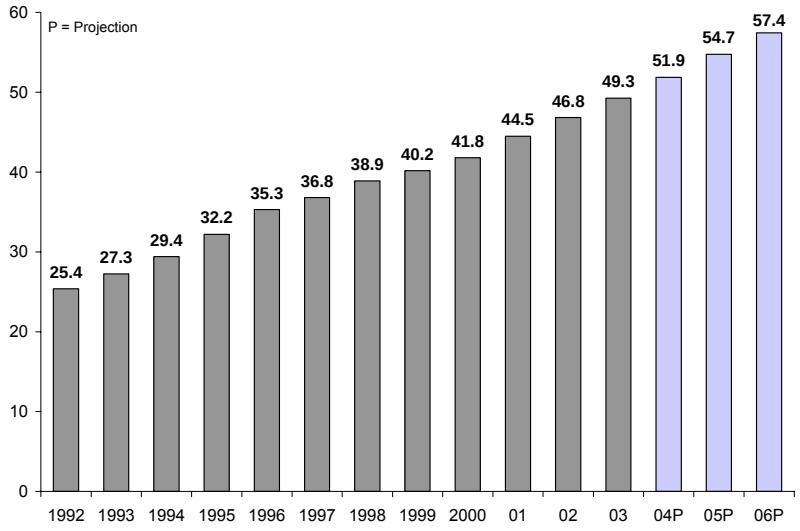

Figure 1.3: Global pharmaceutical R&D expenditures (1992-2006 in US$ bil.) [33]

This trend makes the pharmaceutical industry the most research intensive one compared to other manufacturing industries. Figure 1.4 shows the research intensity of the pharmaceutical industry in comparison to other manufacturing industries. Compared to its total sales, the pharmaceutical industry spends over 12% on research and development activities. This is far more than the electronics industry, which spends with about 7% significantly less on research activities. Other major manufacturing industries like chemicals, automotive or general machine building spend an even lower percentage of their revenues on R&D activities.

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[31] Pfizer followed this approach when it successfully entered the rather undeveloped market for sexual dysfunctions with its blockbuster drug Viagra®.

[32] One of the reasons why some therapeutic areas can be considered underdeveloped is the fact that they are more complex and therefore more resource intensive in terms of time and money to penetrate. Various forms of cancer and AIDS treatments can be considered such underdeveloped markets, which were shielded by high barriers of entry in the past.

[33] Source: PAREXEL (2003)

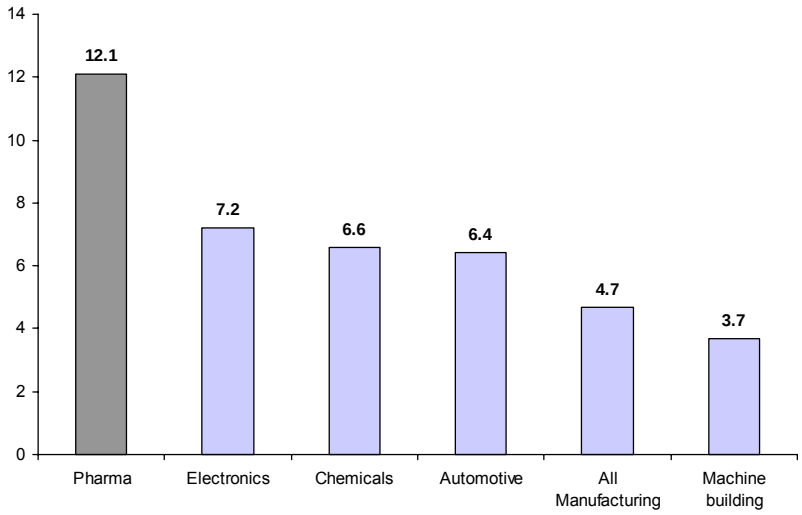

Figure 1.4: Research intensity of selected manufacturing industries (% of revenues)[34]

One effect of the increasing R&D expenditures is, according to Grabowski et al. (2002), that only a limited number of products are able to recoup their full research investment. According to their study, only three out of ten drugs are ever able to earn their total R&D cost, which is shown in Figure 1.5.

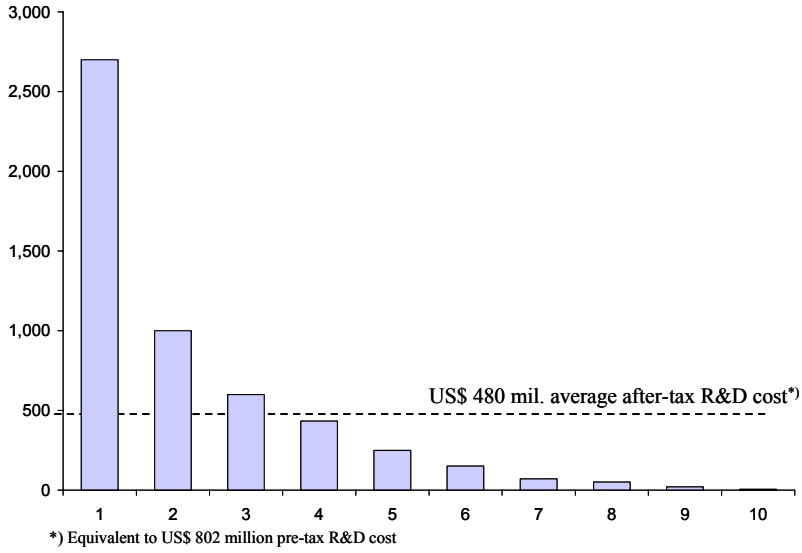

Figure 1.5: Return of new drugs by decile (1990-94 in US$ mil. after-tax NPV) [35]

They conclude that "in the long run, the firm also must have its share of winners for its R&D program to be profitable and remain viable"[36] and are supported by Mauerer (2002) who

[34] Source: VFA (2005)

[35] Source: Grabowski et al. (2002)

[36] See Grabowski and Vernon (2000a, p. 24)

states that "the larger the company, the larger the expected revenue needs to be to justify production and marketing".

One of the results of this development is that some companies start focusing even more on the discovery of blockbuster drugs[37] by selling products that generate minor revenues and by divesting non-growing business units to fund their search for blockbusters[38]. This development created a large dependency of the pharmaceutical players on a small number of promising projects with the potential to result in true blockbuster products. How some of the big pharmaceutical players depend on a few large key projects can be seen in the severe stock market reactions in cases where one of these main projects is delayed or even fails[39].

Weak Product Development Pipelines

As shown above, the pharmaceutical industry is spending more on R&D than ever before to discover those large promising products required for sufficient growth. At the same time the number of substances that can potentially result in a blockbuster drug is decreasing. This widening gap between R&D investments and the number of projects in the pipeline represents the fifth problem area of the industry.

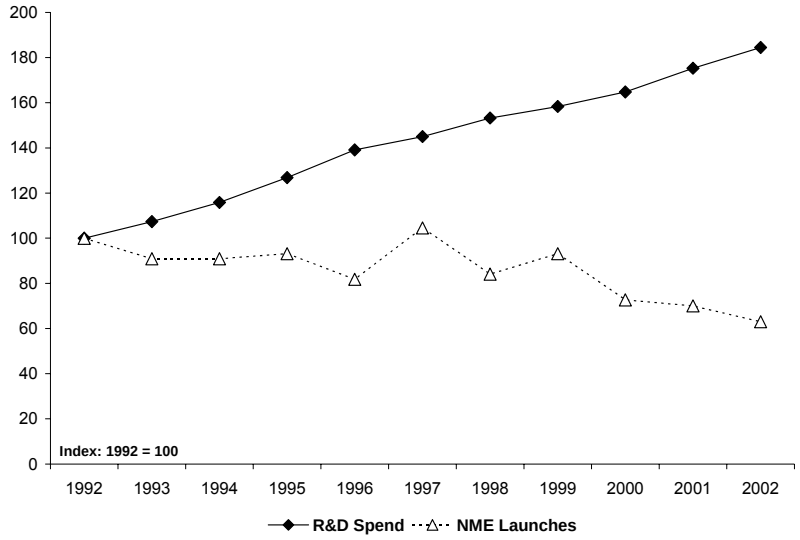

Figure 1.6: Global NME approvals vs. global R&D spending (1992-2002)[40]

[37] Another result was a wave of mergers and acquisitions that went through the industry with the objective of collecting a multitude of promising projects under one roof (e.g. Hofmann (2005b)). For an overview for mergers in the pharmaceutical industry refer to Neukirchen (2005, p. 127). Dzinkowski (2003) concludes that although large mergers are a tool to increase corporate efficiency, they are not a suitable way to solve the problem of the expected upcoming product shortage.

[38] Compare to Hofmann (2002)

[39] Compare to Crolly (2005) or Fischer, Manfred (2005)

[40] Own illustration, input data source PAREXEL (2003).

Figure 1.6 illustrates how global R&D spending of the industry constantly increased since 1992 while the number of approved NMEs dropped by about one third over the same time period. The problem of weak drug development pipelines is well recognized and investigated in recent publications. White et al. (2004) found that the ten leading pharmaceutical companies will not be able to meet investors' expectations if this current trend continues. They estimate that growth with current products and the market introduction of products currently in the pipeline will not be sufficient to make up for patent expiries and price pressure on existing products. With current trends ongoing and investors continuing to expect a ten percent annual growth rate, these ten major pharmaceutical companies[41] will fall US$40 billion short of expectations by 2007.

Potential solutions to fill the corporate development pipeline include the acquisition of small innovative companies as indicated by Handelsblatt (2003b) or the in-licensing of innovative products and technologies.

Conclusion

As Reiß et al. (1997) already concluded in their study there is no single correct strategy for pharmaceutical companies to master these challenges. Based on their work, companies should focus on generating know-how, reducing development times and on improving the efficiency of R&D processes in order to stay competitive.

In line with this conclusion, some key players in the pharmaceutical industry are about to shift their strategic direction from a pure blockbuster approach. The three new trends in the industry are a focus on a few therapeutic areas[42], the penetration of niche markets[43] with limited competition and the offering of more individualized treatments for a limited number of patients[44]. Until this strategic change shows an impact on industry performance, the main problem of successor products for expiring patents will remain unresolved, be it in the form of high-volume blockbuster drugs or in the form of profitable niche products.

1.3.2 Situation of the Biotechnology Industry

Compared to the pharmaceutical industry's situation, prospectives for the biotechnology industry appear more favorable from a product standpoint. While the drug development pipelines of most pharmaceutical players are weak, those of the biotechnology industry are filled. After 2005, Carius (2002) expects that more than 50% of all new drug approvals will be of biotechnological origin. Out of the products under development at least ten have true blockbuster potential. This upcoming wave of new biotech products is expected to increase the revenues of the industry to over US$38 billion in 2005. With industry revenues

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[41] Although companies are affected to a different extent as shown by DiMasi (2000).

[42] See Arnst et al. (2004)

[43] See R&M (2005)

[44] See Augen (2002)

accounting for US$16 billion in 2000, this is equivalent to a CAGR of 19% and therefore the industry is growing at about twice the rate of the traditional pharmaceutical industry.[45]

From a business model perspective, the industry went through different phases in the past, each with its own strategic focus. These trends are the result of market forces and the general economic environment with the main influencing factor being the availability of financial resources according to Ernst&Young (2003, p. 52).

The members of the first wave of biotechnology companies during the 1970s and 1980s focused on developing products and bringing them to the market. Some of the largest biotechnology companies today laid the foundation for their success during that time. Since developing a drug is a capital intensive[46] and risky endeavor, the main focus of the industry shifted to a technology focused approach during the mid 1980s.

This stage was followed by phases where the industry's main focus was put on the development of new platform technologies and the offering of biotechnology based services. Despite the large capital requirements, the trend shifted back to developing new products with the boom of the stock markets at the end of the 1990s because this approach is considered the most profitable one in the long term. Figure 1.7 illustrates the sequence of main business model trends in the biotechnology industry since 1975.

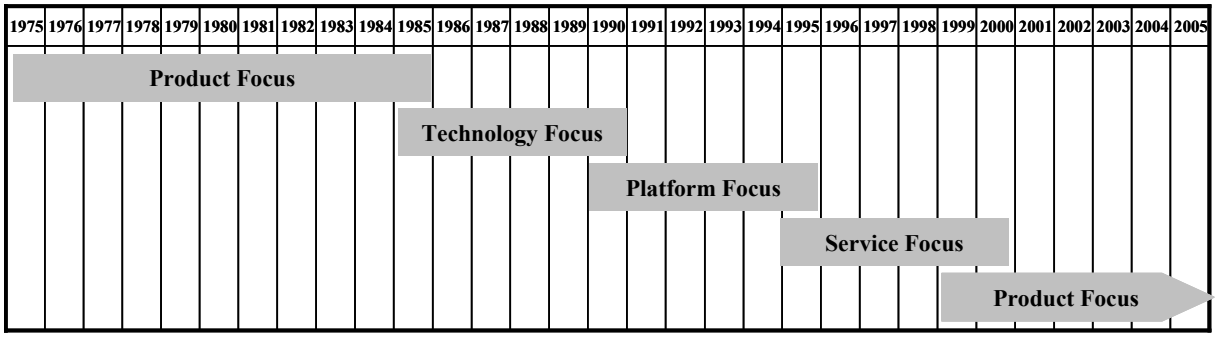

Figure 1.7: Preferred biotechnology business models (1975-2005)[47]

The latest trend that more companies are trying to cover the entire value chain and are attempting to develop their own products exists in the US[48] and in the German[49] market with

[45] A few companies in the biotech industry have already reached a more mature stage of corporate development than most players in the industry and they cannot expect continuous growth rates of this magnitude. Examples of these more mature, integrated biotech players include Amgen, Genentech, Genzyme, Chiron, Biogen Idec, etc.

[46] Three of the largest and most successful biotech companies today are Amgen, Genentech, and Genzyme. According to BIO (1995), these companies required an equity base of US$264 million, US$1.6 billion, and US$328 million respectively to introduce their first products to the market.

[47] Source: Ernst&Young (2003, p. 52)

[48] Compare BCG (2002, p. 31)

[49] The BPI (2002) study confirms this latest business model shift for Germany. For a recent example for this trend in Germany see Handelsblatt (2006).

one major difference. The average US company has a time advantage of about 8-10 years[50] related to the earlier establishment of the industry in the US. In Germany, around 80% of all biotechnology companies belong to the category of young biotechnology companies without any or with only minor revenues[51] that are within the scope of this work. This percentage is lower in the US, where companies of the biotechnology industry are on average more mature. The German industry had to wait until 2003 for its first drug to be approved[52] while at the same time, US companies got approval for 25 new drugs in 2003 and 20 in 2002 according to Ernst&Young (2004d). Another indicator for a more mature US biotechnology industry is a direct revenue comparison. In 2003, 350 German biotechnology companies generated total revenues of €960 million whereas 1,473 US companies were able to generate €20.9 billion[53]. On a company level, these numbers show that the average US company generates with €14.2 million more than five times the revenues of the average German company, which generated only €2.7 million in 2003.

As indicated, the main challenge with a full product approach is that it is risky[54], time consuming[55] and expensive[56] to pursue. Eichener et al. (2001) conducted a study among German biotechnology companies and found that 70% of all companies named financing as the industry's biggest problem. This situation already started to improve in the US where only 15% of the companies had less than one year of cash available in 2003 compared to 32% in 2002[57]. In Germany the situation remains unchanged on a critical level especially for venture capital financed firms where 68% have less than one year of cash available to run their operations[58]. Although the strategic focus of most companies is on independent drug development, the indicated challenge of large capital requirements forces multiple firms to follow alternative approaches. Ernst&Young (2004b) present two of these alternative business models in their study.

One approach is to sell products under development before they enter the most expensive clinical trial phase III. Giesecke (2001) confirms that only a few companies are able to take full advantage of their discoveries and have the potential to bring their own products to

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[50] See Giesecke (2001, p. 45)

[51] See Ernst&Young (2004b, p. 91)

[52] The Munich based company MediGene received approval for its cancer drug Eligard® in 2003.

[53] US$28.4 billion based on Ernst&Young (2004d, p. 26)

[54] Only an small portion of research projects result in a marketable product as shown in chapter 5.1.1.

[55] Depending on the referenced source - as shown in Table 2.1 - it takes between 11 and 15 years to fully develop a drug from base research all the way until final market introduction.

[56] Recent studies summarized at PAREXEL (2003, p. 75) estimate the total cost of bringing one product to market including failed projects to be between US$800 and US$900 million.

[57] Compare to Ernst&Young (2004a, p. 4)

[58] See Ernst&Young (2004b, p. 103)

market. Most biotechnology companies do not have the resources or capabilities to achieve this and are therefore selling their discoveries at some stage to established pharmaceutical companies. These companies complete the remaining capital intensive steps of the value chain and bring the product to market.

The other alternative dedicates some corporate resources to cash generating activities like providing services to other industry players[59] in the form of contract research. While this improves the short-term cash position, the redirection of resources negatively impacts development times and delays market introductions. Primary objective of this business model is still the completion of the entire R&D process for at least one product. Contract research represents a second priority area. This type of work is not of strategic importance and serves as a tool to generate cash flows to close the financing gap evolving from the attempt to become a Fully Integrated Pharmaceutical Company (FIPCO).[60]

How important the generation of additional cash flows is can be seen by the fact that only 5% of the German biotechnology companies[61] are able to finance operations out of their own cash flows. It becomes even more important if one considers that it is difficult within the current situation to raise funds from external sources especially for companies without stable cash flows or products at a very late development stage.

Besides the two presented business models, an increasing number of young biotechnology companies are entering licensing deals to generate cash flows. In Germany an increasing number of licensed products can be observed especially at later stages of the value chain. While 73% of all products undergoing pre-clinical trials are self-developed products, this percentage decreases to 50% for products in phase II clinical trials.[62] This supports the impression that multiple companies do not have sufficient funds to complete the development process on their own and have to out-license their discoveries. On the other hand, it supports the discussed trends of the pharmaceutical industry, whose companies are often partners in those deals and in-license products at advanced project stages. These products strengthen development pipelines and represent candidates for future revenue generators.

For the few mature biotech companies there is also a threat from generic competition according to Wilde Mathews and Hamilton (2004) and Kuchenbuch (2004a). Generic drug manufacturers are starting to target the first biotechnology products losing patent protection although this is generally a problem of established pharmaceutical companies. Since this problem only arises for mature companies it is not relevant in the context of this study that focuses on issues of young companies. Other problems of young companies like insufficient

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[59] Compare to Ernst&Young (2004b, p. 49)

[60] See Mahler and Martens (2002)

[61] Based on BPI (2002). The topic of financing within the biotech industry is discussed in detail in chapter 4.

[62] According to Ernst&Young (2003)

management capabilities, unfocused business models or lacking exclusivity of products under development are not subject of this study and are therefore not discussed.

Conclusion

A small number of mature US biotechnology companies already find themselves in a similar situation as large pharmaceutical players who primarily have to deal with increasing generic competition and the need for replacement products. However, the majority of the young biotechnology companies are facing a shortage in financial resources that prevents them from bringing their own products to market. Although the situation of US based companies improved in that respect and German based companies significantly reduced their burn rates[63] to extend the lifetime of their cash positions, financing issues remain the most critical problem of the industry.

If the industry is not able to open up new sources of financing, Knop (2004) and Kuchenbuch (2004b) expect a growing trend towards consolidation with a large number of insolvencies and merger and acquisition deals. Handelsblatt (2002d) also expects an increasing number of bankruptcies in the German market related to a shortage of financial resources or as Solt (1993, p. 180) states, "if conventional capital budgeting were the only investment vehicle available, most biotechnology firms would be unlikely to undertake innovation independently".

[63] See Hofmann (2004)

2 Pharmaceutical Research and Development (R&D)

This chapter describes the process of developing a new drug and bringing it to market. This is done to the extent necessary for the understanding of the following chapters. More details on the drug development process can be found in recent literature[64], a wide variety of studies[65], laws and regulations[66] or on websites of local authorities[67].

2.1 Pharmaceutical Value Chain

Developing a new drug is a long process with a highly uncertain outcome at the time of initiation. On average, only one out of several thousand components entering the drug development process is carried through the entire process until it is granted regulatory approval and can be marketed as a new drug[68]. Before a drug can be approved, its sponsor[69] has to complete a series of well defined process steps as summarized in Figure 2.1. The figure shows that the pharmaceutical value chain can be separated into seven distinct process steps, each of them with specific scope and objectives.

2.1.1 Base Research

The pharmaceutical value chain starts in the laboratory where scientists search for targets that can be affected by a substance or a chemical compound. Generally these targets are human molecules like enzymes, cell receptors, or other human proteins. Once a target is found, the second challenge is to identify substances that have an impact on a specific target. These substances can be newly developed chemical substances or compounds from a natural source. This is a time-consuming process because the impact of thousands of substances on the identified target have to be screened. With high-throughput screening technologies (HTS), several thousand tests can be performed per day[70] reducing the duration of this process step[71]. Substances passing this test are referred to as “new chemical entities” (NCEs).

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[64] For more information on pharmaceutical R&D refer, for example, to Collatz (1996), Harvey (1998), Cohen and Posner (2000), Collatz (2001), Schumacher and Schulgen (2002), Vogel (2002), Gaus (2003), Hara (2003), Kayser and Müller (2004) or Ng (2004).

[65] See also Bank Leu (2001), BCG (2001), BCG (2002), BPI (2003a), BPI (2003b), EFPIA (2003), PAREXEL (2003), BPI (2004a) or PhRMA (2004)

[66] See also Pabel (2003)

[67] E.g. www.fda.gov or www.bfarm.de

[68] On pharmaceutical project failure rates see Nichols (1994, p. 91), BPI (2003b, p. 25) or FDA (2004, p. 6).

[69] A drug’s sponsor in this context is the person or entity, which has the intention to bring a new drug to market and therefore has the responsibility to ensure compliance with all applicable laws and regulations. Not only can a sponsor be an individual or a company but also a partnership, a governmental agency, or a scientific institution.

[70] Compare to VFA (2003, p. 17)

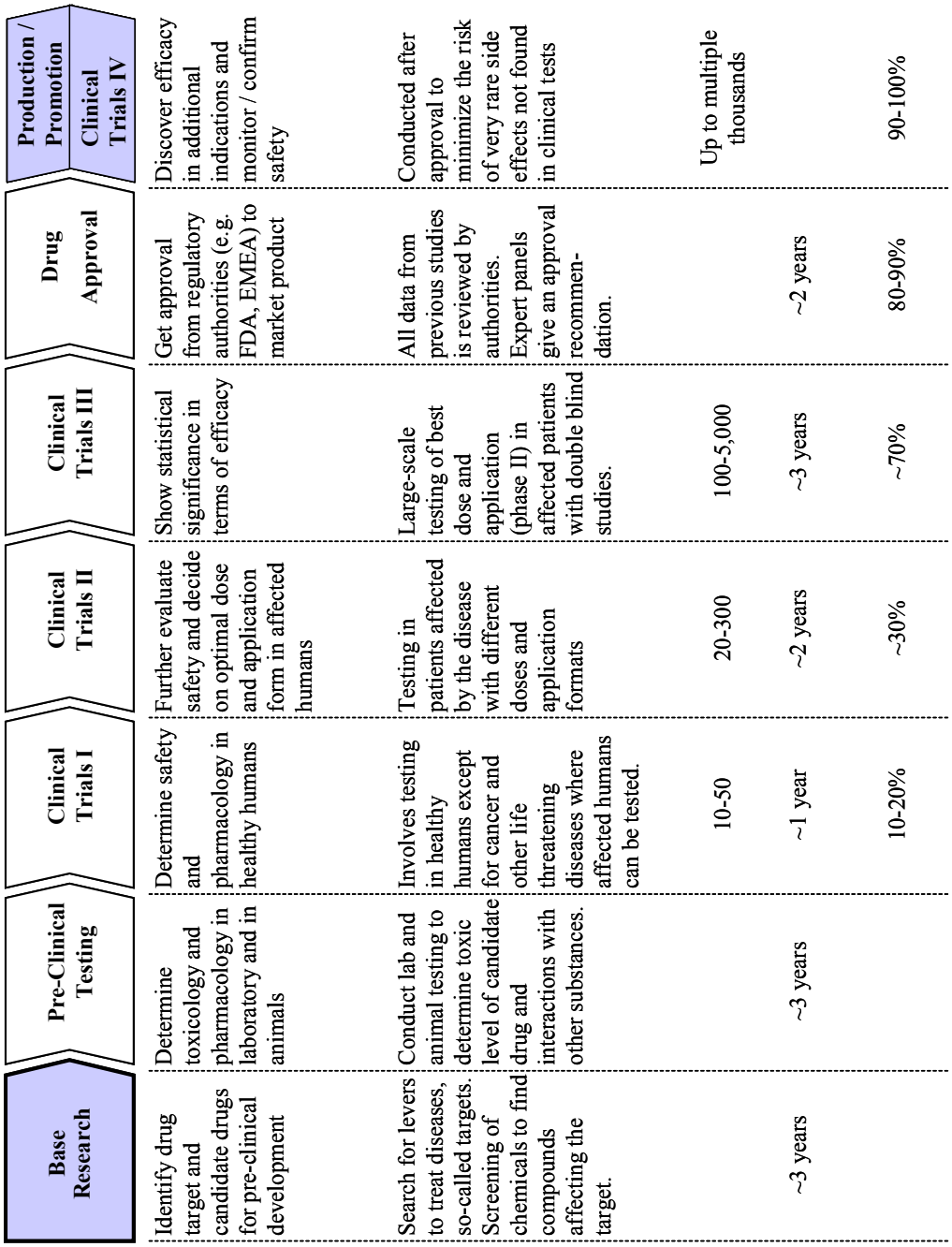

Figure 2.1: Pharmaceutical value chain[72]

[71] These technologies are currently in the process of being further developed into Ultra High Throughput Screening (UHTS) technologies that allow even more substances to be tested within short periods of time.

[72] Adapted from AMB (2004, p. 101)

All identified NCEs qualify for more detailed investigations. After passing additional tests, a multitude of slightly altered variants of the substance are designed and retested on the target. Improving the most promising variants through several iterations leads to a stage where a substance is considered an active component. Active components that appear promising enough to justify additional research are generally patent protected and enter the phase of pre-clinical trials[73] as a potential drug candidate.[74]

2.1.2 Pre-clinical Trials

Objective of the pre-clinical trials is to generate knowledge of a compound's interaction with an organism before it is released for human testing. One focus area is the toxicity[75] of a compound, which is tested in-vitro as well as in animal studies[76] to identify unwanted side effects. This can include a negative impact on fertility, changes to the genetic material or cancer enhancing characteristics. These toxicity studies are performed as single dose toxicity testing[77] and repeated dose toxicity testing[78].

It is also investigated how a compound is absorbed by, distributed in, and released from the organism. To ensure high quality standards during this part of the research process, all tests have to comply with Good Laboratory Practices (GLP). These guidelines not only ensure that the applied testing procedures cover all areas that have to be tested but also ensure a wide acceptance of the generated test results. By following the GLP unnecessary and duplicated testing can be avoided.

The knowledge gathered during this phase is used to determine beneficial application doses of a compound and to generate information about the application frequency and duration to allow safe testing on humans. Once the decision is made that a new drug should go into clinical tests in the US, an initial drug application (IND) is filed with the FDA for review.

In Germany, applications for clinical trials (CTA) are filed with the "Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)" or the "Paul-Ehrlich-Institut (PEI)" and an independent ethic committee for review. These regulatory agencies decide about the initiation of clinical trials based on a risk-benefit profile and have the authority to stop it at any time during phase I, II, or III if the situation changes. This might be the case if unexpected side effects occur and the safety of the trial participants is jeopardized. Another

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[73] Patent protection does not have to take place at that stage of the value chain. It can also take place earlier or later but on average the application for patent protection is filed around that stage.

[74] The entire base research process is done in-vitro, which means it is performed in a laboratory environment not involving any tests on animals or human beings.

[75] Compare to FDA, Center for Drugs and Biologics (1987) and CDER (1989)

[76] In-vivo

[77] See CDER (1996)

[78] See CDER (1997)

reason could be a negative change in the risk-benefit profile caused by adjustments to the objectives of the trials.

In 2004, 33.3%[79] of the entire global pharmaceutical R&D spent was related to base research activities and pre-clinical trials, adding up to total expenditures of about US$16.4 billion.

2.1.3 Clinical Trials I

After an IND/CTA is positively reviewed, clinical trials can be initiated. During the first phase a new drug is introduced to humans for the first time. The drug is given to a small group of 10 to 50 healthy volunteers[80] who receive small doses of the new drug to identify the threshold where side effects can be observed. Multiple series of studies with increasing doses are conducted to verify the indications from pre-clinical testing on how a drug is absorbed, distributed, metabolized, and released from the human organism.

During Clinical Trials I, sufficient information about a drug's pharmacological effects are obtained to permit the design of a well controlled and scientifically valid second phase of clinical trials. To ensure the generation of widely accepted results and to minimize the risk for volunteers in these trials, a project has to follow the guidelines for Good Clinical Practice (GCP). These guidelines define standards for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials and specify, to which extent participants have to be informed about potential risks related to the trial phase.

In addition to the GCP standards, the entity conducting the study also has to prove that the drug samples used have been produced following the Good Manufacturing Practice (GMP) for pharmaceutical products. The GMP guidelines define minimum quality standards for drugs used in human testing. It also requires a series of quality analyses and the archiving of the results and the samples of the drug or substance analyzed.

Of the global pharmaceutical R&D spend in 2003, 7.1%[81] or US$3.5 billion were related to clinical phase I trials in 2003.

2.1.4 Clinical Trials II

During this phase, information on the effectiveness of a new drug in patients affected by the targeted condition is collected. The objective is to determine, which doses of the new drug produce the best results and which side effects can potentially occur. To collect the necessary

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[79] Based on PhRMA (2005, p. 37) with an adjustment for uncategorized costs, which are distributed over the different R&D functions by total spend.

[80] In certain cases this stage of clinical trials can already involve volunteers affected by a certain disease or condition. This becomes especially true for life-threatening diseases where there is no other effective treatment available such as certain types of cancer.

[81] Based on PhRMA (2005, p. 37) with an adjustment for uncategorized costs, which are distributed over the different R&D functions by total spend.

information, the drug is tested in 20 to 300 affected volunteers. Depending on the composition of the patient sample it is also investigated how patients with certain other conditions react to the drug and how they can absorb and metabolize its ingredients. Phase II trials aim at avoiding accumulation of drug ingredients in the human body, identifying negative interactions with other substances, and at developing application strategies to avoid these unwanted effects.

Clinical phase II trials are well controlled and closely monitored. Patients are generally divided into two sub-groups, of which one is treated with the drug while the other one receives a harmless and inactive placebo. To avoid a psychological bias, patients are not informed about which group they belong to. This type of testing is called single blind testing. To ensure equal treatment of all patients, medical staff conducting the study and directly interacting with the patients may also remain uninformed about the composition of the sample groups. In this case the type of study is called a double blind study. In cases where ethical reasons would forbid treating patients only with a placebo, a standard therapy is administered to the entire group of patients in parallel to the actual trial of the new drug.

Clinical phase II trials accounted for 11.5%[82] of the total global pharmaceutical R&D spend or US$5.7 billion in 2003.

2.1.5 Clinical Trials III

If phase II trials show evidence of a drug's effectiveness the study is expanded to collect sufficient evidence to generate a complete risk-benefit profile for short- and long-term use of a drug candidate. The focus during this stage resides on the effectiveness and potential adverse side-effects of a drug candidate under real-life conditions. The effectiveness of the new drug is also compared to other, established therapies for the targeted condition in cases where such therapies exist. Phase III trials are conducted with a larger number of volunteer patients than phase II trials to generate statistically valid conclusions. To have a group of patients that is representative for the entire population, a sample of a few hundred up to several thousand patients can be necessary depending on the targeted indication. The number of patients required and the composition of the sample regarding certain characteristics[83] is determined by the testing team in cooperation with statisticians.

Similar to phase II trials the group of patients is divided into two or more sub-groups with a similar distribution of individual patient's characteristics for blind testing. As a consequence of the large number of patients required, it is often necessary to involve multiple locations, sometimes even globally, into the study. This increases the need for standardized testing

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[82] Based on PhRMA (2005, p. 37) with an adjustment for uncategorized costs, which are distributed over the different R&D functions by total spend.

[83] Selection characteristics for the participants depend on the drug tested but can include age, gender, race, living environment, secondary illnesses and multiple other factors.

procedures and documentation to ensure comparable results. It also drives cost up and makes this phase of testing the most expensive one on an individual product base.

The findings from this stage and their documentation are very important because they not only build the base for the following official drug approval process but also for marketing claims and physician labeling. In the US, a new drug, which is passing clinical trials can potentially be made available to patients outside the actual research group if certain requirements are met. This is the case if a drug showed evidence of effective treatment of a serious or life threatening disease, for which there is no alternative therapy of similar effectiveness available. The drug is then labeled as a Treatment Investigational New Drugs (TIND) and can be made available to patients before regulatory approval[84]. Although these additional drug users do not become part of the actual testing group, it creates the opportunity to obtain additional data on the drug's safety and effectiveness.

The final clinical trial phase requires significant financial resources and accounts for 24.4%[85] of the entire global pharmaceutical R&D expenditures in 2003 being equivalent to about US$12.0 billion.

2.1.6 Drug Approval Process

After successful clinical trials, the sponsor can apply for official approval for the new drug. Regulatory approval is necessary for a company to be able to legally market, distribute, and sell a new drug. Different agencies are involved in drug approval and it depends on the intended use or the production process of a new drug as to which regulatory body has to be contacted for final drug approval. In the US, there are two centers of the FDA that are responsible for approving new drugs for human use. Approval of drugs with a biotechnological origin are filed with the Center for Biologics Evaluation and Research (CBER) while other, chemical based applications, are filed with the Center for Drug Evaluation and Research (CDER).

In Germany there are multiple institutions responsible for the approval of new drugs. Drugs from a biotechnological source are investigated by the European Agency for the Evaluation of Medicines (EMEA). The EMEA submits a recommendation for approval to the European Commission, which grants final approval valid for all EU countries. Non-biotechnological products are approved by either the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) or the Paul-Ehrlich Institute[86] (PEI).[87]

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[84] Compare to CDER (1998)

[85] Based on PhRMA (2005, p. 37) with an adjustment for uncategorized costs, which are distributed over the different R&D functions by total spend.

[86] While the PEI is responsible for all blood products, vaccines, serums and cell or gene therapies, the BfArM is responsible for all remaining drugs or products of non-biotechnological origin.

[87] Starting in 2005, a second, decentralized process was established that gives companies the opportunity to file applications with multiple European local authorities at the same time.

During the drug approval process the sponsor has to submit sufficient information and documentation to prove that a drug is efficient, harmless and safe to use. Such an application is backed up by chemical, pharmacological and toxicological analyses, reports from clinical trials and medical experts' evaluations. Final drug approval is the most important milestone in the drug development process because it determines if a company can enter the market and generate revenues to cover the development cost accumulated over several years. Figure 2.2 shows the mean approval times of regular NDAs and NDAs with biotechnological origin in the US between 1993 and 2003.

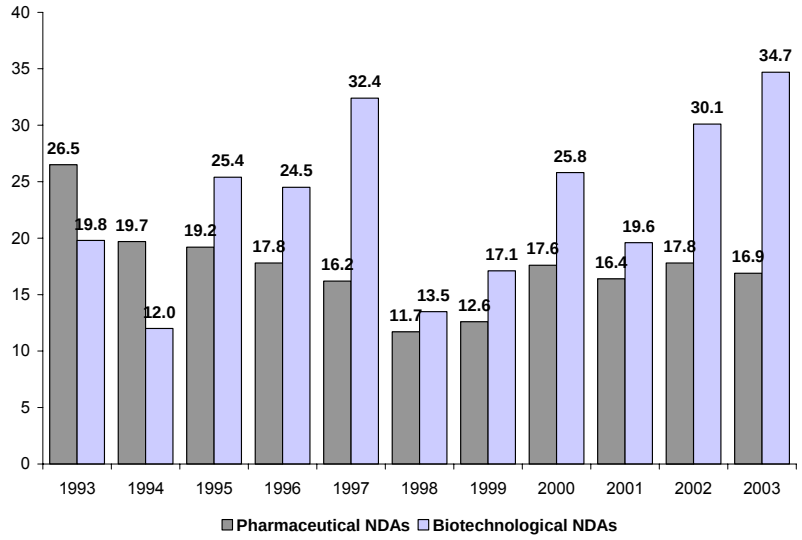

Figure 2.2: Mean NDA approval times US (1993-2003 in months)[88]

The financial burden of the approval process for the global pharmaceutical industry added up to about US$6.2 billion in 2003 or 12.5%[89] of the total R&D expenditures.

2.1.7 Post-Approval Research – Clinical Trials Phase IV

Clinical trials continue even after a new drug is introduced into the market. There are three main reasons for this additional post-approval research:

1. They can be required by the approving agency to resolve open issues.
2. They can be initiated by the sponsor to find additional application areas for the new drug unknown at the time of approval.
3. To study the long-term impact on a large number of patients, which is essential to identify complications only occurring with a very low statistical probability. This can include studying interactions with other drugs or a drug's impact on long-term statistics like disease induced death rates.

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[88] Source: PhRMA (2004)

[89] Based on PhRMA (2005, p. 37) with an adjustment for uncategorized costs, which are distributed over the different R&D functions by total spend.

Phase IV clinical trials can involve a larger number of patients than all other trial phases and the number of participants can grow to over 10,000 individuals. Independent from phase IV trials the sponsor has to closely monitor the application of a new drug. Since the sponsor is responsible for the safety of his product, phase IV trials are necessary to identify adverse side effects that have not been observed in previous clinical trials. Certain side effects occur in such a small percentage of drug users that thousands or even millions of users are necessary to identify them. A drug's impact on such a large number of patients can only be observed after it has been introduced into the market. To ensure market monitoring, drug sponsors are required to file Periodic Safety Update Reports (PSURs) with the regulatory authorities to document their market observations. It does happen that the distribution of a drug has to be discontinued for safety reasons even after it received regulatory approval.[90]

Phase IV trials conducted after regulatory approval required global expenditures of US$5.5 billion in 2003 and therefore account for 11.2%[91] of the total R&D spend.

2.1.8 Summary of Drug Development Process

The previous sections describe the efforts necessary until a drug is approved and can be brought to market. At this point it is important to note that the terms research and development are not used in a standardized way throughout scientific literature. Some sources use the term research only for the initial phase of the value chain and define the remaining steps from pre-clinical testing on as the development phase. Other groups either refer to the entire value chain as research and development (R&D) without distinguishing between the two terms or use one of the terms to summarize the entire value chain. For this study the terms R&D, drug research, drug development, as well as research and development are all used with reference to the activities of the entire value chain until final drug approval. In cases where a specific part of the value chain is referenced, it is explicitly described in the context of the document.

Although every drug development project has its own characteristics, it is necessary to derive some commonalities to better explain the functionality of the R&D option concept later in this study. To do so, the concept of stylized facts[92] is used, which was introduced by Kaldor (1961) and is summarized at Grupp (1997). Using this concept, a sum of figures on historical drug development times is used to derive a general tendency of the duration of the various stages of the pharmaceutical value chain.

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[90] The 2001 case where Bayer had to take its blockbuster Lipobay® from the market is probably the most widely known case although not the only one as recent examples of drug recalls like Redux®, Vioxx®, Bextra®, and Tysabri® show. On recent drug recalls see also Kutter et al. (2004), Handelsblatt (2004a), Handelsblatt (2004b), Handelsblatt (2005), Süddeutsche Zeitung (2005) or Lindner (2005).

[91] Based on PhRMA (2005, p. 37) with an adjustment for uncategorized costs, which are distributed over the different R&D functions by total spend.

[92] Romer (1989) describes the requirements these stylized facts have to fulfill.

The following approximations are derived for the duration of the different stages of the pharmaceutical value chain. For the initial phase of basic research, a duration of 3.0 years is used. For the stage of pre-clinical trials an additional duration of 3.0 years is expected. The three phases I, II, and III of clinical trials are expected to require one, two, and three years respectively in order to be completed. As the final step before a drug is approved and can be brought to market it has to go through the general drug approval process, which is expected to take on average around 2 years.

	Base Research	Pre-Clin. Trials	Clinical Phase I	Clinical Phase II	Clinical Phase III	Approval Process	Total
Kellogg et. al.	1.0	3.0	1.0	2.0	3.0	3.0	13.0
Bank Leu	~2.5	~2.0	~1.5	2.0	3.0	1.0	12.0
BCG	6.1	1.6	7.0				14.7
BPI	4.0	6.0				1.5	11.5
Bain & Company	n.a.	3.7	1.5	1.5	2.5	2.1	11.3+
Cassimon et. al.	2.0	4.0	1.0	2.0	3.0	2.0	14.0
DiMasi	3.8		8.6			1.8	14.2
VFA	2.0	~3.2	~1.7	~1.8	~1.9	~1.4	~12.0
PhRMA	6.5		1.5	2.0	3.5	1.5	15.0
Proxy used in this Study	**3.0**	**3.0**	**1.0**	**2.0**	**3.0**	**2.0**	**14.0**

Table 2.1: Historical average drug development times (in years)[93]

Clinical trials phase IV and other post-approval research activities are ongoing during the entire lifetime of an approved product and are therefore not shown in Table 2.1.

2.2 Cost Structure of an Average Drug Development Project

Developing new drugs has always been a costly procedure and expenses have increased significantly over the last two decades. While an early study from 1979 estimated the cost of developing a new drug including failed projects and excluding post-approval cost at US$138 million, this figure increased to over US$800 million in more recent studies. DiMasi et al. (2003) quantify the fully capitalized cost to develop a new drug at US$802 million including the cost of failure and excluding post-approval expenses. Including the cost of post-approval activities this number increases to US$897 million. Figure 2.3 gives an overview of the results of multiple studies that have been conducted on drug development cost over the last two decades.

[93] Source: Kellogg and Charnes (2000, p. 79), Bank Leu (2001, p. 20), BCG (2001, p. 12), DiMasi (2001a, p. 292), BPI (2003b), PAREXEL (2003, p. 168) and Cassimon et al. (2004, p. 46). The figures represent average drug development times. Development times for new drugs can vary significantly between different therapeutic areas.

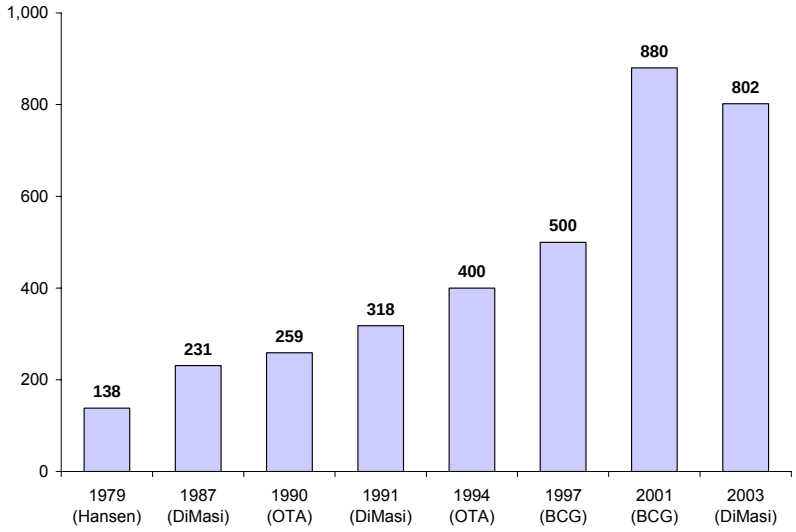

Figure 2.3: Drug development cost (ex. post approval;1979-2003 in US$ mil.)[94]

The major share of these high drug development costs can be attributed to the cost of projects that fail at some stage during the development process. Tiedemann (2002) estimates this share with 70% while PAREXEL (2003, p. 75) quantifies it at 75%.

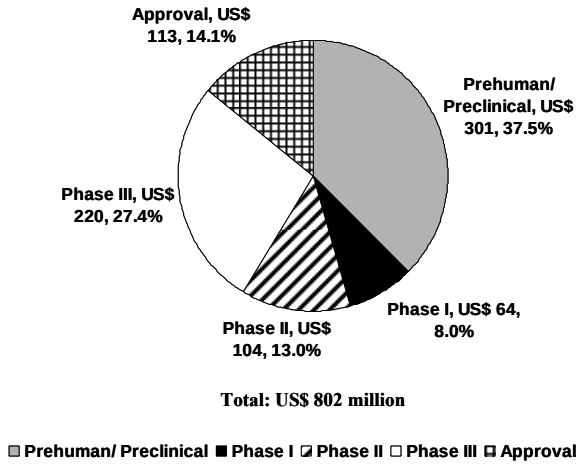

Figure 2.4: Breakdown of drug development cost by R&D phase[95]

Since the majority of projects fail early in the process a significant share of the total cost is related to the initial base development phase. Based on PhRMA (2005), 37.5% of total

[94] Total capitalized cost until drug approval (ex post-approval cost) including cost of failed projects. Studies might vary in scope and approach. Sources: Hansen (1979), DiMasi et al. (1991), Office of Technology Assessment (1993), BCG (2001), DiMasi et al. (2003) and PAREXEL (2003).

[95] Numbers shown are based on PhRMA (2005) and are adapted by excluding cost for phase IV clinical trials and allocating uncategorized cost proportionally over all remaining cost positions.

project R&D expenditures can be allocated to these base development activities[96]. Figure 2.4 shows a breakdown of the total research and development cost excluding post-approval activities by development stage. Although the major share of the total cost is related to base research activities, phase III clinical trials are more expensive on a per project base because only a minor share of the projects covered in the initial research activities is ever carried through to phase III due to the significant failure risk of drug development projects[97].

To understand the real financial burden for a company pursuing drug development projects it is essential to consider the time perspective of the cost incurred by these projects. Using the average R&D stage durations presented in Table 2.1 and assuming linear cost accumulation within the different development stages, it can be concluded that the total financial burden is close to a linear function of time. Figure 2.5 illustrates this relation between cumulated total drug development cost and standardized drug development times.

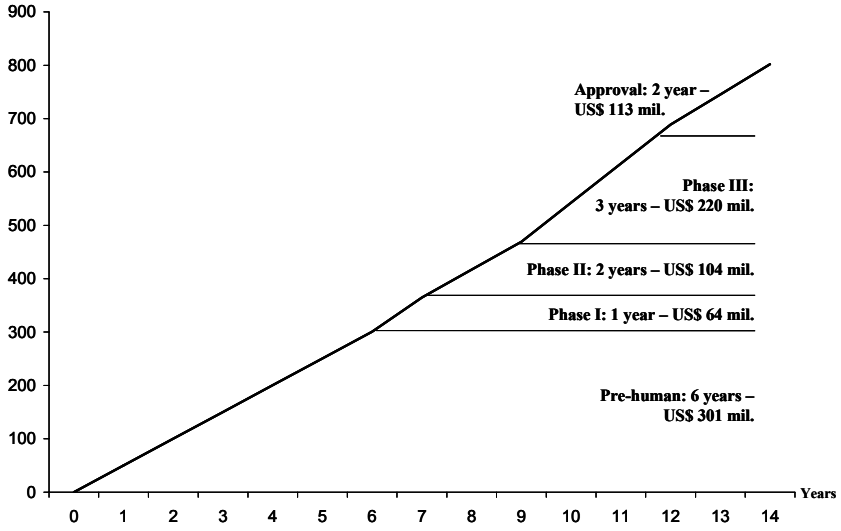

Figure 2.5: Cum. R&D cost of a standard drug development project (US$ mil.) [98]

It has to be considered that the numbers in Figure 2.5 are related to the entirety of all initiated development projects necessary to produce one approved drug and not to one single project. As an intuitive conclusion related to the failure risk of drug development projects it is known that only a minor share of the early cost is related to the successful project while almost all costs are related to this single project when the end of the observation period is approached.

It is important to note that drug development costs heavily depend on the type of research project, the indication targeted and the type of company pursuing these research activities and

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[96] PhRMA (2005, p. 37) report a share of 31.9% but against a total base including post-approval and uncategorized cost. After excluding costs for phase IV clinical trials and allocating uncategorized cost proportionally over the remaining cost positions a cost share of 37.5% can be derived.

[97] For details on the risk of technical failure of a drug development refer to Table 7.3.

[98] Own analysis based on Table 2.1 and Figure 2.4.

that the figures presented above only represent an industry-wide average. DiMasi et al. (1995) already showed in their study that smaller firms have shorter clinical development times and lower costs than larger corporations but also have a cost disadvantage when it comes to preclinical trials.

2.3 Financing Requirements of an Average Drug Development Project

To create an understanding of the financing requirements of a drug development project it is essential not only to evaluate the cost structure but also to consider the characteristics of the average revenue streams of an approved product. To create a net financial performance profile of an average new drug, findings of multiple scientific sources are combined. In addition to the average development times and cost investigated above, Grabowski and Vernon (2000b) provide insights on the profitability of an average project. In addition, Grabowski et al. (2002) give valuable details on the life-cycle sales of the average drug.

While Grabowski and Vernon (2000b, p. 100) find that it takes an average NCE about 16 years to break even, Grabowski et al. (2002) investigate how drug sales develop over time. They find that annual sales figures of a new drug approval increase constantly over a multiple year ramp-up period until they reach a plateau level. At this stage, sales volumes remain relatively stable until the point of patent expiration. Past the point of patent expiration, sales volumes drop due to generic competition. This life-cycle sales profile of a successful new drug introduction is shown in Figure 2.6.[99]

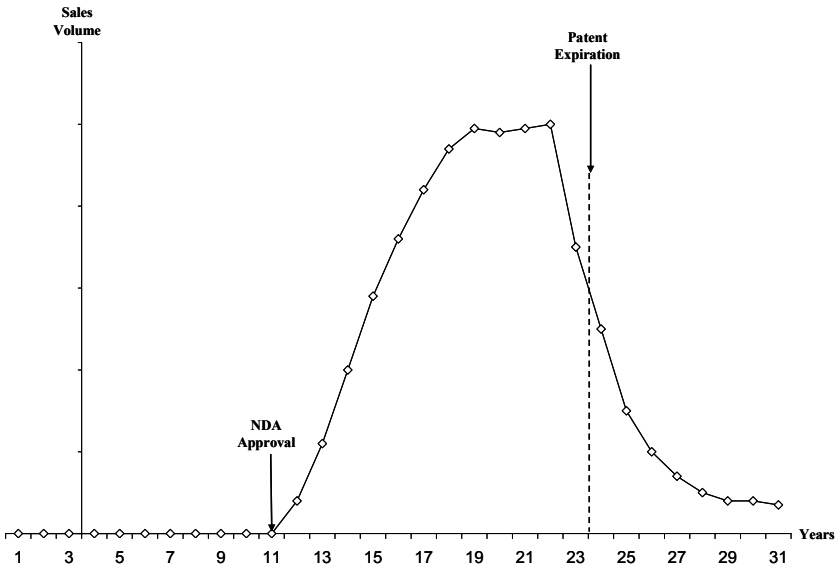

Figure 2.6: Illustrative annual sales profile of successful new drug introduction[100]

[99] Under the assumption that no alternative products directly competing with the product on sale are introduced in the market and are able to capture significant market share.

[100] Adapted from Grabowski et al. (2002, p. 17)

Based on the described cost structure of an average drug development project and the information on life-cycle sales, Figure 2.7 summarizes the characteristics of the cumulated net financial performance of an average development project over time including the cost of the related development projects, which have failed.

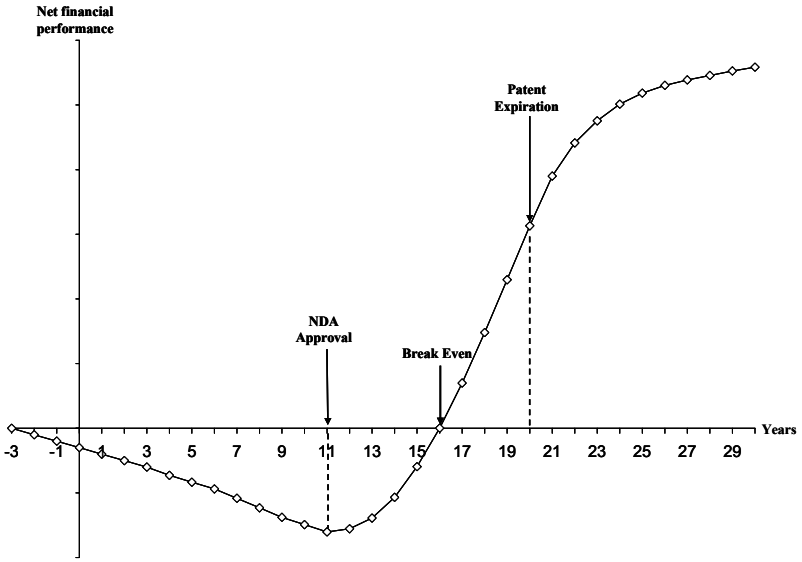

Figure 2.7: Cumulative financial profile of successful new drug introduction

For the purpose of this study, the cumulated net financial performance of an average drug development project shown in Figure 2.7 is adjusted for simplification purposes. Without limiting the findings of this study, two assumptions are made:

1. Annual sales volumes and contribution margins of an approved drug are constant over time between drug approval and patent expiration.
2. Generic competition entering the market after patent expiration eliminates any margin from product sales immediately upon patent expiration.[101]

This results in a linear accumulation of financial resources from the point of market entry until patent expiration. In addition, the maximum financial performance generated by a project occurs at the time of patent expiration and is not increased over time beyond this point. Figure 2.8 illustrates this adjusted simplified financial performance of a standard drug development project.

[101] This can either be attributed to an immediate total loss of market share or to severe price pressure eliminating any opportunity for profitable product sales.

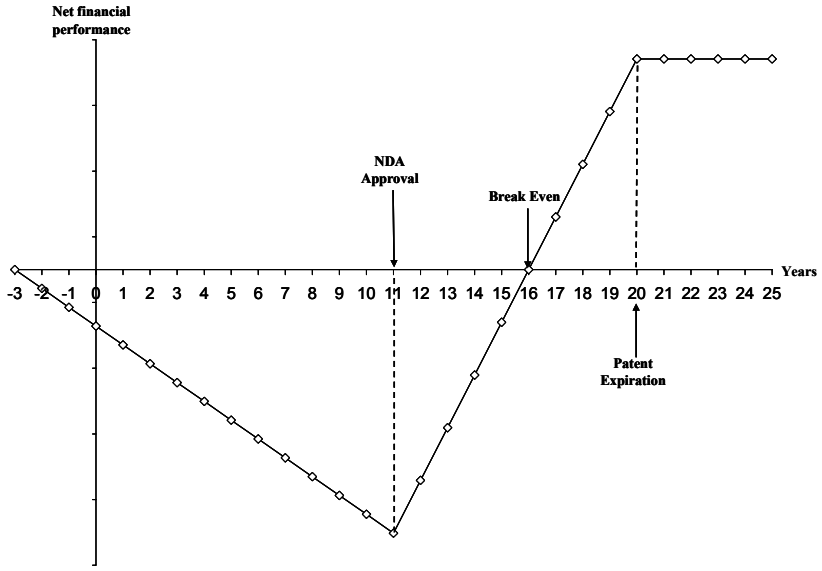

Figure 2.8: Simplified net financial profile of a new drug development project

This simplified net financial position of a single drug development project illustrates the financing need of a single product company. This need increases until it reaches its maximum at the point of regulatory approval. Beyond this point, cash flows from product sales reduce the net financing need until break even, after which surplus funds are generated that can be distributed as profits among investors or can be used to fund additional projects.

3 Financial and Real Option Concepts and Applications

This chapter introduces selected background information from the fields of financial and real option theory that are relevant for the upcoming discussions of the study. At the end of the chapter a conclusion is drawn as to which extent theoretical valuation concepts from financial option theory can be transferred to the valuation of real option problems in general and to the valuation of drug development projects in particular.

3.1 Financial Options

A financial option represents a contractual right to carry out a financial transaction under predefined conditions. The two most basic types of financial options give the owner either the right to buy (call option) or to sell (put option) a financial instrument, the so-called underlying asset. It is important to recall that an option represents a right, not an obligation for the owner to take a specified action. For the writer of an option on the other hand the option represents an obligation. This obligation arises from the fact that the writer has to fulfill the contractual agreement if the owner chooses to exercise the option right he owns.

Besides these two basic types of options there is a wide variety of more complex financial options offered in the market today. From these so-called exotic options[102] the concept of compound options is referred to at multiple points throughout this study. The theoretical functionality of puts, calls[103] and compound options[104] are assumed to be known to the reader and not further explained at this point.

3.1.1 Selected Key Concepts of Financial Option Theory

The purpose of this section is to give a short introduction to some of the main theoretical principles often used in financial option theory and that are also relevant for the remainder of this study.

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[102] The topic of exotic financial options is not directly relevant for the purpose of this study and is therefore not discussed at this point. Interested readers can find more background information on exotic options at Müller-Möhl (2002, p. 291), James (2003, p. 143) or Hull (2006, p. 529). For a comprehensive work on theory, pricing, and applicability of exotic options targeted to the practitioner see Nelken (1996).

[103] If necessary readers can refer to introductory textbooks on financial option theory for more details. Selected examples are Ryan and Henin (1977), Jarrow and Rudd (1983), Ravindran (1993), Hull (2006) or Jarrow et al. (1995).

[104] For early scientific work on compound options that received the most attention in option literature refer to Geske (1979) and Carr (1988).

Frictionless Market

One of the basic assumptions often used throughout financial option literature is the concept of frictionless markets. Such a market represents an ideal trading environment that imposes no costs or restraints on transactions.[105]

In particular this means that there are no transaction costs, no taxes, any amount of funds can be borrowed at the same rate as funds are loaned out, all traded securities are infinitely divisible, short selling is allowed[106] without penalties related to it and trading takes place on a continuous basis.

Duplication

The term duplication refers to the concept of rebuilding the payoff structure of one security or portfolio with a combination of other securities. If the initial and the duplicating portfolio have the same payoff structure, a rational investor is indifferent to which portfolio to own. Hull (2006, p. 328) presents the example of the following portfolio A, whose payoff structure can be duplicated with a second portfolio B. Duplication is also the key idea behind the so called Put-Call-Parity often referred to in scientific literature and extensively used in option pricing theory.[107]

Portfolio A: One European call option on a stock S with maturity T and exercise price X plus an amount of cash equivalent to X discounted back over the lifetime of the option.

Portfolio B: One European put option on a stock S with maturity T and exercise price X plus the underlying stock itself.

The following Table 3.1 shows that both portfolios have the same value at maturity T, irrespective if the stock price at T is above or below the exercise price X. If the stock price exceeds X at T the value of both portfolios is equal to the value of the stock S, while the value is X if the stock price at maturity is below or equal to X.

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[105] This concept represents a theoretical simplification because in reality there are no truly frictionless markets since trading is always associated with certain costs or restraints, such as transaction costs, taxes or constraints on short selling.

[106] I.e. that the underlying asset can be sold today at current prices but the final settlement including full payment and delivery occurs at a pre-determined future date.

[107] The Put-Call-Parity refers to the static price relationship, given a stock's price, between the prices of European put and call options of the same class (i.e. same underlying, strike price and expiration date). This relationship is derived over the described duplication approach. These option and stock positions must all have the same return or arbitrage opportunities would exist. Option pricing models that produces option prices that do not satisfy the Put-Call-Parity should be rejected because of the resulting arbitrage opportunities.

Portfolio A	**Case S>X**	**Case S≤X**
Value of Call Option at Maturity MAX(S-X; 0)	S-X	0
Value of $Xe^{-r(T-t)}$ Bond Investment at Option Maturity T	X	X
Resulting Value of Portfolio A at Maturity	**S**	**X**

Portfolio B	**Case S>X**	**Case S≤X**
Value of Put Option at Maturity MAX(X-S; 0)	0	X-S
Value of Stock Investment at Option Maturity	S	S
Resulting Value of Portfolio B at Maturity	**S**	**X**

Table 3.1: Example of a portfolio duplication strategy

Arbitrage

Arbitrage refers to the concept of attempting to take advantage of market imbalances and to generate profits by exploiting price differences of identical or comparable goods or financial instruments. These imbalances can exist between different markets or between the underlying asset and a related derivative security. The objective of arbitrage is to generate profits without bearing any investment risk.

A simple illustrative example of a potential arbitrage opportunity can be derived from the duplication strategy explained above. It is known that both portfolios have the same value at the time of option maturity T being either the value of the stock S or the value of the exercise price X depending on the stock price development. Now it is assumed that at any time t the price $P_A(t)$ of portfolio A exceeds the price $P_B(t)$ for portfolio B. With $P_A(t)>P_B(t)$ an arbitrage opportunity exists.

An investor can sell portfolio A at time t and at the same time buy portfolio B with the proceeds of the sale of A. The remaining proceeds $[P_A(t)-P_B(t)]$ are a profit for the investor because at time T both investments have the same value and their payoffs eliminate each other without creating a profit or loss for the investor. This strategy therefore represents a risk-free arbitrage opportunity.

Complete Market

In a complete market the payoff structure of any traded security can be duplicated through investments in other market traded securities. In such a complete market, all possible future states of an asset can be constructed with other existing assets.

With the size and transparency of today's markets it is an often used assumption that financial option markets represent complete markets[108]. Stiglitz (1989) argues that

[108] According to Ryan and Henin (1977, p. 3), institutionalized financial option trading did not start until 1973 with the opening of the Chicago Board Options Exchange (CBOE). Since that time, multiple exchange markets trading financial options have been established worldwide and trading volumes have increased significantly. Examples of some of the major option markets are the

complete[109] markets can only exist if there is absolutely no cost related to gathering information, which does not hold true in real business settings. This would make the assumption of complete markets an idealistic one, even in today's markets.

Risk Neutral Valuation

Risk-neutral valuation summarizes valuation concepts that do not include any risk preferences of individual investors[110]. Under the risk-neutral valuation concept an investor always prefers the investment with the highest expected return irrespective of the related risk. Although the real world is realistically not a risk-neutral environment and investors can generally be considered risk-averse[111], the concept is still applicable if certain conditions are met. This is the case if the risk involved in an investment is market traded. This means that risky assets can be combined into a portfolio in a way that the portfolio has a known value in the future irrespective of the way the market develops. The resulting portfolio then has the same value to a risk-neutral investor as to a risk-averse investor. An investment into this portfolio therefore does not justify a risk premium and generates the risk-free rate of return.

Since risk-neutral valuation methods do not consider the risk preferences of individual investors, their expectations do not affect the result of such a valuation approach. This is the reason why risk-neutral valuation can also be considered an objective valuation technique.[112]

Subjective Valuation

Subjective valuation approaches, as opposed to risk-neutral approaches, explicitly include risk preferences and investors' expectations into the valuation. To determine the potential future payoffs of an option investment, assumptions about the stochastic processes behind the value of the underlying asset are made. Once the future payoffs are estimated their present value is determined to estimate today's value of the investment. The applied discount rate in this approach is not the risk-free rate of interest but includes investors' subjective impression about the investment's risk level. The subjective discount rate is usually equal to the return, an investor could earn from another investment with comparable risk characteristics[113].

London International Financial Futures and Options Exchange (LIFFE), the Tokyo International Financial Futures Exchange (TIFFE), the French Futures & Options Exchange (MATIF), or the European Exchange (EUREX), which was formed by the merger of the German "Deutsche Terminbörse" (DTB) and the Swiss "Schweizer Terminbörse" (SOFFEX).

[109] And arbitrage free markets.

[110] For a more detailed introduction to the concept of risk-neutral valuation one can refer to Jarrow and Rudd (1983, p. 88) or Hull (2006, p. 244).

[111] Risk-averse investors prefer less risky assets over risky assets unless they are compensated by a risk premium to take on the additional risk.

[112] Widely known examples of risk-neutral valuation approaches in financial option literature include Black and Scholes (1973), Merton (1973), and Cox and Ross (1976).

[113] This return of a comparable alternative investment is called opportunity cost. An introduction to this topic can be found at Perridon and Steiner (2002, p. 87).

3.1.2 Applications of Financial Options and Fund Raising Effect

Generally there are three different uses of options, which are extensively discussed in basic option literature[114]. These three are speculation, hedging and arbitrage[115]. While these uses of options are widely known this section focuses on a specific secondary characteristic of certain speculation and hedging strategies that can be considered a fund raising effect.

This effect can occur in cases where market participants act as option writers in the market. It results from the fact that the option premium is generally due at the time a contract is initiated while closing takes place at the end of the option's lifetime for a European type option[116]. During the lifetime of the contract the option writer remains in possession of the option premium. These funds can be used to finance other investments at the discretion of the option writer. From the known payoff behavior of simple option contracts like calls and puts it is intuitively clear that this way of fund raising can either be free of charge or be extremely expensive for the option writer depending on the market development of the underlying asset during the option's lifetime and on the option use, under which the option was written. This is demonstrated by the following two examples of a speculation and a hedging strategy.

First assume an investor who is not present in the market and sells a European call option on a stock for speculation purposes[117]. This investor expects a constant[118] or decreasing stock price. In the event his expectations are correct, the option expires worthless and raising the premium at deal initiation is free of charge. In the event stock prices increase during the lifetime of the option, the owner of the option requests delivery of the stock at the agreed exercise price. Since the writer is not present in the stock market and has to acquire the stock, he incurs a loss in the amount of the difference between actual stock price and agreed exercise price. This can be considered his cost for raising funds equivalent to the amount of the option premium. It is needless to say that this cost can be indefinitely large since there is theoretically no upper limit on stock prices.

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[114] For more detailed information on this topic one can refer to basic option literature or one of the various more specific scientific articles on option use. A random example could be the work of Ravindran (1995) who discusses hedging strategies to reduce currency exposure.

[115] Some sources like Wilmott et al. (1993, p. 12) list only two types of option use and consider arbitrage a specific type of hedging.

[116] While the option owner might be able to sell his formalized right in the market the writer himself has no obligation until the maturity date of the European option.

[117] This is called a naked or uncovered position.

[118] Depending on the exercise price. If it is set below the actual stock price the investor expects decreasing prices because the option is already in the money at the initiation of the contract.

As a second example assume an investor who sells the same European call option while being present in the market with the corresponding stock investment[119]. In this case selling the option represents a hedging strategy[120] to reduce potential losses from the stock investment. In this case the fund raising is not free of charge even if the option expires worthless because the writer incurs a loss from his stock investment in this case. On the other hand the indefinitely large cost is reduced by a profit from the stock investment if stock prices increase. No matter which strategy a market participant pursues, the obtained premium from selling the European call is available from the time of option contract initiation until the contract is closed at the agreed expiration date.

3.1.3 Financial European Call Option Price Influencing Factors

Following the Nobel-price winning study of Black and Scholes (1973), prices of financial options on non-dividend paying stock depend on five different factors being the exercise price of the option, the market price of the underlying asset, the time to maturity, the risk involved expressed in volatility of the price of the underlying asset, and the risk-free interest rate to be earned on the financial market. At this point the behavior of the price of a European call option on a non-dividend paying stock with respect to parameter changes is qualitatively described. [121]

Exercise Price X

The decision about exercising or not exercising a European call option at maturity only depends on the exercise price and the stock price at expiration. With S_T being the stock price at expiration date T, the option right is worth $MAX[S_T\text{-}X; 0]$ to the owner of the call option at time T. Since $S_T\text{-}X_1 > S_T\text{-}X_2$ with $X_1 < X_2$ it can be concluded that increasing the exercise price decreases the final payoff of a call option. In return, the reduced payoff also reduces the value of the call option.

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[119] This is called a covered position.

[120] A different hedging strategy would be the acquisition of a put option. Assuming a perfect correlation, a sold call option only reduces the downside risk of the stock investment by its premium. At the same time buying a perfectly negatively correlated put option can limit losses at a certain level due to its different payoff structure. The strategies also differ if stock prices increase. While the stock in combination with the purchased put option still has an unlimited upside potential the other strategy does not. Since the sold call option can cause an unlimited loss if stock prices increase, it eliminates the profit of the stock investment setting a cap on the maximum profit that can be achieved by this strategy. Since the hedging strategy of purchasing a put option does not have the secondary fund raising effect important in the context of this study the other example of the sold call option was selected.

[121] The formal derivation of these relationships is presented in section 6.2. A more detailed discussion of the sensitivity of the Black-Scholes option pricing formula to its input parameters can be found at Jarrow and Rudd (1983, p. 119), Hull (2006, p. 341) or Chriss (1997, p. 162).

Price of Underlying Stock S

The impact of changes in the price S of a non-dividend paying stock on the price of a European call is straightforward. Since the call option represents a value of MAX[S_T-X; 0] to its owner at expiration T, this value increases as S_T increases because S_{T1}-X>S_{T2}-X with S_{T1}>S_{T2}. This increases in most cases the anticipated payoff of the European call and therefore an increasing stock price also increases the price of the call option with all other parameters remaining unchanged.

Time to Maturity (T-t)

Time to maturity describes the period between time t and the exercise date T of an option. There are two effects that have an impact on the price of the call option with respect to time to maturity. The first one is related to the lump sum an option owner has to pay at maturity to exercise his option right. Due to the time value of money the present value of this lump sum payment decreases as time to maturity increases and therefore the buyer is willing to pay a higher price at deal initiation. The second, more important effect is the fact that in the absence of dividends, the longer the time to maturity, the higher the probability of favorable price increases of the underlying stock and therefore the higher the price of the option.

Since both effects work in the same direction for the European call option it can be said that the longer the time to maturity the higher the price of this option on a non-dividend paying stock with all other parameters remaining unchanged.

Risk/Stock Price Volatility σ

Stock price volatility measures the uncertainty related to the future price development of a stock[122]. It can be shown that higher volatility increases the price of a European call option with all other parameters remaining unchanged. Larger uncertainty increases the possibility of positive as well as for negative market developments and increases the value of the option. This is the case because the owner of a call option can benefit to a full extent from positive movements but only has to participate to a limited extent in negative movements.

Risk-free Interest Rate r

The last factor to be described is the risk-free interest rate r, whose impact can simply be described using the time value of money concept. The owner of a call option knows the contractually required future exercise payment X today and therefore is going to discount it back over the lifetime of the option to put it into relation to the known current stock price. Knowing this, one can argue for a call option that the higher the interest rate, the larger the impact of discounting X back over time and therefore the more promising the call option and the higher its price. This is the case because todays value of X is effected by changes in discount rate but the known and observable stock price today is not.

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[122] While Black and Scholes (1973) assume constant stock price volatility over time, Nagel (2001) investigates potential option valuation approaches with stochastic volatility.

Some sources in option pricing theory explain the impact of changes in the risk-free interest rate in an alternative way, which is not as intuitively clear as the one above but generates the same result. On one hand, increasing interest rates tend to increase the expected growth of stock prices but on the other hand, it also decreases the value future cash flows have to the option owner. The first effect increases the value of the call option while the second one reduces the price a buyer is willing to pay to acquire a call option. Hull (2006, p. 362) and Stoll and Whaley (1993, p. 229) show that the first effect always outweighs the second and therefore the price of a European call option increases as interest rates increase with all other parameters remaining unchanged.

Table 3.2 summarizes how changes in the five option price influencing variables affect the price of a European call option in the absence of dividend payments.

Influencing Factor	**Increasing factor value causes Call price to …**
Exercise Price	**▼ - decrease**
Price of Underlying	**▲ - increase**
Time to Maturity	**▲ - increase**
Risk / Volatility	**▲ - increase**
Risk-free Interest Rate	**▲ - increase**

Table 3.2: Price influencing factors of European call option[123]

3.2 Real Options (RO)

Just like financial options, real options represent a right to take a specific action in the future. As opposed to financial options, the underlying of a real option is not an abstract financial instrument but a real business situation.[124] The theory of real options stretches back to the early 1950s when Dean (1951) developed the first ideas to quantify the value of managerial decision alternatives[125].

3.2.1 Academic Types of Real Options

There are six types of decisions that make up managerial flexibility and that are generally considered the basic types of real options in academic literature.[126] These types are the

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[123] In the absence of dividend payments. Table based on Jarrow and Rudd (1983, p. 16)

[124] As Amram and Kulatilaka (1999, p. 6) state, "in a narrow sense, the real options approach is the extension of financial option theory to options on real (nonfinancial) assets. While financial options are detailed in the contract, real options embedded in strategic investments must be identified and specified. Moving from financial options to real options requires a way of thinking, one that brings the discipline of the financial markets to internal strategic investment decisions".

[125] For a short summary on the history of real options refer to Hilzenbecher (2000, p. 218) and for a more detailed introduction to Kulatilaka and Marcus (1988) or Trigeorgis (1995).

[126] There is a consensus in most publications about the meaning of the term real option and its connection to managerial flexibility. While most authors agree on the description, their individual classifications do vary slightly. Examples of early classifications and some good summaries on real

option to grow, the option to wait, the option to change scope, the exit option, the option to switch, and the option to learn.

Option to grow

Some projects or investments in real assets open up the opportunity to invest in new projects or subsequent project stages. This opportunity is called the option to grow throughout real option literature.[127] Growth options represent a value to their owner and are sometimes used as an explanation as to why some companies are valued higher on the stock market than someone evaluating their fundamental indicators would expect.[128]

A growth option can be the development of a new product or any other activity that grants access to and establishes a company in new markets or market segments. Such a project might even be pursued if results from traditional valuation techniques generate negative results for the project if evaluated individually.[129] Growth options are not limited to products or other physical assets. Intangible assets like internal knowledge, patents, reputation or a strong management team can also be considered options for future growth.

Industries that are characterized as dynamic, volatile and unpredictable are generally associated with growth options. The telecommunication, high tech electronics[130], pharmaceutical and biotechnology[131] industry are some frequently quoted examples[132]. In a drug development context an option to grow can be identified in a potential expansion of a drug into new fields of therapeutic use or in the development of alternative application methods to expand the initial target market.

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option classifications can be found at Kilka (1995, p. 3), Trigeorgis (1995, p. 3), Trigeorgis (1996, p. 9), Amram and Kulatilaka (1999, p. 10) or Copeland and Antikarov (2001, p. 5).

[127] Basic work on growth options has been done by Myers (1977), Kester (1984), Pindyck (1988), Trigeorgis (1988), Kester (1993) and Brealey and Myers (2000).

[128] Boer (2002) for example describes the case of the biotech company Genentech that became a US$ billion company without substantial cash flows. Kellogg and Charnes (2000) use a similar growth option based approach to value a biotechnology company. Garner et al. (2002) explain the market capitalization of a sample of Biotech and Internet companies with negative earnings with corporate growth options. Schwartz and Moon (2000) explain extraordinary market valuations of internet companies with a valuation model based on future growth options, which they further refine in their later study Schwartz and Moon (2001). Other case examples can be found at Copeland and Antikarov (2001, p. 301) for a high-tech company and at Bühler and Uhrig-Homburg (2003, p. 129) for an IT company and a brewing company.

[129] Before the development of real option theory, decisions to pursue projects with unfavorable outlook resulting from standard NPV analysis but finally resulting in big corporate success stories were often described as entrepreneurial business acumen or managerial intuition.

[130] Boer (2002, p. 124) describes the case where developing a microcomputer becomes a favorable project because of the option to invest in a second generation of microcomputers in the future.

[131] Ottoo (1998) builds a model to evaluate a research project in the biotech industry as a corporate growth option.

[132] See Dixit and Pindyck (1995, p. 105) or Freihube (2001, p. 27).

Option to wait

When investment decisions are made in a business environment they are generally not bound to specific investment dates unless dictated by existing contracts or bid processes. In most cases management has the flexibility to decide when a certain investment is made. While delaying an investment potentially results in later market entry and lost market shares, waiting can also have a positive value for a company.[133] Two main reasons are responsible for the positive value of the option to wait. Within the period a project is delayed, new information can arrive about risk and reward of the project that allow better decision making. In addition to the arrival of new information, market conditions themselves might change while the project is delayed allowing the investor to adjust his investment strategy accordingly. In cases of positive market changes the financial outlook of the investment can turn more positive justifying an immediate investment or it can turn unfavorable preventing management from investing in an unfavorable project altogether. In certain industries the option to wait can represent a highly valuable asset to the owner.

Often quoted examples are companies that are involved in the exploration of natural resources, the development of land, commercial real estate or the agricultural industry.[134] In a drug development context the option to wait can be considered less important especially after a company has already applied for patent protection status of a new drug. Waiting in this context reduces the effective patent protection period of a new product, which is essential for a company to break even with a new product.[135]

Option to change scope (expand/reduce)

Most investment projects can be altered in terms of scope even after an initial investment has been made.[136] This opportunity to adapt to changing market conditions is another valuable type of real option. If market conditions turn more favorable, management can decide to

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[133] Early efforts to quantify the value of an option to wait have been made by Titman (1985) who investigated how long land should be kept vacant and when it should be developed. Other studies quantifying waiting options are the one by Paddock et al. (1988) and Bjerksund (1991) who both examine when a firm should explore and develop a petroleum lease. Brennan and Schwartz (1985) also investigate the timing of natural resource investments. More general work on waiting options has been done by McDonald and Siegel (1986) and by Ingersoll and Ross (1992). The latter conducted simulations indicating that it might be beneficial not to initiate investment projects until the expected benefits are twice as high as the required investment. Ingersoll and Ross (1992) concluded in their study that even very simple investment projects have waiting options that need to be considered in the decision making process.

[134] Waiting options are not limited to these industries. Schwartz and Zozaya-Gorostiza (2003) show that waiting options are also relevant when investing in information technology under uncertainty.

[135] See also Figure 1.5 and Figure 5.2 in this context.

[136] A study explicitly considering this type of option is the one by McDonald and Siegel (1985) who consider the option to temporarily shut down production. Pindyck (1988) investigates the value of the option not to use an installed production unit and Abel et al. (1996) show how opportunities to expand or contract future activities can be considered options that add value to a project.

expand production to increase sales and maximize profits. During times when markets turn unfavorable, the opportunity to reduce production can be a valuable alternative to sustain profitability. An extreme case of reducing production scope is the option to temporarily shut down production.[137]

An example[138] of an option to change the scope of a project is the installation of production lines whose capacity can be adapted depending on existing demand. Such a flexible line enables a company to satisfy peaks in demand if the market is strong and can avoid overproduction if the market indicates flagging demand. The option to change scope is relevant for all manufacturing industries but especially valuable for those with cyclical production like consumer goods or fashion apparel.

In drug development the option to change scope is of little relevance but once a product is approved and introduced into the market, the ability to change the scope of production is as relevant for the drug producer as it is for other manufacturing companies.

Option to exit

Only a small fraction of real investment projects have to be carried all the way through to the end of their scheduled lifetime. Most investment projects leave management the opportunity to discontinue a project and sell the related assets. This kind of exit option serves as an insurance[139] if things develop in the wrong direction and a project does not meet defined project milestones and objectives.[140] As opposed to the option to temporarily shut down production, the exit option is an ultimate decision because the assets are liquidated and not available for further production once the exit option has been exercised.

Capital intensive industries are extremely interested in owning exit options. Examples are airlines, railroad companies or companies introducing products to uncertain markets. In drug development the option to abandon ongoing projects for whatever reason is essential to remain profitable and concentrate resources on the most promising projects. Since the drug

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[137] Kilka (1995, p. 35), Freihube (2001, p. 24) and Lucke (2001, p. 17) consider the option to temporarily shut down production as a separate type of real option. This is contrary to the classification used in Trigeorgis (1995, p. 3), Meise (1998, p. 107) or Brach (2003, p. 84) treating the option to shut down as an extreme case of the option to reduce scope.

[138] Another example often cited in this context is the ability of the mining or oil drilling industry to increase or decrease their production speed within certain limits depending on current market prices. A similar behavior can be observed in the energy market depending on current energy prices as discussed at Leslie and Michaels (1997), who investigated real options in the energy sector.

[139] Brach (2003, p. 80) describes this type of real option as “a hedge against an economic downturn”.

[140] Studies on abandonment options like the one conducted by Myers and Majd (1990) or Berger et al. (1996) support the view that this kind of option adds value for the investor. Another study investigating this topic is the one by Dixit (1989) who builds a model that derives trigger prices for entry and exit decisions in an uncertain market environment.

development process does not require large physical assets compared to the physical assets required for large-scale production, the exit option can be exercised relatively easily.[141]

Option to switch

Switching options can be described as the flexibility to alternate between different modes of operation. Switching can occur between production inputs[142], between production outputs[143], between different production technologies or processes, or between manufacturing locations. The multitude of switching opportunities shows the complexity of this option type. To reduce complexity, most studies apply a more focused point of view and limit their scope to changes in input parameters[144] to produce the same output or to changes in output[145] produced with the same input.[146]

Switching options are valuable but generally not free of charge and result in switching costs. These costs can be related to idle time in production, installation of alternative technologies, cleaning cost for equipment, training of employees or other costs caused by the decision to switch from one mode of operation to another.

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[141] For industries that require valuable physical assets the existence of a liquid second hand market increases the practical applicability of an exit option. This is the case for car rental companies whose fleets can be sold in the used car market in case of market exit. This market has a broader customer base than the used aircraft market for example, where it is more difficult to exercise the exit option.

[142] Depending on the infrastructure in place, an electrical power company might have the option to use coal, oil, gas or other energy sources to generate the same output, which is electrical power. Another example for an industry with good input switching options is the farming industry when raising livestock. Here farmers have the option to switch between various types of feed for their animals to generate the desired growth.

[143] Switching options in output parameters are most relevant for industries that have to deal with frequent changes in demand. The more universal the production equipment, the greater the option to switch with respect to output. Car manufacturers might have the option to manufacture product B instead of product A on an existing line. Agricultural corporations can also alter the output mix of their "production sites" but only with a relatively long lead time depending on harvesting cycles. Another good example for switching options would be a company using injection molding to manufacture plastic parts. Within a short period of time they can switch from producing parts for the car industry to producing parts for toys simply by exchanging the molding tool used.

[144] Early work on switching options in financial arrangements has been done by Margrabe (1978). Based on this study, Kensinger (1987) developed a model to value the flexibility related to switching between two different input parameters. Kulatilaka (1993) also investigated switching flexibility with respect to input parameters on the example of a dual fuel burner with the option to switch between different input fuels in comparison to a single fuel burner.

[145] Output flexibility was investigated by Kulatilaka (1988) who investigated the value of Flexible Manufacturing Systems (FMS) and by He and Pindyck (1992).

[146] Two other interesting applications of switching options can be found at Baldwin and Ruback (1986) and Botteron et al. (2003). Baldwin and Ruback (1986) studied switching options for investments in fixed assets and found that short lived assets are more valuable to a company than long lived assets. Botteron et al. (2003) modeled the flexibility of multinational companies to switch production and sales between different countries in a real option framework.

Option to stage/learn

Most long-term investment projects do not have to be pursued as one single project but can be separated into stages. During each stage information about the outcome and the environment of the project are collected creating the opportunity to adjust the following stages to the new situation. This opportunity to continuously learn allows for better decision making during the course of a project. At the end of a project stage, management can decide based on its acquired knowledge whether the project should be carried on, altered in terms of scope or timing or if it should be abandoned.[147]

Four industries[148] are often mentioned when staged investments are discussed, namely the exploration of natural resources[149], the pharmaceutical industry, aircraft manufacturers[150] and the motion picture[151] industry. The idea of a staged process with an option to learn is well suited for drug development projects because of their distinct project phases, which are explained in chapter 2.1. This way of thinking is widely accepted and used throughout scientific literature. Brach (2003, p. 97) uses a six stage process model to introduce the idea of a staged investment in drug development and so do Cassimon et al. (2004) to value a pharmaceutical NDA.

The explanations above already show that a drug development project does not represent a single type of real option but a combination of multiple types just as most other real life business transactions can also be considered a combination of multiple academic real options.

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[147] Early discussions on staged investment decisions and the related option value can be found at Majd and Pindyck (1987) who derive optimal investment rules in sequential projects and Carr (1988) who estimates the value of sequential exchange options in multiple settings. Other studies have been conducted by Teisberg (1994) who evaluates an investment in a utility power plant, which is described as a process with multiple stages to be completed sequentially and by Weitzman et al. (1981) describing how large-scale government subsidized research can be evaluated as staged investments. More recent work on sequential real options has been conducted by Cassimon et al. (2002) trying to evaluate the value of research conducting pharmaceutical companies with a compound option model based on the work of Geske (1979) for financial compound options.

[148] These are four examples while Willner (1995) describes all start-up ventures as multi-step compound options. Boer (1999, p. 21) describes every industrial R&D project leading to new technologies as a multi-stage project consisting of six different stages. Kotler and Bliemel (1995, p. 505) support the view that industrial research projects are structured along different project stages.

[149] Stensland and Tjostheim (1991) and Mun (2002, p. 36) describe a typical oil or gas exploration project as a four stage investment consisting of an exploration, a development, a production, and a decommissioning phase and their view is supported by BP's CEO John Browne at Prokesch (1997). Another good example for a learning option when natural resources are explored is the case study from the mining industry to be found at Copeland and Keenan (1998, p. 134).

[150] Majd and Pindyck (1987) describe the process of developing a new aircraft as a four step process consisting of engineering, prototype production, testing and final tooling, which can in total take eight to ten years to complete.

[151] For the motion picture industry, Boer (2002, p. 253) characterizes a project with a four step process consisting of script development, movie production, box office release and advertising/promotion.

This makes it difficult to precisely classify real business transactions in this academic framework.[152] For that reason an alternative classification scheme is presented below.

3.2.2 Real Options in a Business Oriented Framework

In contrast to the academic real option framework above, Hilzenbecher (2000, p. 224) describes a more business oriented view that enables better differentiation between different types of business activities representing real options from each other and from financial options. This approach divides real options into four different categories and allows a better classification of a drug development project and is therefore more appropriate for the purpose of this study.

Table 3.3 summarizes the comparison of the main characteristics of a financial option with the characteristics of these real options classified as type 0, I, II, and III.

Characteristics	Financial and Type 0 Real Options	Real Options		
		RO Type I	RO Type II	RO Type III
Investment Method	One time: • buy option	One time: • buy products	Ongoing: • Production Infrastructure • Variable Production Cost	Ongoing: • Research Infrastructure • Research & Development • Production Infrastructure • Variable Production Cost
Compoundness	Depending on option type	sometimes	always	always
Trading	Institutionalized - continuous	Not institutionalized - discontinuous		
Pricing	market prices	individual pricing based on negotiation results		
Maturity	fixed date	variable	variable	variable
Exclusivity	Yes	no	no	no
Contracts	standardized	not standardized		
Valuation Method	risk-neutral valuation methods	(incorrect) risk-neutral valuation, subjective valuation methods or simulations		
	Flexibility			**Complexity**

Table 3.3: Direct comparison of financial and various types of real options[153,154]

[152] For more information on the limitations of real option thinking see Copeland and Antikarov (2001), Adner and Levinthal (2004a), Adner and Levinthal (2004b) or McGrath et al. (2004).

[153] Because type 0 real options have characteristics very similar to the ones of financial options they are represented by one column in the table. To improve readability, statements referring to financial options in this chapter also apply to real options type 0 without explicitly being mentioned.

[154] Adapted from Hilzenbecher (2000, p. 229)

RO Type 0: Options on Market Traded Real Assets

Real options type 0 represent standardized option contracts on real assets that are acquired through one time investments. As for financial options, exercise price and maturity date are generally fixed and known at the time of entering the agreement. The option itself and the underlying real asset are traded on institutionalized, regulated markets. While this is the case for stocks and stock options in the financial market, it is also the case for options on assets such as gold, oil, other raw materials and some agricultural products traded on commodity markets.[155]

As opposed to the market traded type 0 real options there are other business transactions that are not traded on institutionalized markets. These options are more complex and include a higher degree of uncertainty. In the introduced classification scheme these more complex business transactions are divided into three real option types.

RO Type I: Purchased Product Trading

Real options type I represent the business transaction of selling purchased products.[156] In this type of transaction the real option owner bears the risk of changes in product prices and demand. The investment risk on owner's side is limited to the financial resources invested in products currently in stock. For this type of real option flexibility is relatively high and reaction times to environmental changes are short.

RO Type II: Self-manufactured Product Trading

Type II real options represent type I real options expanded in scope by the manufacturing process of the products to be sold.[157] While type I included acquiring, storing and selling products, type II real options include the acquisition of raw materials or parts, the production process of goods, product storage and the final sales activities. The financial risk is larger and the complexity increases because additional funds have to be invested to set up and run the infrastructure required for production. In addition to the production infrastructure, type II real options also contain the risk associated with the production process itself while this risk resides with the product supplier for type I real options. Managerial flexibility is reduced and reaction times increase in this type of business transaction.

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[155] It is important to note that the real options type 0 only include options on trading oil or raw materials but not on their exploration or production. Exploration projects represent a different type of real option as described later in this chapter.

[156] Examples of industries holding these types of real options are department stores, car dealerships as opposed to car manufacturers, supermarkets and the entire retail industry.

[157] Examples of industries with this type of real options are contract manufacturers in various industries and generally all industries manufacturing basic or standardized products requiring none or only minor research activities.

RO Type III: Self-developed/Self-manufactured Product Trading

Type III represents the highest type of real option in this framework and is a further extension of the type II RO. In addition to type II, type III also incorporates research and development activities to bring a new product to market and keep it up to the latest technological standards and trends.[158] Real options of type III contain all risk factors of type II plus the risk involved in setting up the R&D infrastructure and running these processes. This risk mainly contains a technical component[159] and the risk related to uncertain development timing[160] and cost. The additional risk makes the investment cost and timing for type III real options more uncertain than for type II. With R&D activities generally being a time-consuming process requiring significant financial resources, businesses holding type III real options can only react slower to environmental influences than the ones operating with type I and II real options.

3.2.3 Real Option Characteristics of a Drug Development Project

In the academic real option framework, drug development projects represent a combination of several types of real options. The growth aspect of a drug development project is obvious because all activities are conducted to create a new drug that is supposed to result in product sales. Additional growth options exist in the form of three different types of expansion options. The first one being the option to expand a project in terms of potential applications a product can be used for in the future. While a pharmaceutical compound is generally developed in one specific form, management has the option to invest funds to develop additional application forms to increase its market potential.[161] The second expansion option is represented by the opportunity to cover new therapeutic areas. In this case management can invest in additional research to test the effectiveness of a new drug in other therapeutic areas. These expansion options can be considered call options on future cash flows with the cost for the required additional research being their exercise price.

The third form of expansion option exists in the form of potential patent extensions. While patents are generally granted for a period of twenty years there is an opportunity to extend this period under certain circumstances.[162] In this case a company has a call option on additional years of patent protected cash flows with the exercise price being the filing cost for the required application.

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[158] Examples of industries holding type III real options include aircraft manufacturers, computer chip producers, car manufacturers or pharmaceutical companies.

[159] The risk that research activities do not lead to a new product or technology that can be sold in the marketplace.

[160] Research and development can be a very time-consuming process. E.g. it take eight to ten years to bring a new aircraft to market and up to 14 years to develop a new drug.

[161] An example would be the development of an injectable drug that already exists in oral form.

[162] In the US as well as in Germany this opportunity exists in form of so-called Supplementary Protection Certificates (SPCs). More details on potential patent protection extensions and the effect of the Waxman-Hatch Act in the US can be found at Grabowski and Vernon (2000b).

In addition to the growth option, the exit option is another type of flexibility in the drug development process. It represents the freedom to stop a project at any time with no obligation to finalize it later. As opposed to the growth option, this type can be considered a put option with an exercise price equivalent to potential liquidation cost. The value of the underlying asset in this case is equivalent to a potential salvage value of the project.[163] The exit option is closely related to the learning option because the research conducting company constantly generates new information on the prospects of a project during its research activities therefore reducing the related uncertainty. Based on the additional information generated, the company is able to make the decision to exercise its exit option or to continue the development process.

With all of these options being linked to each other the drug development project has to be considered an interdependent real option in the academic sense. There are studies on interdependent real option like the ones by Kemna (1993), Trigeorgis (1993), Kulatilaka (1995), Rose (1998, p. 711) or Lucke (2001) but no such study is known to the author directly investigating a drug development project. In the context of drug development authors tend to simplify complexity by neglecting one or more types of options. Copeland and Keenan (1998, p. 140) for example avoid the option to expand and divide the future market potential in great and mediocre products without explicitly considering the opportunity to develop new drug application. Brach (2003, p. 98) follows a similar approach by splitting future potential into a best and into a worst case scenario while Shockley et al. (2003, p. 46) keep the future market potential constant without considering different scenarios at all. In later chapters of this study the option to expand is modeled with potential positive jumps in the market potential simulation for a new drug.

Within the more business oriented real option framework a drug development project can be assigned to the real option type III category. With the classification in this framework being unambiguous, it is used to compare real options to financial options with the objective of deriving indications about the transferability of existing option valuation methods.

[163] In case of technical failure of a project this salvage value can be zero.

3.3 Comparison Real vs. Financial Options

Comparing the key characteristics of real and financial options[164] is a prerequisite of chapter 6 of this study where the applicability of existing valuation methods on an option sold on a drug development project is investigated.[165] For this purpose the business oriented real options view is used. This approach allows an unambiguous classification of business activities into non-interacting real option classes.

Comparing a type 0 real option with a basic financial stock option reveals similar characteristics. Besides the fact that both options are formalized in standardized contracts, are initiated through a one time investment and that exercise price and maturity date are known at the initiation date, another key similarity is related to the way these real options are traded. In this case both option types are traded on institutionalized markets as are the related underlying assets. With the option contract and the underlying asset being market traded, tracking portfolios[166] can be created to duplicate the payoff of these types of option contracts. Under the no-arbitrage assumption of regulated markets, the same risk-neutral valuation methods can therefore be applied to type 0 real options as used to price financial options.

Because they are market traded, type 0 real options do not need to be held until maturity but can be sold at any time. This allows the owner to react quickly to environmental changes and remain flexible in his decision making. With real options of type 0 having financial option like characteristics they are combined into one single category in the following discussion. The remaining statements in this section on financial options therefore also apply to real options type 0 and vice versa.

From the RO type I over type II to the highest type III, certain characteristics develop in a straightforward way. As the type of a real option increases so does the uncertainty related to the size of the required initial investment and the one related to the time period required to create the real option. This is the case because every step to the next higher category involves a new process adding uncertainty. At type II, the production process is included with unknown set-up cost and timing. For type III, the even higher uncertainty is related to the additional research and development activities not included in type II.

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[164] The term financial option in this context refers to simple financial option contracts such as a European call option and not to all financial options. This limitation is necessary because financial options can be constructed in a wide variety of ways with very different characteristics and therefore it is not possible to draw conclusions relevant for all financial options.

[165] There are multiple studies like Kilka (1995, p. 49), Meise (1998, p. 47) or Freihube (2001, p. 122) that include a comparison of real options with financial options. A simple comparison of "the" real option with financial options represents an oversimplification of the issue failing to capture the individual characteristics of the different real option types. How an economic real option compares to a financial call option also depends on the classification type in the introduced framework and therefore the classification of type 0 to type III real options is used for the purpose of comparison.

[166] On constructing tracking portfolios on commodities refer to Dixit and Pindyck (1994, p.178).

The investment method itself also differs between the types of options considered. For financial and for type I real options, a one time investment is necessary to acquire the option contract or the goods to be sold. While financial options do not include any investment timing risk because the time of the one time investment is known, there is a small risk remaining in type I real options because of the lack of institutionalized markets for certain products. The small uncertainty is related to finding the appropriate business partner and closing the necessary contracts. For type II and type III real options the option right needs to be created and cannot be bought at one point in time. The payouts to create these option rights are stretched over an unknown time period. Since type III real options include the largest scope of investment activities, the largest risk in investment timing is also associated with it. Type II real options exclude the entire research process and therefore the investment timing is generally shorter and less uncertain compared to type III. As shown, significantly less timing risk is involved in type I real options and financial options.

Another point distinguishing financial options from real options is the way options are closed. While financial options have a contractually fixed maturity date and can be sold in the market, this is not the case for real options type I to III. It is intuitively clear that generally the time of product sales[167] cannot exactly be predicted in advance and depends on supply and demand for the goods to be sold. For type II and III there is also the uncertainty that the real option holding company cannot exactly predict at what time the production or the R&D process of a product will be completed and the product can be sold.[168] Considering these points shows that time to maturity is not known for real options type I, II, and III with the uncertainty increasing for every classification step. This is an important characteristic of most real options while financial options generally have contractually fixed maturity dates.

Just as uncertainty in the maturity of real options increases with each category so does the compoundness. Compoundness describes the degree, to which an option can be divided into subsequent project or investment stages. Simple financial options do not include multiple stages therefore no compoundness needs to be considered. Whether compound characteristics can be observed for type I real options depends on the characteristics of the traded products and can exist in certain cases. Type II real options are always related to compoundness and can at least be divided into a production and a sales stage. This compoundness is larger for type III caused by the additional research and development stage.

The issue of exclusivity is another characteristic to be considered in this context. Financial options grant the owner an exclusive right to take a specific action. This is different for RO

[167] Except contracted production with predetermined delivery dates.

[168] With modern production scheduling systems this uncertainty can be reduced to a minmum for the production process but can still be considered more uncertain than the maturity date in a virtual contract not involving a physical asset.

type I, II and III, which are shared options[169]. Consider a retailer who has an option to generate cash flows by selling purchased products. This retailer has the exclusive right to sell his own products in stock but competing retailers have the same option to sell their own products to the same customer base[170]. In a second example consider a pharmaceutical company attempting to develop and sell a patent protected drug A to treat the symptoms of an HIV infection. While the company has the exclusive right to sell drug A to the market, other pharmaceutical companies share the option to generate revenues with the same customer base by selling a competing drug B to also treat the symptoms of a HIV infection[171]. Exclusive options represent a higher value to the owner because of the absence of competition.

Apart from the points described above, the main difference between financial and real options I, II and III is the fact that there is only an institutionalized market for financial options where the option and the related underlying asset are traded. An existing market ensures continuous trading at market prices with publicly available pricing information. This type of trading does not take place for RO type I to III. They can only be traded under certain conditions[172] and if they are traded, markets are not complete. Trading in these cases occurs discontinuously and prices are the outcome of individual negotiations.

It is known that the applicability of objective risk-neutral option valuation techniques depends on the requirement that markets are complete and that the risk associated with an investment is fully market traded. Traditional academic literature usually assumes market completeness[173] for financial markets and therefore supports the applicability of risk-neutral option valuation techniques. This assumption is not fulfilled for real options type I, II, and III. The existence of private, not market traded risk is the reason why risk-neutral valuation techniques are not applicable when evaluating real options of a higher type. As opposed to financial options the valuation of real options I, II and III require a subjective valuation approach that explicitly considers non-market traded risk components of real options and

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[169] Instead of referring to the different types of options as exclusive and shared, Kester (1984, p. 156) labels them as “proprietary” and “shared”.

[170] Copeland and Tufano (2004) use the option to build a plant in a foreign country to visualize the point of shared option rights. While a company might have this opportunity, several other companies have exactly the same opportunity to open a plant in the country considered.

[171] As a similar real life example consider the development of Viagra where Pfizer exercised its option to grow by penetrating a entirely new market segment. If the development of Viagra© had been an exclusive option no company could have entered this market but in reality GlaxoSmithKline entered the market with the competing product Levitra© and Eli Lilly with Cialis©.

[172] Real options created by real investments are generally not traded. However, they can be traded if the company discontinues the project and sells all assets required to exercise the option. In most cases the option is inseparably connected to these assets. Real options are more tradable if the option right is based on an intangible asset. These assets like patents or licenses can more easily be transferred than entire production facilities.

[173] There are also studies investigating valuation problems in incomplete markets, which are not further investigated at this point.

their dissimilarities compared to financial options. There are early studies on real options like the ones of Garman (1977), Constantinides (1978), Harrison and Kreps (1979) or Cox et al. (1985) that attempted to duplicate non-market traded real options with a tracking portfolio of market traded securities to allow the application of financial option valuation methods. Based on Amram and Kulatilaka (1999, p. 52) this approach always results in a tracking error therefore the applicability of risk-neutral valuation techniques is also related to a valuation error. Mello and Pyo (2003, p. 90) also conclude that a replication of the risk involved in drug development cannot be replicated with market traded securities.

4 Corporate Financing of Young Biotech/Pharma Companies

The objective of this section is to assess young biotechnology companies' need for innovative financing strategies[174] such as the presented concept of selling research options on ongoing drug development projects in the current[175] market environment.

4.1 Availability of Traditional Financing Methods

In a traditional corporate financing framework, corporations have two main types of financing sources available to raise funds for their operations. One being internal financing where funds are generated within the corporation itself and the other being sources from outside the company that make funds available to the company due to different reasons and with different objectives.[176]

Internal Financing

Four main financing methods are generally considered when internal financing is discussed, being the retention of earnings, financing by depreciations, financing through regrouping of assets and financing through building reserves.

Recalling the definition of a young biotech company as being a company conducting research activities without generating continuous revenue streams through product sales it becomes obvious that internal financing is of no practical relevance to these companies. Without revenues these companies are not capable of generating substantial earnings and therefore the opportunity to finance themselves through the retention of earnings is not feasible.

A similar situation exists when it comes to financing through depreciations[177] or reserve building. Conceptually these opportunities are open to all companies fulfilling certain criteria. One main point is the fact that the depreciations and reserves considered for financing need to be covered by excess cash flows[178]. Since young biotechnology companies lack regular cash inflows, this way of financing is generally not a viable approach.

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[174] For a more detailed presentation of the traditional methods of corporate financing appearing in this chapter refer to basic corporate financing literature such as Schmalenbach (1966), Jensen and Meckling (1976), Sandig and Köhler (1979), Schmidt and Terberger (1999) or Betsch et al. (2000).

[175] The relevant time period for this assessment is the industry situation during the years 2003/2004. The statements in this section might change over time because they strongly depend on general market trends, the entire economic situation, maturity of the industry and legislative initiatives affecting the industry.

[176] Perridon and Steiner (2002, p. 354) consider the breakdown into internal and external financing the traditional source-based classification approach. They also present a second classification approach, which is based on the legal status of the capital providing entity. This second approach is not used in this study but can be found at Perridon and Steiner (2002, p. 353).

[177] Good examples on the financing effect of depreciations can be found at Keun and Wiese (1977, p. 27) or Langen (1970).

[178] Cash inflows exceeding cash outflows.

The last main internal financing method is the opportunity to finance operations through the regrouping of balance sheet items. This can be done by disposing assets not essential for operations and transforming them into monetary funds. This approach is also not available to young biotech companies because it is very unlikely that young research intensive companies have accumulated significant disposable assets. During the start-up phase where corporations operate on limited budgets, usually only those assets are acquired that are essential for operations and are therefore non-disposable. The only assets that young biotech companies are potentially able to sell are intangible by nature. Patent rights on discoveries not related to their core development projects might be of interest to other companies and can be sold[179].

The alternative way of financing by regrouping assets is through corporate restructuring instead of fixed asset disposal, which can also be considered a minor financing opportunity. In the absence of large inventory or accounts receivable positions the opportunity to transfer working capital into funds is minor. If rationalization activities are conducted, which is extensively done in the current market environment[180], these activities can generally not provide additional funds. This is the case because they rather affect the cost structure of a company and reduce the corporate burn rate instead of freeing up financial resources[181].

This brief qualitative assessment of internal financing opportunities revealed that they are only available to young biotech companies to a minor extent. Compared to these internal financing sources, external types of financing are more relevant for young biotech companies. Their availability is assessed below.

External Financing

The main external sources of financing discussed at this point are additional investments by existing stakeholders, venture capital investments, public stock offerings, public grants, credit substitutes and financing through common debt.

When discussing external financing methods available to young biotech companies[182], it is important to create an understanding of the stage of corporate development they operate in. This is essential because during each corporate development stage, companies have specific financing methods available while they have only limited access to others. In return, these types of financing methods might then be more easily available during other corporate development stages. While there are different stage models available in recent publications[183], this study builds on the financing stages defined at Schefczyk (2000, p. 24).

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[179] On the value of patent rights see Reitzig (2002).

[180] Compare to Firn (2003)

[181] These rationalization efforts rather avoid future cash outflows than generate current cash inflows.

[182] Kaminski (1988) and Fischer, Barbara (2003) discuss this topic on a general level for medium size and start-up companies.

[183] An example of an alternative model can be found at Giesecke (2001, p. 89).

In general, the type of young biotech companies discussed in this study operates in a "Start-up" phase conducting development activities and getting ready to introduce a product into the market. Table 4.1 shows the different stages of corporate development and the different financing options most likely to be available during each stage.

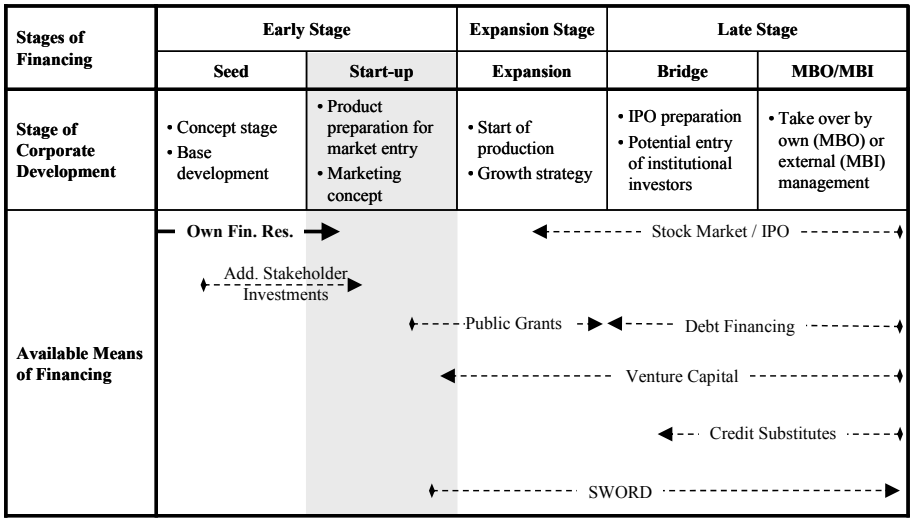

Table 4.1: Stages of corporate development and available sources of financing[184]

One of the main findings of Schefczyk (2000) is the conclusion that companies operating in this "start-up" stage experience distrust and suspicion from investors as one of the main management issues. As a result, the general number of available financing methods at that stage is reduced and an external financing gap can be observed. This finding also holds true for the young biotech companies as shown in the following sections discussing the availability of the various financing methods in more detail. At this point it is important to recall the fact that the majority of German young biotechnology companies are lagging behind their American counterparts in terms of corporate development and therefore different observations are made at certain points for the industries of these two countries.

Going Public

After the stock market boom of the 1990s it has become more difficult for the entire biotech industry to raise money through Initial Public Offerings (IPOs). Figure 4.1 shows how the number of IPOs developed in Germany and the US since the last boom year 2000.

[184] Adapted and expanded from Schefczyk (2000).

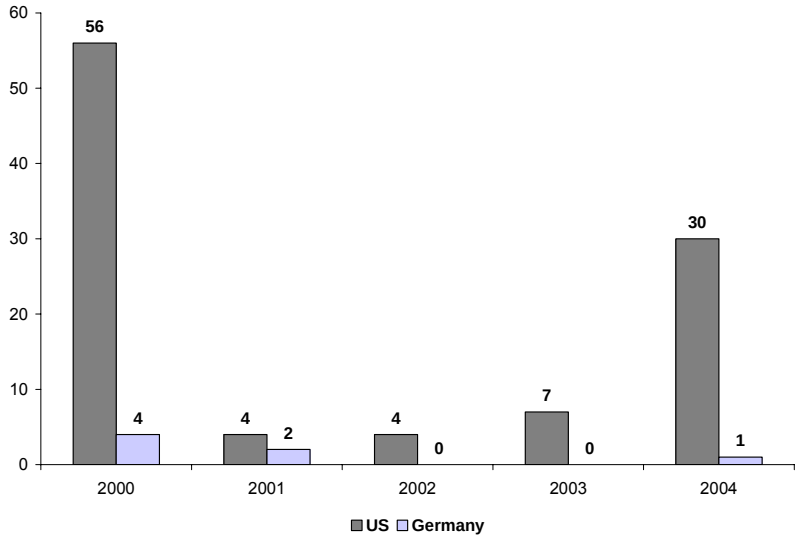

Figure 4.1: Biotech IPOs in the US and Germany (2000-2004)[185]

In Germany the IPO market and the biotech bubble on the stock markets collapsed at the beginning of the new century. There were still four IPOs in 2000 while there were only two placements in 2001 and not a single one during the following two years. It took until July 2004 for the next biotech company[186] to place its shares in the German market. For the US biotech industry the situation was similar during the years 2001 and 2002 with only a few biotech IPOs. As opposed to Germany, the number of IPOs recovered from four to seven in 2003 and in 2004, thirty companies placed their stock for the first time.

The US is currently a more favorable market for IPO financing than Germany because US companies better meet the requirements for a successful IPO. The first requirement is that companies should have a product out in the market or at least in the late stages of clinical trials. The guideline for a minimum requirement is the successful completion of phase II clinical trials.[187] From a size perspective, investors expect at least a market capitalization of US$200 million to consider a company being of sufficient size for a successful IPO.[188]

These minimum requirements should be fulfilled because IPO investors have become more risk sensitive and require a discount to be compensated for the risk that early R&D activities might fail. Hall (2002) already found that as R&D intensity increases, so does the cost of capital for the research conducting company. Such a discount is also required by underwriting banks to ensure a successful market placement[189]. Without this discount the

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[185] Sources: Ernst&Young (2004b), Ernst&Young (2004d), Burrill&Company (2005), and DAI Factbook 2004.

[186] Epigenomics AG

[187] According to Markus Mann / Union Investment, in DPA (2005).

[188] Comment by the COO/CFO of Atugen AG, Berlin in Ernst&Young (2003)

[189] On the issue of signaling through underpricing at IPOs refer to Allen and Faulhaber (1989).

willingness of underwriters to take over risky public placements is limited because of the fear of reputational damage in case of an unsuccessful placement.[190] These discounts explain why multiple offerings in the US failed to meet their fund raising potential.[191]

With the pipelines for biotech IPOs being filled in the US[192] as well as in Germany[193], this financing opportunity is still not available for many young biotech companies because of the requirements mentioned. Since US biotech companies are on average more mature and have more products in later development stages, they are expected to attract investors faster than their German counterparts. Although a study by Ernst&Young (2004b, p. 108) found that 52 German biotech companies expect to go public within the next three years this strongly depends on the progress of ongoing research activities. As for now, privately owned companies in Germany do not have a single approved product out in the market and most of their products are still in very early stages. Here resides the problem of IPO financing in Germany. With successful completion of phase II clinical trials being a mandatory requirement for a successful IPO and only 3 products of privately held companies in Germany currently passing phase III clinical trials[194], this mode of financing will not be available in the very near future.

Blättchen (1996) goes one step further by concluding that fund raising should not be the reason for an IPO at all. The reason for this is that a company that needs money does not give a promising signal to investors. In his opinion, companies only qualify for an IPO if they fulfill minimum requirements in terms of profit margins.[195] Following his argumentation young biotech companies in urgent need of funds to finance R&D activities are not suited for an IPO because they rarely generate any profits from ongoing operations.

Stakeholder Investments

From a theoretical standpoint it is always possible for existing owners of a privately held company to provide additional funds to operate and grow the business, irrespective of the corporate development stage in which a company operates in. This also applies to the biotech industry but it is accompanied by is a practical limitation. Once a research conducting biotech company has started its drug development activities, the need for financial resources continuously increases to keep operations running. Figure 2.5 shows the cost structure of a typical pharmaceutical development project from base research to market approval.

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[190] See also de Matos (2001, p. 160)

[191] Compare to Hennessey (2004)

[192] According to Hennessey (2004)

[193] According to Knop (2005)

[194] According to Ernst&Young (2004b)

[195] A minimum profit margin of 4% is quoted, which increases as company size decreases. It can be up to 10% for very small companies.

With capital requirements significantly increasing during the stages of clinical trials II and III, chances that existing owners are able and willing to provide the funds needed to keep operations running decrease. Recalling the fact that it can cost multiple hundred million dollars to bring a product innovation through the entire drug development process it becomes clear that the chances one or a few initial investors are willing to finance the entire venture with their own financial resources are reduced to a minimum. Except for selected rare cases, additional stakeholder investments alone can therefore be considered insufficient in terms of financing power for the completion of an entire drug development project. In return, the support of investors from outside the company can be considered mandatory.

Venture Capital

The availability of venture capital (VC)[196] to the biotech industry differs between the countries in scope of this study. While the US VC market is increasingly targeting the biotech sector again with its investments, the market remains on a moderate level in Germany. In the US, the VC situation has already become favorable for biotech investments while Germany is still struggling. In 2003 there were over 30% more VC funds flowing into biotech deals than the year before. This figure reached its peak in 2004 when another 30% increase led to a total VC investment volume in the US of around €3.3 billion[197]. Figure 4.2 compares VC biotech investments from 1998 to 2004 in the US and Germany.

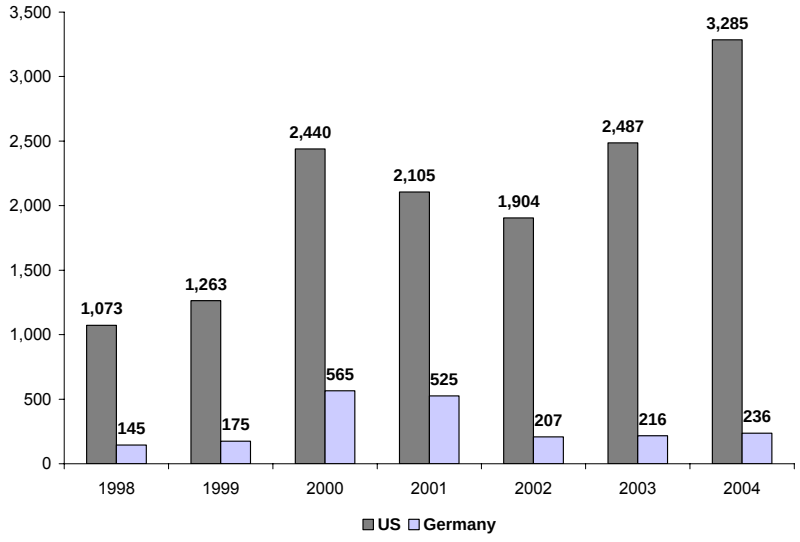

Figure 4.2: VC Biotech research funding US and Germany (1998-2004 in € mil.)[198]

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[196] For a more detailed discussion on venture capital investments see Schween (1996), Weitnauer and Guth (2000), Stadler (2001) or Stadler (2004). For a detailed description of the VC investment process refer to Giovannini (2004) and for regional differences between the venture capital markets in the US and Germany refer to Gaida (2002).

[197] US$3,733 million at an exchange rate of 0.88€/US$; Source: Burrill&Company (2005).

[198] Source: Ernst&Young (2005, p. 105) and Ernst&Young (2004d, p. 48) at an exchange rate of 0.88 €/US$ 2004 from Burrill&Company (2005).

While recovery on the US market appears to be a relief for the companies in urgent need of funds, only a selected group of companies actually benefit from this development. New engagements are selected carefully and tend to be closed with larger, more mature companies operating in later development stages.[199] It is essential for investors that profits are generated in the foreseeable future because VC investors "are not there to save the world, they're there to show an ROI[200],,[201]. For smaller, early stage companies without a product near market introduction, the availability of VC funds remains critical.

After the VC biotech investments dropped from 2000 to 2002, the German market did not recover significantly and remained at a level of €236 million in 2004. Despite this development, venture capital is still the most important financing tool for German biotech companies[202]. Three trends have evolved in Germany over recent years:

1. The share of medium sized investments has decreased while the number of small and large deals has increased[203]. This can be explained with investors becoming more risk-averse with their investment strategies. Either low risk, large-scale investments are made in the few solid and promising deals or small investments are spread across multiple deals for diversification purposes.
2. With regard to deals that were closed in 2003 and 2004, negotiating power was on investor's side because of the urgent need for financial resources on the biotech side. If investments were made during this timeframe, then generally at a price discount for the venture capital investor[204].
3. The third trend, which is especially relevant for young biotech companies requiring early financing, is the trend towards later stage investments. While 60% of all VC investment deals were related to early stage financing in 2001, this share decreased to 47% in 2003[205]. This development is similar to the one in the IPO market where investments are shifted towards companies that are involved in development stages close to market entry and therefore also close to revenue generation.

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[199] Compare to Knop (2004)

[200] ROI = Return on Investment

[201] Neil Ryan, founder and managing partner of Oxford Biosciences in Chiruvolu (2002).

[202] Around 40% of all German biotech companies use some kind of venture capital financing according to Ernst&Young (2004b, p. 49).

[203] Small < €5 mil.; medium €5 - €20 million; large > €20 million.

[204] As explicitly emphasized by Ernst&Young (2003, p. 81).

[205] If this trend is expressed in share of invested capital, the ratio becomes even less favorable for companies operating in early stages of the value chain. Only 4% of the total investment volume in Germany was related to seed- and first-round financing. This share was significantly higher in 2001 when it reached 29% of the total investment volume. Compare to Ernst&Young (2004b, p. 95).

These trends make it increasingly difficult for very young biotech companies in Germany to raise VC funds and they are potentially unattractive because of the risk discounts required.

Besides the availability of VC investments, it is also important to state that VC investments are not always the financing method of choice for young biotech companies. While VC investors typically target young, innovative companies with significant growth potential[206] there are some VC characteristics that make young biotech companies prefer other financing sources if available. This is related to the wide range of individual rights generally granted to the VC investor through the investment contract.[207] In extreme cases, the combination of such rights might lead to a complete loss of control over the company for the initial owners in situations where the company does not fulfill certain contractually fixed performance or progress expectations.[208] In addition to these rights, the founders' willingness to exit the company is, in certain cases, a requirement of VC investors[209], which is often not in the interest of the initial owners.

Debt Financing

Raising funds through bank loans or issuing bonds can, in certain cases, represent an attractive financing tool because it has multiple positive characteristics compared to equity fund raising[210]. Although it has some theoretical advantages there are four main reasons why common debt financing usually disqualifies as a financing method for young biotechnology companies:

1. In general, debt financing contracts have a certain maturity date and therefore the financial resources are only available to the financing company for a limited time and have to be paid back at the end of the contract's lifetime. Since most young biotechnology companies are not certain when they will be able to generate revenues to fund their operations, the obligation to pay back debts might precede the time of revenue generation and force the company into liquidation.
2. During the lifetime of the contract the financing company is obligated to make interest payments. Since most young biotech companies do not generate sufficient revenues to cover interest payments, these obligations slowly but consistently hollow out their capital base, which in return reduces their operational flexibility.

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[206] On VC objectives see Klemm (1988) or Schuster (2003). Some sources further distinguish between true venture capital firms that focus on young, innovative, high growth companies and a second form that mainly invest in more mature and established companies. See Gerke (1972), Juncker and Schlegmilch (1976), Schefczyk (2000, p. 8) or Perridon and Steiner (2002, p. 365).

[207] Typical rights covered in VC contracts are cash flow allocation rights, board rights, voting rights, liquidation rights and other control rights. On investors' rights see Berrios (1999) for more details.

[208] For a detailed study on Venture Capital contracts refer to Kaplan and Strömberg (2003).

[209] As explicitly emphasized by Ernst&Young (2003, p. 83).

3. It is an expensive type of financing because entities investing in young, research intensive companies expose themselves to a high degree of risk of loosing their investments. As a compensation for the accepted risk they require a higher rate of return[211] on their investment resulting in large interest obligations[212] for the financing company that can finally lead to the biotech company's inability to cover them.
4. Since young biotech companies do not have a reputation in the credit market, lack any type of credit rating and have only limited securities to cover debt positions it is difficult for young biotech companies to find a partner willing to enter into a common debt agreement with them.

These four points make it extremely difficult, if not impossible, for young biotech companies in Germany as well as in the US to implement a financing strategy based on common debt.

Public Grants

Another form of financing that might be available to selected companies in certain industries are public grants. Grants are funds provided by private, federal, state, or regional entities[213] that are usually tied to a specific purpose[214]. General purposes[215] can be the economic strengthening of geographic regions, the targeted support of key industries to encourage settlement by providing a favorable business environment, the direct support of selected development projects to ensure their completion or the support of industry cooperations[216] that might result in new key technologies or products. Besides the true grant representing funds that support an activity and do not have to be paid back, funds can also come as interest free or interest reduced loans or in multiple other ways.

Especially in the early days of the biotechnology industry, public grants played an important role in the financing strategies of young biotechnology companies. With the increasing financial problems of public authorities a lot of public funding programs suffered from tighter budget control. In 2002, a BPI (2002, p. 38) study found that 38% of the German biotech companies still used some type of public grants to finance their operations. The study also

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[210] For example, profit leveraging tax effects or the general inability of debt investors to influence operations as opposed to equity investors.

[211] Uhrig-Homburg (2001, p. 42) shows that required interest rates with equal maturities decrease as the default risk of a fund raising company decreases.

[212] Compare to Hall (2002)

[213] For a discussion on regional support programs for the biotechnology industry in Germany refer to Reiß and Koschatzky (1997).

[214] For an overview on selected German public funding programs see Ernst&Young (2004b, p. 99).

[215] More specific purposes can be the requirement of sharing discoveries with other institutions Begley (2004), the integration of new equity investors Reiß and Koschatzky (1997, p. 110) or for the development of treatments against biological weapons Barbaro (2004).

[216] See Wolff et al. (1994)

revealed that this share is decreasing significantly. Main reason being the mentioned decreasing availability of funds and the bureaucracy companies have to go through when applying for these grants.

For an assessment of the ability to solve the financing problems of young biotech companies by using grants, one should consider the following figures. From 2000 until 2003, €51 million in public grants were awarded to German biotech companies. Although in some selected cases, biotech companies could significantly benefit from these grants and raised up to €4 million[217], public grants cannot solve the problems of the industry considering a short-term estimated financing gap of around €800 million[218] in Germany alone.

Financing with Credit Substitutes

The area of financing with credit substitutes includes the three fund raising methods Factoring[219], Asset Backed Securities[220] and Leasing[221] in its various forms.

There are obvious and intuitively clear reasons why credit substitutes are not relevant when it comes to financing strategies for young biotechnology companies. Young, research conducting companies without operative revenues do not accumulate accounts receivable positions and therefore do not qualify for Factoring or for issuing Asset Backed Securities.

Regular leasing agreements on the other hand can only reduce the immediate need for financial resources by eliminating asset purchases but cannot generate funds that are available for daily operations. Significant funds could only be raised through sale-and-lease-back agreements. Since young biotech companies generally operate on a minimized asset base and have not accumulated excess assets during their short existence, this type of agreement is not a relevant fund raising strategy either.

4.2 Availability of Industry Specific Financing Methods

In addition to the traditional general financing methods discussed above, the biotechnology and pharmaceutical industry have additional ways of fund raising. These industry specific types of financing include industry cooperations, product licensing and stock warrant off-

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[217] Biofrontera Pharmaceuticals/Leverkusen

[218] According to Ernst&Young (2004b, p. 103)

[219] On Factoring see Bette (1997) or Schwarz, Werner (2002).

[220] On Asset Backed Securities see Dickler (1990), Ohl (1994), Eisenächer (1994) or Bartelt (1999).

[221] For details on Leasing agreements refer to Leasing specific literature like Mukherjee (1991), Kratzer and Kreuzmair (2002) or more general introductory finance textbooks such as Van Horne (1971), Copeland and Weston (1979), Brealey and Myers (2000), Ross et al. (2005). For the critical conceptual differences between renting and leasing see Spittler (2002).

balance sheet research and development[222]. The following section briefly describes[223] and discusses these additional ways of financing.

Cooperations

One way of raising funds, which becomes especially attractive during times when other financing sources become unavailable are inter-company cooperations. When entering into a cooperation, the research conducting biotechnology company decides to share its future revenues or profits with a strategic partner in return for financial support for its operations. Strategic partners have multiple ways to make these funds available. The following provide some examples as to how payment agreements can be structured:

- One-time upfront payment at the beginning of a cooperation.
- Continuous partial absorption of research and development cost.
- Milestone payments after successful completion of pre-defined project steps.
- Payment of so-called "Fees for Services" for specific research activities.
- Partial or entire absorption of marketing and distribution cost.

Large pharmaceutical companies or larger biotechnology companies with more mature product portfolios and stable revenue steams are common partners of young biotech companies for inter-company cooperations.

Large companies in the pharmaceutical industry and the companies of the biotech industry are currently mutually dependent on each other[224] and therefore cooperations are of significant importance to both industries. While large pharmaceutical companies need the innovation power of young biotech companies to achieve their corporate growth targets[225], biotech companies need support to complete the product development process and establish the resulting products in the marketplace. Cooperations represent the interface between the two industries allowing each of them to achieve their own individual objectives.

While cooperations during the bull market in 1998-2000 usually took place in form of the small biotech companies being acquired by large pharmaceutical companies, this situation

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[222] Another tool often cited when financing is discussed in the context of the biotech industry are Private Investments in Public Equity or PIPEs. Since this strategy requires a company to be present in the public market, PIPEs represent a form of secondary offering. Since secondary offerings are not a form of early stage financing, they are not considered within the scope of this study.

[223] While traditional ways of financing are not described in the previous section, it appears reasonable to give a short description of the industry specific approaches as their functionality cannot be considered public knowledge.

[224] Except the few large biotech players like Amgen, Genentech, Genzyme, Chiron, Biogen Idec, etc.

[225] Growth rates already had to be reduced from 10% to 8.5% as a five year industry average according to Scodari (2004).

has changed. Already in 2001, the number of direct acquisitions decreased and the number of technology, product and marketing cooperations increased significantly[226].

Although anticipated, a revival of mergers and acquisitions did not take place to the expected extent when the economic situation and stock markets turned more favorable in 2003. The number of merger activities increased only slightly in the US and Germany. Biotech and pharmaceutical companies clearly favored cooperations over direct mergers. While biotech companies are most concerned about their independence, the reasoning behind this behavior is another one for large pharmaceutical companies. They hesitate to acquire solely research conducting companies because they constantly burn cash and do not contribute to corporate profits. With such an acquisition there would be a dilution in earnings and some pharmaceutical companies try to avoid such negative signals that could make the company look less attractive to potential investors in the marketplace.

Instead of entering into more acquisition deals, pharmaceutical companies rather take on greater risk by pushing the qualification border for new cooperations down the value chain.[227] While large pharmaceutical companies were not interested in cooperating with biotech companies during early stages of the development process to a large extent in recent years, this situation changed in 2003 and 2004 as the industry is seeing an increasing number of early stage cooperations.

As soon as research activities have reached a mid-stage level, cooperations with large pharmaceutical companies are and will remain one of the predominant tools for young biotech companies to resolve their financing problems. This becomes increasingly true as development projects mature and the biotech companies' negotiating position improves[228].

Cooperations between young biotech and medium-size pharmaceutical companies on the other hand are generally not pursued[229] because these companies often operate on similar tight budgets[230] as the average young company of the biotech industry.

The trends described in cooperations develop to a large extent analogously in the US and in Germany. The major difference is the stronger negotiating power of the average US biotech company resulting from its more advanced research portfolio and larger number of products being close to market introduction.

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[226] In Germany technology cooperations +96%, product cooperations +86% and marketing cooperations +73% from 2000 to 2001 according to Ernst&Young (2002, p. 32).

[227] In this environment acquisitions mostly take place under two conditions. The first one being that the biotech target company owns promising experimental projects close to completion and the second one being that it is in urgent need of funds and therefore in a weak negotiating position unable to achieve some other type of funding. In this context see Bowe and Dyer (2004).

[228] "For those with coveted products, deal terms are becoming more generous and lucrative than ever before" according Ernst&Young (2004c, p. 36).

[229] Except for very specific purposes in niche markets.

Licensing

Licensing[231] represents a special but popular form of cooperations between companies of the biotechnology and the pharmaceutical industry[232]. The licenses used in such a cooperation "transfer the right of disposal of a newly developed technology from one company or R&D institution to another"[233]. Under a licensing agreement the so-called licensor grants patent rights[234], know-how and relevant data to a so-called licensee. The licensee in return offers his expertise in product development, production, approval, marketing and distribution to bring a product to market. The license is granted for a specific period of time[235] during which the licensee is required to compensate[236] the licensor for the use of its intellectual property rights. Although no two licensing agreements are alike, the typical licensing deal in the biotechnology industry consists of three principle financing features[237]:

- An upfront licensing fee.
- Milestone payments depending on the achievement of defined project stages.
- Royalties on the sales of the product.

Since there is no established market for licenses, agreements are closed on a bilateral basis between licensor and licensee. The final terms depend on the negotiation strength of the parties involved. The terms also depend on the extent, to which rights are granted. As opposed to a non-exclusive agreement, where multiple licensees can acquire rights to use intellectual property, rights can also be granted exclusively to one single partner, in which case a financial premium is required. Another price determining factor is the type of right covered by a licensing agreement. Generally they can be separated in three groups.

1. Established products or technologies: The licensee acquires the right to make use of a product or technology that has already been successfully introduced into the market.[238] This is the least risky form of licensing but it also requires the highest fees.
2. Products or technologies under development: In this case the licensor does not complete the entire research and development process himself but grants the usage

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[230] Compare to BPI (2002, p. 39)

[231] For more details on licensing see Megantz (1996) or Henn (2003).

[232] But licensing is not limited to these industries. It is also frequently used in the chemical, high-tech, and all other research intensive industries where intellectual property rights play a vital role.

[233] See Jungmittag et al. (2000, p. 77)

[234] Patents can be related to a product or a technology as emphasized by Ernst&Young (2002, p. 29).

[235] Usually but not necessarily until the time of patent expiration.

[236] On the valuation of licensing projects see Boer (1999, p. 264) or Hommel et al. (2001, p. 79).

[237] The three components of a typical agreement can also be used individually or in any combination.

[238] It is often used to regionally expand availability of a product or technology to regions where the initial owner is not present.

rights on an unfinished invention to the licensee.[239] Since the licensee takes over part of the development risk, this type requires smaller fees than the first case described above. This type represents the most common type of licensing in the biotechnology and pharmaceutical industry.

3. Mere patent right: In cases where an initial inventor possesses even less development know-how, market expertise and financial resources he might choose to sell rights on a simple patent without a specific product related to it. In this scenario achievable fees are further reduced because the entire development risk is transferred to the licensee. On the other hand the inventor might be able to sell multiple pseudo-exclusive rights to licensees within non-competing industries.[240]

Licensing agreements offer large biotechnology and pharmaceutical companies the opportunity to expand their product portfolios and achieve the growth rates required by the market. At the same time it allows them to avoid the risky as well as time- and resource-consuming process of base development.[241] On the other hand licensing offers an opportunity for the large number of small biotechnology companies to benefit to a maximum extent from their product or technology innovations without the necessity to build up their own production, marketing and distribution capabilities.

As a specific type of cooperation, licensing agreements follow a similar trend as cooperations in general. Large pharmaceutical players are also rather interested in mature product deals that allow them to license-in products from late stages of the value chain with a higher potential to become revenue generators.[242] This situation is changing as well because competition between licensing companies for promising products intensifies. The increasing competition leads to a rapidly decreasing number of mature candidates available for licensing deals forcing pharmaceutical companies to move further down the value chain in the search for licensing candidates. A study by BCG (2004a) revealed that approximately 20% of all biotech compounds being in phase I to III of clinical trials were available for licensing in 2004. With the trend towards licensing continuing to increase at a rate of 10% a year, the

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[239] Generally this type of licensing deal is closed if the licensor does not have the required infrastructure, know-how or financial resources to complete the development process himself.

[240] Boer (1999, p. 266) describes the hypothetical case of the discovery of a new molecule that might serve as a pharmaceutical compound, a pesticide or a food additive. The inventor now has the possibility to license this molecule out to companies from each industry with an exclusive usage right for their individual industry.

[241] Biotech companies are also in-licensing products from pharmaceutical companies or other biotech companies. This is usually done to bring projects into the company that have been introduced into the market or are close to market introduction to make the company make look more attractive to investors and potential partners. From a financing perspective, the situation of in-licensing by pharmaceutical company and out-licensing by biotech is the most important one.

[242] Compare to Ernst&Young (2003)

pool of compounds available for licensing from biotech companies is expected to be entirely dried out by the year 2010.

For young biotech companies with development projects being in the stage of pre-clinical trials the licensing market is currently not a significant source of financing but this might change as the market becomes more competitive and licensors are forced to move down the value chain in the search for new products. This clearly shows how important licensing agreements are for both industries but it also shows that the market will become increasingly competitive within the next few years.

Stock Warrant Off-Balance Sheet Research and Development (SWORD)

Another form of financing, which is specific to all types of research intensive industries, is known as stock warrant off-balance sheet research and development or SWORD. The concept was first used by biotechnology companies in 1988[243] and for the first time scientifically investigated as a financing tool by Solt (1993).[244]

When using SWORD as a financing tool a Resource Requiring Company (RRC) sets up a new entity, a so-called Research and Development Limited Partnership (RDLP), which is theoretically independent and maintains its own, separate balance sheet. In a Technology License Agreement (TLA) this RDLP receives the unlimited, exclusive and royalty-free rights on a product or technology currently under development. While the RDLP owns all rights on the new product or technology, the development process is still pursued by the RRC itself. As a compensation for incurred research and development expenses, the RDLP regularly transfers funds to the RRC as defined in a development contract.

Since the RDLP is not a fully operating company but rather a financial intermediary unable to physically use the product or technology rights it owns, an additional License Option Agreement (LOA) is closed. Under this LOA the RRC has the opportunity to use the rights owned by the RDLP under predefined conditions. Potential conditions would be lump sum payments or continuous royalty payments.

The RDLP on the other hand closes financing agreements with external parties to raise funds to pay for ongoing research activities conducted by the RRC. Under this agreement common stock of the RDLP is sold to outside investors. The shares sold are callable by the RRC, which means they can be bought back at predefined conditions to avoid that competitors or unwanted third parties can acquire stock of the RDLP. Together with each share the investors receive an option that grants the right to purchase stock of the RRC. This option serves as a protection for the investor by giving him indirect access to cash flows generated by the RRC that are not related to the project controlled by the RDLP. This form of

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[243] Early SWORD announcements included ALZA founding the company Bio-Electro Systems, Centocor founding Tocor, Immunex founding Receptech, and Genzyme founding Neozyme.

[244] An additional study dealing with off-balance sheet financing by using research and development limited partnerships was conducted by Carment et al. (2001).

protection becomes necessary because the management of the RRC has more information about the R&D project than outside investors do. This situation may potentially result in an adverse selection[245] problem where the RRC could move the least promising projects off its balance sheet into RDLPs[246]. The added option on the stock of the RRC therefore represents a signal to investors about the value of the R&D project that cannot entirely eliminate the risk of adverse selection but can reduce its negative impact on the investor.

It is important to state that these two option rights are independent from each other. Even if the RRC exercises its right to buy back stock of the RDLP, investors can still benefit from the innovation by exercising their right to acquire shares of the RRC. Table 4.2 shows the ownership structure and the duties related to a SWORD after closing all contracts[247].

	RRC	RDLP	Investor
Owner of …	• Option to acquire license from RDLP and bring new product/ development to market	• Unrestricted rights on new product/ development • Funds to finance R&D	• Common stock of RDLP (callable by RRC) • Call Option on common stock of RRC
Duties	• Conduct R&D on new product/ development • Provide admin. services to RDLP	• Manage funds • Compensate RRC for R&D activities	• Transfer funds to RDLP for stock and option rights

Table 4.2: Rights and duties of parties involved in a SWORD financing deal

Using a SWORD as a project financing tool has several advantages for the fund raising company. The most important one being that all funds come from equity not requiring any interest payments from the RRC during the course of the project.[248] In addition there is an increase in transparency of corporate reporting because funds related to a specific project are reported on an individual balance sheet and are not mixed with other corporate assets on the RRC's main balance sheet. Especially if a company has multiple other activities ongoing this gives potential creditors a clearer view of the economic situation. Another advantage is the

[245] An introduction into the research field of adverse selection with an overview of the academic literature can be found at Wohlschieß (1996).

[246] On the related issue of selling corporate stakes under asymmetrical information refer to the work of Akerlof (1970) on the so-called "lemon" problem.

[247] In addition to the four contracts mentioned above (Technology License Agreement, Development Contract, License Option Agreement, and Financing Agreements) there is an additional Service Agreement between the new organization and the biotech company. This statement regulates the provision of administrative services that allow the new organization to remain a pro forma company without its own employees and administrative overhead.

[248] Debt financing would require significant interest payments due to the risk involved in drug development. Since the only asset of the new organization is intangible by nature there would not be any security for potential debt creditors, which would result in a risk premium. Considering the long development times there would be a high-risk of corporate default irrespective of the projects outcome, due to ongoing interest payments without corresponding cash inflows.

distribution of project risk because the shares of the RDLP can be sold to multiple investors who are able to diversify the related risk within their own investment portfolios.

The favorable characteristics come at a cost for the RRC because the option of the investor to call shares of the company causes dilution for existing shareholders if exercised.[249] In addition to the effect that exercising these options dilutes future profits for existing shareholders, it can also introduce new owners into the company trying to influence the future corporate strategy. Solt (1993) shows evidence that the influence of these new owners can become of significant magnitude[250]. Especially in young, dynamic companies this is not always a desirable development.

In his study Solt (1993) also shows that SWORDs are not the result of adverse selection effects from the RRC trying to move unpromising projects off its balance sheet[251] and Carment et al. (2001) support this view in an additional study[252]. The findings of Solt (1993) and Carment et al. (2001) indicate that SWORD offerings are a viable financing alternative for research intensive companies, such as companies from the biotech industry. They emphasize that this is especially true for smaller companies[253].

In the absence of recent market figures on number and size of initiated SWORD deals, no valid conclusions can be drawn about the practical relevance of this type of financing for young biotech companies. While the concept appears attractive at the first glance it has drawbacks beyond the potential adverse selection problem related to it. Investors in a SWORD deal are generally financial investors and the construction of a SWORD deal does not consider the other need of young biotech companies for support in bringing their products to market. A SWORD deal might provide the funds necessary to carry a project through the R&D process but it does not provide additional support. This support can be essential for young biotech companies when it comes to large-scale production, marketing strategies or setting up a global distribution network. This type of support cannot be provided if a multitude of investors acquire shares in an RDLP. Licensing deals or any other form of direct cooperation can be considered the more appropriate way of financing for young biotech companies because it ties a partner more closely to the operations of a company.

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[249] In the sample Solt (1993) uses for his study, this potential dilution effect ranges from 9.7% to 29.4% if all options are exercised.

[250] Considering the maximum dilution effect of 29.4% from his study.

[251] Solt does so by evaluating stock price behavior around the announcement of a SWORD deal. Decreasing stock prices after the announcement of a SWORD deal indicate that either project prospects are not satisfying or that SWORDs are not a viable financing tool. On the other hand, an increasing stock price would indicate that generally promising projects are selected for SWORD deals and it is positively valued that they are offered. The analysis could not support the existence of adverse selection and showed a general positive market reaction after SWORD offerings.

[252] Carment et al. (2001) confirm a positive market reaction for companies sponsoring a RDLP.

[253] „RDLP financing is a more significant source of financing for smaller firms […]", Carment et al. (2001, p. 168)

Another negative factor is the complexity of a SWORD deal from a legal and from a valuation standpoint, which potentially reduces the attractiveness of the concept.

4.3 Consequences of Lacking Financing Power

Besides the fact that a lack of financial resources in the industry leads to a decreasing number of independent companies[254], there are other trends arising from a lack of financing power:

Out-licensing: While the predominant strategy within the industry is the full product approach, multiple companies have to discontinue their research activities and license out or sell their products before they enter expensive clinical trials II and III. Only 13% of the German biotech companies[255] expect that they will be able to carry a product all the way through clinical trials. This lack of financial resources to complete the product development process is one of the reasons for the increasing out-licensing trend in the industry.

Services: Companies are forced to either move away from product development or at least have to include service operations to generate cash flows. This does not mean they are abandoning product development as their strategic focus but they have to include activities to stretch their financial cushion. This can have a negative impact on the products currently under development. Additional operations tie up resources and therefore other projects might be delayed, resulting in a reduction of effective patent protection period and the loss of a potential first mover advantage.

Corporate takeovers: In the absence of outside partners willing to finance their operations, owners of companies with promising prospects might be forced to sell the operation to avoid bankruptcy, sometimes below estimated fair market value. This trend can be documented with the increasing number of foreign investors buying companies in critical situations. Sometimes companies are even bought that have already filed for bankruptcy[256].[257]

Cooperations: The last trend is the increasing number of various forms of cooperations. Handelsblatt (2003a) concludes that the lack of financial resources forces biotech companies at a certain point to enter a cooperation because otherwise operations have to be discontinued. These cooperations allow companies in critical conditions to continue operating but also deprive them from their future benefits, which have to be shared with the new partners.

This development does not only have an impact on every single company affected but also on the entire industry where a trend towards consolidation is expected to occur. For Germany it

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[254] As a result of mergers, acquisitions or bankruptcies. For Germany, Ernst&Young (2005, p. 11) show that five times as many biotech companies filed for bankruptcy in 2004 than in 2001.

[255] According to Ernst&Young (2004c, p. 54)

[256] With Abeta, bioLeads and Memorec Stoffel, three cases have been reported in 2003.

[257] This trend not only holds true for companies that are close to bankruptcy. The existing or even the expected lack of financial resources generally causes an increasing number of biotech companies to be acquired by large pharmaceutical companies as shown in Hofmann (2005b).

is expected that the biotech industry will enter a stage of severe consolidation significantly reducing the number of independent companies[258]. A similar prediction was made for the US several years ago but in fact, it never took place on the predicted scale.

4.4 Conclusion

Although there are many different methods of corporate financing, not all of them are available to young biotech companies. While internal financing, common debt and credit substitutes are not an option because of lacking revenues and securities for investors, the situation is different for other financing methods. Fund raising through public grants or additional investments of existing owners exist but are limited in terms of scale and are only in rare cases sufficient as a stand-alone source of financing. IPOs and VC investments, the sources of abundant financial resources as little as five years ago, have become more difficult to be opened up because of increasing investors' selectivity and risk aversion. While US biotech companies are in a better position in this financing area with their further advanced product development pipelines, German companies are often left with industry specific financing strategies, such as cooperations and licensing agreements.

When pursuing an integrated product approach, young biotech companies face a dilemma. On the one hand, VC and IPO investors as well as potential licensing partners expect them to have products in late development stages in order to provide funds. On the other hand, these funds are, as a result of the absence of stable revenue streams and the increasing cost during the R&D process, often a necessary prerequisite to reach these later stages. This reveals that especially those companies are likely to find themselves in a critical situation that operate at the end of their initial seed capital without having reached at least phase II clinical studies.

These companies are in urgent need of innovative financing strategies to overcome this potential financing gap. Such a strategy ideally allows them to pursue their R&D activities to final drug approval or at least until they become more attractive for outside investors. Since the funds are available on the investors' side[259] but are often not made available to young companies, the objective is more to find a way to adjust the investment risk structure for potential investors so that funds are made available earlier during the drug development process. The following sections investigate if selling option rights on ongoing drug development projects can serve as a tool to close this potential financing gap for young biotech companies.

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[258] Compare to Frankfurter Rundschau (2003)

[259] "There is plenty of money for companies with products near to market", Ernst&Young (2004c).

PART II: Concept & Scientific Context

5 Concept of Writing Options on Ongoing R&D Projects

To obtain a judgment as to whether writing options on ongoing R&D projects for financing purposes represents a practically applicable concept it is qualitatively and quantitatively investigated. The qualitative investigation in this chapter describes the various risk factors associated with the R&D process of a new drug and the structure of the option financing concept itself. The chapter is concluded by a description of the advantages and disadvantages such a concept has for the buyer and the seller of the option. The quantitative analysis is conducted in subsequent chapters of this study.

5.1 Risk Factors in Drug Development

During the process of drug development a company is exposed to five main sources of uncertainty affecting the prospects of a project. These five areas of risk are the technical risk of project failure, the uncertainty about the point of market entry, the unknown lifetime of a product, the risk related to the economic environment and the potential risk arising from competing products and technologies[260].

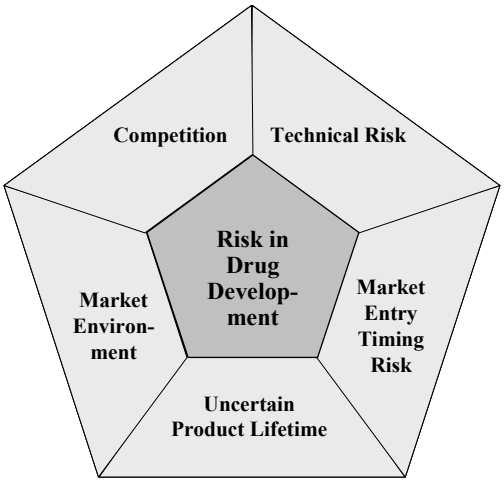

Figure 5.1: Five main areas of risk in drug development

5.1.1 Technical Risk

The technical risk involved in the drug development process represents the risk that an ongoing project fails before the final regulatory approval process is completed and a product can be introduced into the market. It also includes the risk that approval is not granted by regulatory authorities during the final review process. Multiple reasons can be responsible

[260] Boer (2002, 231) defines legal risk as another risk factor for the pharmaceutical industry. This risk factor is predominantly relevant for the US market but not considered within the classification of this study.

for this type of project failure.[261] A drug candidate can fail because severe side effects are discovered during the required testing activities making it unsafe for human use. In addition to the potential health hazard, it is also possible that an initially promising candidate fails to demonstrate its effectiveness during clinical trials or its risk-benefit profile is not promising enough to justify further development.

Various studies have been conducted investigating the probability of technical failure in drug development, all with similar results. Table 5.1 shows the probability that a drug candidate fails to reach the point of final drug approval when entering the indicated process stages. The chance that a product, which enters the stage of pre-clinical trials fails before final regulatory approval is therefore between 89.7% and 91.7%. After this point the risk of technical failure decreases as research activities continue. When the drug sponsor finally applies for regulatory approval at the end of the development process, there is still a remaining risk of about 9% that the drug candidate fails to meet all necessary requirements to get approved.

	CMR International[262]	VFA[263]	Bain & Company[264]
Pre-clinical Test	89.7%	91.7%	91.7%
Clinical Phase I	81.6%	79.2%	75.0%
Clinical Phase II	71.9%	70.6%	63.0%
Clinical Phase III	34.2%	44.4%	28.6%
Approval Process	9.4%	9.1%	9.1%

Table 5.1: Expected failure risk entering different stages of drug development

5.1.2 Uncertain Market Entry Timing

In cases where a product does not fail from a technical perspective at some time during the R&D process there is still uncertainty about when the process will be completed and the new drug can be launched on the market. As shown in chapter 2.1, a new product has to go through five distinct phases of the pharmaceutical value chain after it has been patent protected and before it can be introduced to the market. These five stages of the pharmaceutical value chain do not have a predefined duration but can vary in length depending on a multitude of different factors.[265] The duration of the process stages is stochastic by nature and therefore the final date of market introduction is also a stochastic variable and can only be described "ex post". In addition the entire process can be delayed through additional requirements imposed onto the drug developing company by regulatory authorities before final approval is granted.

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[261] Villinger and Bogdan (2005) discuss the different reasons for project failure and investigate their relevance for pharmaceutical drug development valuation.

[262] Source: PAREXEL (2003, p. 184)

[263] Source: FDA (2004, p. 5)

[264] Source: PAREXEL (2003, p. 170)

[265] For detailed studies on drug development speed see PAREXEL (2003, p. 170) where multiple studies on various aspects of drug development times are summarized.

The uncertainty related to market entry timing is of high importance to all drug developing companies because it has a significant impact on the value of a drug development project. This is caused by the relatively early point of patent protection in the value chain and the direct link between market entry timing and effective patent protection period. This relationship is described in more detail in the following section on uncertain product lifetime. Table 2.1 shows the results of various studies regarding the duration of the different stages in the pharmaceutical value chain.

5.1.3 Uncertain Product Lifetime

As shown in the previous section, the point of final drug approval is related to uncertainty. In the pharmaceutical and biotechnological industry this uncertainty has a direct impact on the lifetime of a product. This is related to patent protection issues and the rapid capturing of market share by generic drug companies as soon as the status of patent protection expires.[266]

In the US and Germany, patent protection on new drugs is granted for a period of 20 years. The application for patent protection status is generally filed around the time a product enters pre-clinical trials. Therefore the 20-year protection period can be divided into two separate periods. The first period is represented by the time between when a company files for patent protection and the time of market introduction. The second period is represented by the time following market introduction until the patent expires after its 20-year protection period. Since a company is only able to generate revenues during the second time period it is also referred to as the "effective" patent protection period. Lanjouw (1998, p. 695) shows in his study that patent protection status is extremely valuable in the pharmaceutical industry if a product turns out to be successful and reaches the second time period where actual product sales take place.[267] Figure 5.2 shows the relationship between the general patent protection period and the effective patent protection time.

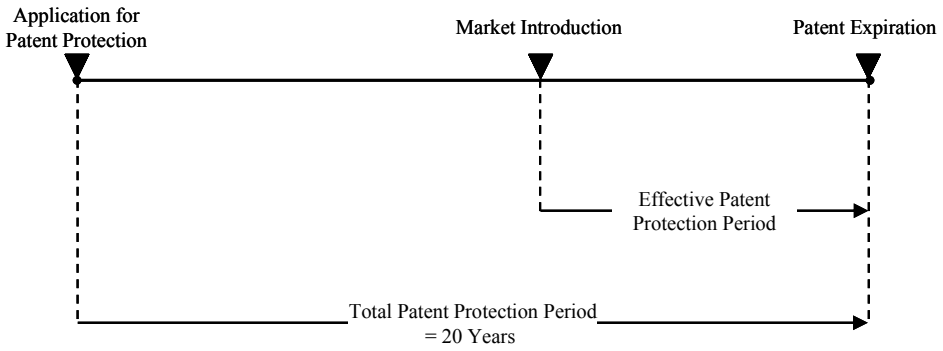

Figure 5.2: Effective patent protection period timeline

[266] A very comprehensive work about the value of patent rights can be found at Reitzig (2002).

[267] This situation is different in other industries. In the computer industry for example over half the patents become worthless within ten years of their application according to Lanjouw (1998, p. 672).

A distinction between the regular and effective patent protection period is essential because it is only the effective patent protection period companies have available to generate revenues necessary to cover their research and development cost and generate a sufficient return for their investors.[268] BPI (2003b, p. 15) states that it is not unusual for pharmaceutical companies to operate with an effective patent protection period of less than ten years. Based on the standardized R&D process of Table 2.1, the average effective patent protection period is as low as nine years. In the US as well as in Germany there is a possibility to further extend patent protection by applying for a so-called Supplementary Protection Certificate (SPC). In the US the SPC can extend the effective patent protection period to a maximum of 14 years[269] while it can extend it to 15 years[270] in Germany[271].

The main reason making effective patent protection such an important issue for drug developing companies is the increasing market pressure from generic drug manufacturers[272]. In some cases big pharmaceutical companies are trying to delay the market entry of generic competition with complex and costly lawsuits to extend their effective patent protection period but only with limited success.[273] This opportunity to use legal actions to extend the effective patent protection period of a product is not considered in this study. The comments in this section show that there is a direct relationship between market entry timing and the effective patent protection period of a new drug and therefore this relationship will be modeled in the quantitative analysis later on in this study.

5.1.4 General Market Uncertainty

The fourth type of uncertainty related to a new drug development can be labeled market uncertainty and can be split into two dimensions. The first dimension is the uncertainty related to the environment companies operate in. The second one can be described as the general uncertainty about the future market potential of a new drug in terms of volumes, prices and cost. The environmental risk is mostly determined by laws and governmental restrictions that affect the entire industry. Exemplary factors are safety regulations for dealing with biologically active agents, tax treatment of R&D cost, general tax laws,

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[268] On effective patent protection times and the benefits of speeding up the drug development process see DiMasi (2002).

[269] More details on potential patent protection extensions and the effect of the Wayman-Hatch Act in the US can be found at Grabowski and Vernon (2000b).

[270] The duration of the SPC may thereby not exceed a term of five years Screen and Jones (2002, p. 5).

[271] Grabowski and Vernon (2000b, p. 109) found in a study of 126 drugs introduced between 1990-1995 that on average an extension of the patent protection period of three years has been granted.

[272] As an example, Baumann and Salz (2002, p. 74) state that every single day of additional effective patent protection period for Prilosec® represents a profit of ~US$7 million for its manufacturer AstraZeneca.

[273] See also Baumann and Salz (2002), Handelsblatt (2002b), Handelsblatt (2002c), Sleegers (2005) or Hofmann (2005a).

availability of public grants, the educational system to ensure availability of skilled research personnel and multiple other factors.

Although new drug developments have in certain cases a quasi-monopolistic position that allows for maximum pricing flexibility and high profits, there are certain risk factors with a potentially negative impact on the profitability of a company. The most relevant market forces in this context are price control mechanisms imposed by public authorities. In addition there is also a certain degree of uncertainty related to sales volumes and the ability of a company's sales force to penetrate the market with an innovative product. Market uncertainty can be summarized as the inability of a company to precisely predict profit generation with its drug innovations. Grabowski and Vernon (2000a, p. 31) state that "even very large firms with sizeable portfolios of R&D projects are subject to substantial volatility in the sales performance of their new drug introductions" and are therefore exposed to market uncertainty.

5.1.5 Competition

In addition, there is uncertainty related to the fact that patents can only protect a company against direct competition. A patent does grant the owner the right to exclusively market and sell a specific drug but it does not grant the right to exclusively serve a specific market. In reality a company can have a patent on a drug to treat a specific disease but at the same time it can face competition from substitute products targeting the same medical indication despite an existing patent protection status.

This can best be illustrated using a real life example. When Pfizer was granted approval for its innovative drug Viagra®, it received the right to exclusively produce and sell a product, which consists of a certain chemical compound and treats erectile dysfunctions. At the same time this patent did not give Pfizer the exclusive right to treat the indication of erectile dysfunctions. Since this proved to be an attractive market it did not take long until GlaxoSmithKline entered this market with the competing product Levitra® and Eli Lilly with its product Cialis®. These products treat the condition in a different way and are based on different chemical substances therefore they did not violate Pfizer's Viagra® patents. Although these products are not directly violating Pfizer's patent rights they do compete in the same therapeutic area. If the patent for Viagra® was exclusive for the therapeutic area, no other company could enter this market. Since this is not the case and patents do not grant exclusivity within a therapeutic area there is always the risk that competitors will enter the market and seize market shares from the initial innovator.

5.2 Classification of Risk Categories

For the purpose of this study it is important to determine which risk factors in drug development are relevant for the valuation of a research project as the underlying asset of a R&D option. In general, real life investors can be considered being risk-averse according to

Brigham et al. (1999, p. 168) and therefore they require a compensation for the risk they expose themselves to. In contrast to this opinion Loch and Bode-Greuel (2001) assume that large diversified companies are risk-neutral when making an individual investment[274]. Although their work directly targets the drug developing industry their point of view is rejected for the purpose of this study. Considering large pharmaceutical companies as risk-neutral implies that there is no risk these companies expect compensation for, which is not a realistic assumption in a real life setting. Although these companies can be considered as being well diversified within their industry there is still a valuation relevant risk these companies are exposed to as described in the following paragraphs.

To which extent investors require additional compensation depends on their individual willingness to tolerate risk and the extent to which they can eliminate some risks through diversification over multiple investments. Considering the opportunity to reduce some risk through diversification reveals that not all risk categories are relevant for every investor to the same extent and excessive adjustments can lead to inappropriate estimates regarding the financing potential of a R&D option[275]. To determine valuation relevant risk factors they are classified into two main categories frequently used in quantitative analysis. Following Brealey and Myers (2000) risk factors can be divided into market risk factors and unique risk factors. They define unique or private risk[276] as a risk that can be diversified and market or shared risk[277] as a risk that is not diversifiable. The key difference between these two types of risk is the way they are considered in quantitative analysis. In situations where market participants have the opportunity to diversify unique risk it has an assigned value of zero and investors do not require a premium for being exposed to it. Since market or shared risk on the other hand cannot be diversified, all market participants are exposed to it and always require an appropriate compensation.

Hommel et al. (2001, p. 263) consider the risk related to regulatory and political uncertainty as market risk all industry players are exposed to and therefore it cannot be diversified. Even very large companies holding extensive research portfolios are exposed to this type of risk. Since this risk cannot be avoided, every market player expects to be compensated for it. Specific incidents that fall into this risk category are changes in tax laws affecting the treatment of R&D expenses, mandatory drug rebates for health care organizations or the introduction of a general drug sales tax on all products.

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[274] "A large company […] is typically risk-neutral, as the projects under discussion are small relative to the company's business" Loch and Bode-Greuel (2001).

[275] This is confirmed by Hodder and Riggs (1985, p. 135) who investigate the value of research projects itself and conclude that "key is that these risks are likely to be highly diversifiable. Failure to recognize this fact represents a systematic bias against R&D projects".

[276] Sometimes also referred to as diversifiable, company-specific or unsystematic risk according to Brigham et al. (1999, p. 178).

[277] Sometimes also referred to as nondiversifiable, systematic or beta risk according to Brigham et al. (1999, p. 178).

As opposed to this general market risk, all other introduced sources of risk in drug development can be considered private by nature and specific to an individual project. The first risk to be mentioned in this category is the risk of potential project failure before the drug development process is completed. This technical risk is only related to the individual project itself and is independent from the technical risk of other projects. With this in mind it can be considered a private and therefore a diversifiable risk factor.

The same holds true for the risk of substitute products entering the target market of a drug under development. If the situation occurs that a competitor enters the target market of a drug under development with a substitute product it only affects this one individual project of a research conducting company. All other projects where products for other indications and therefore for other target markets are developed are not affected by this market entry. This demonstrates that the risk of competition of substitute products represents a private risk factor that can be reduced by building large research portfolios.

In his study, Boer (2002, p. 215) qualitatively investigates pharmaceutical research projects as real options and confirms that technical failure risk and the risk of competitive products entering the market represent private risk factors, which can be diversified over multiple research projects. This point of view can be shared if one follows the definition for private risk given at Brigham et al. (1999, p. 178). They consider all events as private by nature that "are unique to a particular firm", which is the case for the potential technical failure of a drug project and also for the potential entry of competitors threatening the economic success of an individual project.

Private risk in drug development is not limited to failure risk and the risk of competitive products. The uncertainty related to the unknown duration of a drug development project and therefore the related uncertain product lifetime also fall into this category. How long it takes to complete the R&D process of a new drug is specific to an individual project and therefore the risk related to a potential delay falls under the definition of a private risk factor. With the lifetime of a product being directly related to the day of final drug approval the uncertainty in a product's lifetime also represents private risk. Reason for this is the direct relation between final drug approval and effective patent protection period representing the lifetime of a product[278]. Knowing that the uncertainty related to the date of final drug approval represents private and diversifiable risk it can be concluded that the risk related to an unknown effective patent protection period also represents private risk.

Figure 5.3 visualizes the classification of the various risk factors involved in drug development.

[278] Under the assumption that generic competition takes over the entire market immediately at the point of patent expiration.

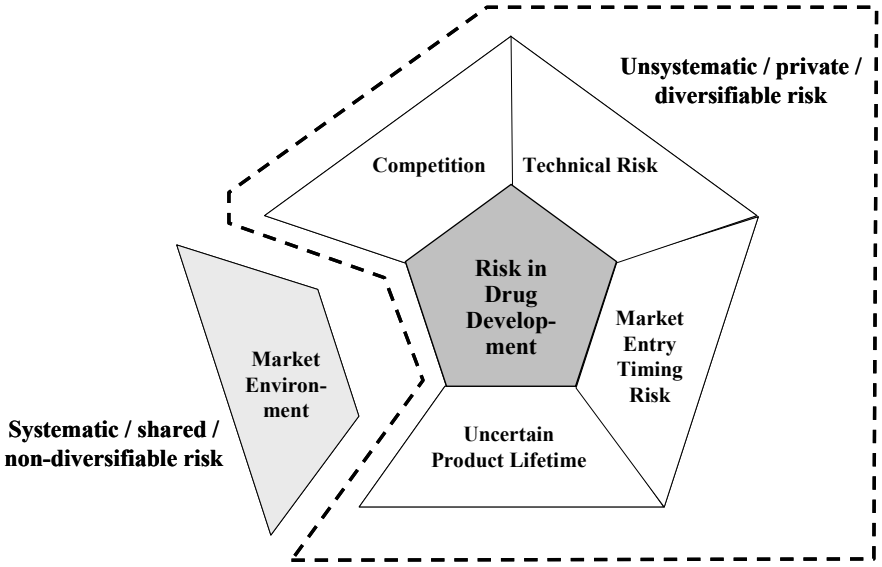

Figure 5.3: Classification of five main risk dimensions in drug development

All risk-averse investors expect a compensation for the exposure to market risk because irrespective of size and composition of their research portfolios of different drug development projects it cannot be diversified[279]. For this reason an appropriate valuation approach considers an expected return equivalent to the risk-free rate of return plus a premium compensating investors for the non-diversifiable risk of general market uncertainty. This explicit consideration of a market risk premium applies to every investor who operates within the drug development industry. The consideration of private risk factors in a valuation model is different from the risk category of market risk because they do not apply to all investors to the same extent.

For the remaining private risk factors not all investors require an additional premium because of their different possibilities to diversify risk. A fully diversified investor[280] with a large research and development portfolio consisting of a wide variety of different drug development projects does not require an additional premium for the exposure to private risk factors. The situation is different for smaller, less diversified companies that are exposed to different levels of private risk. These companies expect a risk premium equivalent to the amount of private risk they are not able to diversify within their research portfolios.

Amram and Kulatilaka (1999, p. 56) confirm this view and state that in cases where not all private risk is diversified, it has to be included explicitly in quantitative valuation approaches. As opposed to market risk where factors for an appropriate risk premium can be inferred

[279] Diversification effects could be observed if a drug developing company started research activities in other industries but within this study, such theoretical opportunity is not investigated. Maximum diversification in the context of this study is defined as total diversification within the industry but not within the entire economy.

[280] Fully diversified in this context refers to being fully diversified within the industry and not across the entire economy.

from public data, the consideration of private risk has to be based on personal experience and historical observations. A natural consequence of this lack of public data sources is the higher subjectivity related to the valuation of private risk compared to the valuation of market risk.

5.3 Concept of Corporate Financing using R&D Options

Chapter 4 describes the problems young biotech companies experience when attempting to raise funds through traditional ways of financing. The main reasons for these financing problems are their lack of stable cash flows and that their most valuable assets are intangible by nature. These intangible assets do have a value to the research conducting company[281] therefore an alternative way of financing could be the attempt to transform these intangible assets into cash flows. Since selling these assets is generally not a desired alternative, a different approach to unlock the value of these intangible assets for financing purposes could be by selling option rights on the outcome of the related R&D projects. This chapter describes how such a concept could be structured, which assumptions are made and describes the theoretical advantages and disadvantages of its implementation from the perspective of the company selling the option as well as from the perspective of a potential buyer.

5.3.1 Description of R&D Option Financing Approach

The approach of selling a R&D option is conceptually similar to selling a basic financial call option. The difference between these two types of options is their underlying asset. While a basic financial call option is written on stocks or other financial instruments, the R&D option is written on a drug development project with its potential outcome being the underlying asset. Since the compounds investigated in the drug development process are generally patent protected after the base research phase, these patents and all related rights represent the potential underlying asset of a R&D option for the purpose of this discussion.

In the R&D option deal, a research conducting company grants another company or investor at time t_1 the right to acquire the unlimited, exclusive and royalty-free rights on a product under development at time t_2 for a predetermined price X. In return, the investor purchasing the option pays an amount C to the selling company as the option premium at time t_1. At t_2, the buyer of the R&D option has the right to take over the results of the research project including all potential future cash flows resulting from it. If the buyer exercises this right, the research conducting company receives the amount X in exchange for the research project. Figure 5.4 summarizes the main characteristics of such a R&D option deal.

[281] Compare to Kester (1984, p. 160)

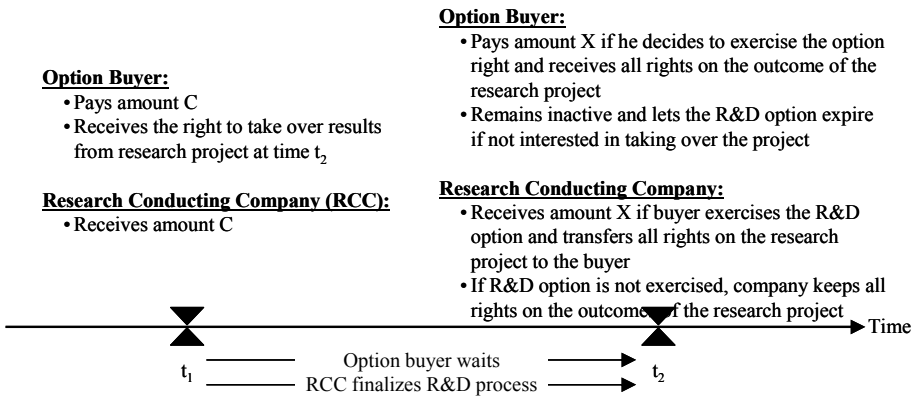

Figure 5.4: Concept timing of a R&D option deal

5.3.2 Framework Assumptions

For this study, certain assumptions are made to better define the R&D option and to reduce complexity later in this study. This becomes necessary because a R&D option represents an individual, non-standardized contract between two parties, which can be constructed in a variety of ways making it difficult to derive general conclusions.

The first assumption is related to the value chain as described in chapter 2. In reality, promising substances found in the phase of base research are patent protected after their potential has been identified and before they enter the phase of pre-clinical trials. For the purpose of this study it is assumed that the application for patent protection occurs exactly at the time a project has completed base research and enters the phase of pre-clinical trials.

The second assumption is related to the initiation time t_1 of a R&D option deal. At this point the limitation is introduced that the time of patent protection represents the first possible time a R&D option can be sold to another company or investor. This is a reasonable assumption since patent protection legally secures technical "know-how" and turns an intangible asset with an unascertainable life[282] into an intangible asset with an ascertainable life.[283] Especially in the environment of drug development, patents are the basis for value generation.[284] The main reason for this assumption is the fact that before patent protection there is no formalized intangible asset that can serve as the underlying asset for a R&D option deal. It also eliminates the necessity to investigate potential patent races between multiple competitors doing research on the same compound.[285] To reduce complexity during the formalization of the R&D option valuation problem later in this study, all times denoted as t in this study are measured against the time of patent protection with t = 0.

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[282] Referred to as "Goodwill" in balance sheet analysis.

[283] Detailed definitions and examples of intangible assets with an unascertainable or ascertainable life can be found at Vaughan (1972, p. 128).

[284] On the importance of patent protection in the pharmaceutical industry see Boer (1999, p. 354).

[285] For a detailed discussion on competition in R&D before patent protection see Weeds (2002).

The third assumption is related to the exercise date t_2. As opposed to most financial options where the maturity date is a fixed calendar date, t_2 in this study is fixed relative to the value chain. The time t_2 is defined as the time the development process is completed and approval is granted or refused for a new drug. Exercising the option is only possible at time t_2. With this assumption the R&D option can be described as a European type call option with an uncertain time to maturity. This is in line with most publications treating development projects as real options and considering them as being European style[286]. The exercise decision at time t_2 is assumed to be a fully rational decision. This implies that an investor always exercises the option if the value of the underlying project exceeds the exercise price at the expiration date of the option. For all cases where the value of the project is below the exercise price, the option expires unexercised. By assuming rational behavior, individual cases can be avoided where investors pursue strategies although rational behavior would suggest the contrary.[287] Figure 5.5 shows the timeline of a typical drug development project relative to the time of patent application, which is defined as t=0.

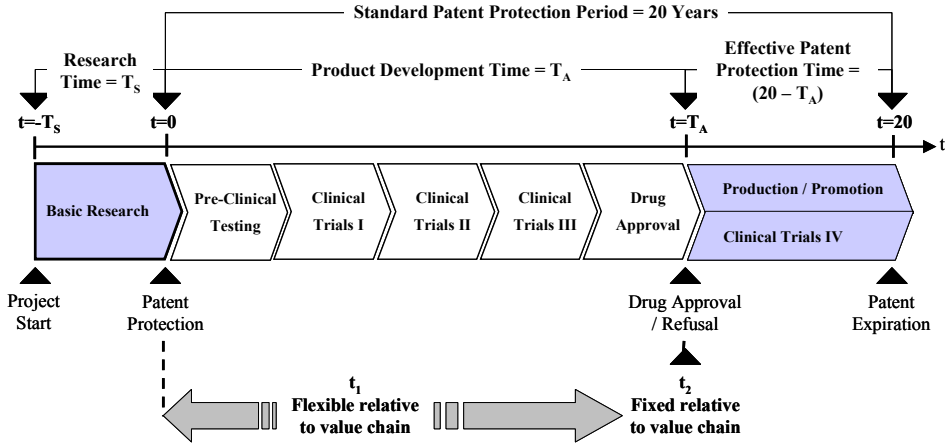

Figure 5.5: Drug development timeline relative to patent protection

With:

T_S : Time to complete base research until a discovery can be patent protected

$t = -T_S$: Start of the drug development project relative to patent application

$t = 0$: Time of patent application

T_A : Time period until a drug is approved or refused by regulatory authorities

$t = T_A$: Time of final drug approval relative to the point of patent application

t_1 : Deal initiation date relative to patent application with $t_1 \in D_{t1}$, $D_{t1}=[0;T_A[$

$t_2 = T_A$: Expiration date of a R&D option

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[286] As an example see Pennings and Lint (1997, p. 84).

[287] For a discussion of this issue of non-rational behavior see Zardkoohi (2004).

In addition to the assumptions above it is critical to discuss the distribution of information between the research conducting company and the buyer of the R&D option. It is obvious that the research conducting company has superior information about progress and prospects of a project and therefore the assumption is made that all information is shared in preparation for and during a R&D option deal. It is described above that a detailed investigation on asymmetric information issues represents an independent study in itself and therefore this assumption is made for the purpose of this study.

In addition it is assumed that the research conducting company continues its R&D activities based on rational evaluations after selling an option as it would do without selling it. For the buying side this assumption of rational behavior means that it does not interact with the research conducting company while it holds the option. Without interactions the buyer does not influence the decision to discontinue the project and only decides about exercising the option at the point of final drug approval.

There is an important additional definition to be introduced at this point. If the term fund raising or financing potential is used during the course of this study it exclusively refers to the cash inflow that is generated at t_1 that supports ongoing research activities until regulatory approval. If on the other hand the term total fund raising or total financing potential is used, the term refers to the total cash inflow a company can expect from a R&D option deal. This total fund raising or total financing potential therefore consists of the initial cash inflow C at time t_1 plus the potential cash inflow X at t_2, which is only relevant if the option is exercised.

5.3.3 Concept Advantages and Disadvantages

To describe advantages and disadvantages of a R&D option it is necessary to recall the financing requirements of an average development project. These requirements have shown that the drug development process can be divided into two parts.

Part one lasts from the initiation of a project until the date a new drug is approved. This part is characterized by cash outflows to finance expenditures during base research, pre-clinical testing, the different phases of clinical trials and the drug approval process itself. Since product sales cannot start until a drug is approved there are no corresponding cash inflows during this part of the project resulting in a maximum financing need at the time of approval. After drug approval, part two of a project starts with the generation of cash inflows resulting from product sales. These cash inflows reduce the total net financing need of a project. Eventually the cumulated cash inflows exceed the maximum net financing need resulting in the break-even of the project. After break-even the project generates excess funds that can be used to finance other projects or can be distributed among owners of the company.

Once a drug receives final approval from regulatory authorities there is a theoretically unlimited upward potential to create funds in excess of the maximum net financing need. In reality this upward potential is limited by factors like market size, remaining patent protection period, pricing restrictions and the presence of competitive products in the market. The following sections build on the simplified net financial performance of an average drug development project as shown in Figure 2.8.

5.3.3.1 Seller's Point of View

When a company enters a R&D option deal the net financing profile changes compared to the traditional profile visualized in Figure 2.8. The constant cash outflows resulting from base research, pre-clinical testing, the different phases of clinical trials and the drug approval process are subsidized by a cash inflow equivalent to the option premium C at time t_1.

Assuming that the R&D option is exercised, the second major change in the financing profile is related to the cash inflow during final drug approval. Instead of a long period of cash inflows that are expected to exceed the maximum financing requirements at some time in the future, there is only one additional cash flow. This cash flow of size X occurs at time t_2 when the option owner decides to exercise his option. The resulting simplified cumulated cash flow profile is illustrated in Figure 5.6.

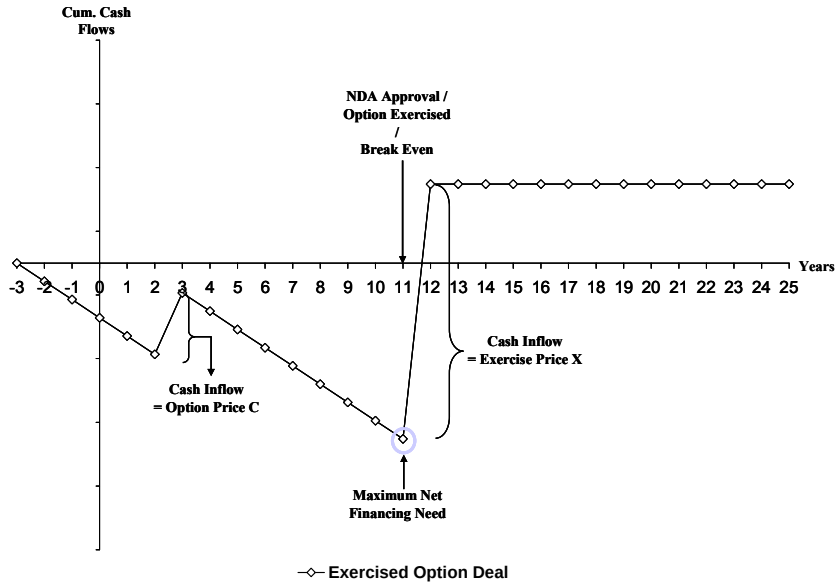

Figure 5.6: Cumulated cash flows of a R&D option deal - seller's view (exercised)

Entering a R&D option deal as a method of raising funds has multiple theoretical advantages and disadvantages for the seller of the research option.

Advantages

One advantage for the seller of the R&D option is related to the time cash flows are generated. With a R&D option the research conducting company receives its first cash inflow already at time t_1 when it enters into the option agreement. At this point it receives the option premium C from the buyer of the option. This anticipated cash flow reduces the maximum financing need because the amount C can immediately be used to reduce its financial obligations from early cash outflows.

Another advantage for the seller of the option is a reduced uncertainty about future cash flows. After a research conducting company enters into a R&D option deal it knows exactly that it is going to receive the contractually fixed amount X if the project is successful and the option owner exercises his option right. Since the amount X is received at once the option seller also experiences the advantage of an anticipated break-even resulting from an

immediate cost recovery at time t_2. In case the option premium C and the agreed exercise price X exceed the total financing need, the seller of the option immediately breaks even at time t_2 when the option is exercised. In this way profits can be generated earlier as in a traditional project where break even does not occur until a product has been sold in the market for an extended period of time.[288]

In addition to the points mentioned, a young biotechnology company gains another advantage by selling a R&D option. Large pharmaceutical companies with extensive research portfolios are likely to associate a higher value with a project under development than the research conducting company does internally. This is a result of potential risk diversification[289] opportunities on the side of the large company resulting in the willingness to invest more in the R&D option than the research conducting company would itself. Through this effect the research conducting company can indirectly participate in the risk diversification opportunities of the option buyer.[290]

In contrast to other financing methods, raising funds by selling R&D options has the advantage that there is no transfer of company ownership involved in the transaction. In way the company selling the option can take full advantage of all other corporate activities and claim their future outcomes and profits to their full extent, which is especially relevant for fast growing companies with a broad research pipeline. This characteristic appears to appeal to companies that experience a short-term financing need due to multiple promising ongoing projects that require immediate funding. Anticipating cash inflows with the use of option sales can potentially generate the funds necessary to keep a company going without a transfer of ownership. The resulting corporate independence is desired by most owners of small dynamic companies but is generally hard to achieve with traditional financing methods[291].

In addition to the anticipation of cash flows it also has to be noted that the end of an entire project is anticipated for the company selling the option in the event that the owner exercises the option. If the option is exercised by the owner the project is finalized for the seller before large-scale production starts. This eliminates the need for the research conducting company to set up large-scale production facilities and build up the related production, marketing and distribution expertise.

Disadvantages

The opposite holds true in cases where the option owner does not exercise his option right and the research conducting company continues to own all project related rights beyond the

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[288] Grabowski and Vernon (2000b, p. 100) found that it takes 16 years for an average drug to break even. On one hand this period is much shorter for Blockbuster drugs while drugs with below average sales rates might never recoup their investment.

[289] For the difference between diversifiable and non-diversifiable risk factors refer to chapter 5.2.

[290] The ability of some buyers to reduce risk through diversification is discussed in chapter 7.2.1.

[291] See chapter 4 for more details on corporate financing methods.

point of drug approval. In this case the company does not receive the exercise price X of the option but has the opportunity to market the approved drug itself[292]. Whether this can be considered an advantage or a disadvantage depends on the future sales potential of the approved drug as shown in Figure 5.7. One characteristic that represents a disadvantage if the option is not exercised is the fact that the research conducting company has to build production, marketing and distribution capabilities to sell a product in the marketplace if the project cannot be sold to a third party. Alternatively the product can be brought to market through a co-marketing arrangement with another party not involved in the R&D option deal.

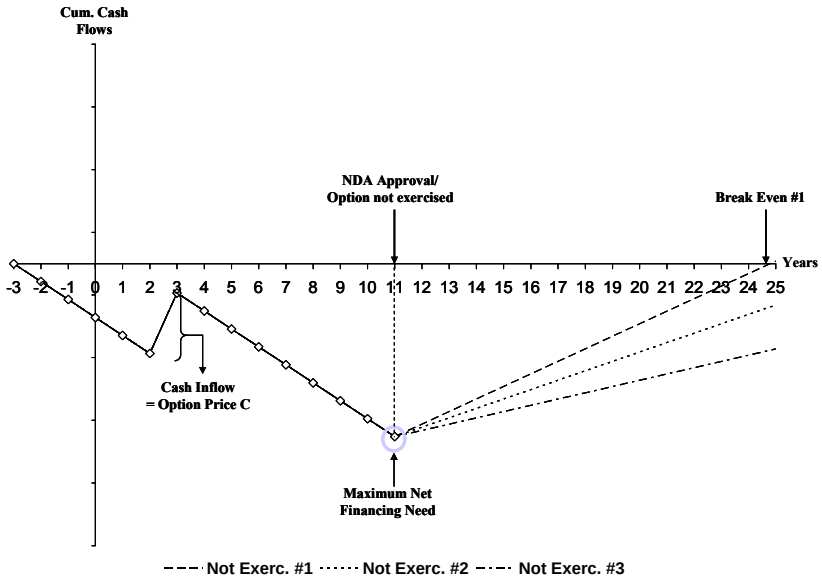

Figure 5.7: Cumulated cash flows of a R&D option deal - seller's view (expired)

While entering a R&D option deal has several theoretical advantages for the research conducting company it has also negative characteristics that need to be considered. The main disadvantage arises from the fact that the option right can be exercised at a contractually fixed price X. A fixed exercise price allows the owner of the option to take over a project irrespective of the real value of the project at the time of approval, therefore limiting the maximum benefit a research conducting company can achieve. While the option deal deprives the option writer of a potential upside he receives the premium C as an anticipated compensation for this characteristic at time t_1.

Another disadvantage is the loss of know-how related to exercising a R&D option. Once exercised, the research conducting company misses out on the opportunity to develop additional applications from the innovation or expand it into new therapeutic areas. This elimination of future options to grow from a project is hard to quantify in early stages of a project but has to be considered when quantifying a R&D option deal.

[292] Alternatively the entire project can be sold to a third party.

5.3.3.2 Buyers Point of View

While a R&D option deal has favorable characteristics for the research conducting company as shown above it also has advantages for the company acquiring the option. To enter this discussion, Figure 5.8 shows the cumulated cash flow position from the perspective of the option owner in case the option right is exercised.

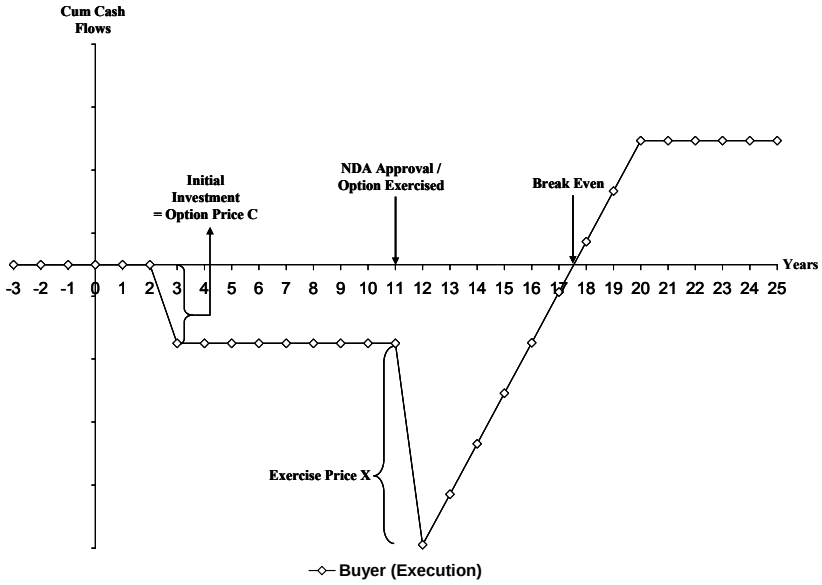

Figure 5.8: Cumulated cash flows of a R&D option deal - buyer's view (exercised)

Advantages

The main advantage is that a company can secure access to innovations and new products without internally maintaining the related R&D organization, which resides with the company selling the option. By holding an option the owner can receive full access to an innovation of the research conducting company if the agreed amount X is paid. To acquire this right the option premium is paid to the research conducting company at an earlier date t_1. This amount C represents the maximum financial risk taken over by the option owner in case of project failure therefore increasing the accuracy of cash flow planning. Additional planning security arises from the fact that the option owner knows in advance the cost related to taking over the project once it is approved and a product is ready to be introduced into the market. It is known at time t_1 when the option contract is finalized what additional amount X it costs to acquire all rights to the project if it proves successful.

Securing access to a new innovation by acquiring an option right requires a smaller initial investment than conducting the project internally[293]. Therefore a company can spread a fixed budget over multiple projects and an R&D project portfolio can be set up. By building an

[293] "The cost of an option on an asset is small, relative to the cost of purchasing the asset. Thus, with the same resources to spend, more opportunities can be explored using options", McGrath and Nerkar (2004, p. 3).

R&D project portfolio a company can reduce its exposure to private risk[294], which is impossible for small companies because of the capital intensiveness of drug development. The large capital requirements generally allow young companies to focus only on one or a few projects without the opportunity to diversify private risk.

The ability to spread a fixed budget over multiple projects appears beneficial for large pharmaceutical companies in their search for blockbuster drugs. It allows them to secure rights on a larger number of drug candidates, in turn strengthening their development pipelines.[295] With more candidates in the pipeline the probability increases to own access rights on a project that turns out to be a blockbuster. Currently, pharmaceutical companies are endeavoring to strengthen their product pipelines through acquisitions[296] requiring significant financial resources or through licensing agreements.

By owning access rights to a project while leaving research activities to the option seller also allows the buying company to benefit from the more flexible working environment and the resulting shorter development times of smaller companies.[297]

Disadvantages

As for the writer of a R&D option there are also disadvantages for the buyer compared to an internal drug development approach. When acquiring an option the buyer decides to leave research activities with the option writer resulting in reduced control over structure and progress of these R&D activities.[298] In addition, a company acquiring multiple options instead of conducting projects in-house misses out on the opportunity to realize synergy effects between individual projects. Synergies can exist in the form of a more efficient deployment of resources or better asset utilization.

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[294] Private or "non-market" risk represents the risk that is unique for a specific project and cannot be replicated by securities traded at security markets. This is opposed to market risk, which is the risk related to the market environment. All companies in a market face this kind of risk and it cannot be diversified. Since the different stages of drug development are related to a high risk of technical failure related to exactly one specific project, this risk is private by nature and cannot be replicated in the capital market. This ability of management to diversify some risk components is one of the most common pitfalls when evaluating risky projects according to Hodder and Riggs (1985, p. 129).

[295] On the importance of creating research portfolios and the project selection process see Sharpe, Paul and Keelin (1998).

[296] Compare to Bowe and Dyer (2004)

[297] Quinn (1986) questions the existence of this phenomenon. He argues that unsuccessful projects are fully visible at large companies while a multitude of small, unsuccessful ventures remain unrecognized creating the impression that small companies are more effective innovators.

[298] This disadvantage can be limited through appropriate clauses in the legal option agreement allowing co-management under certain conditions.

	Advantages	Disadvantages
Seller: Research Conducting Company	• No transfer of ownership • Immediate cash generation • More predictable cash flows • Rapid cost recovery if exercised • No need to develop internal production/distribution • Long-term independence • Benefit from risk diversification opportunities of investor • Reduced total financing need	• Limited upside potential • Potential loss of know-how for subsequent products
Buyer: Large Pharmaceutical Company	• Assures access right to new developments without own R&D • Potential increase of drug pipeline • New products with limited upfront investment • Risk diversification by building option portfolios • Increasing probability to get access to Blockbuster product • Potentially faster drug development process	• Limited control over R&D process • Loss of potential synergies between individual projects

Table 5.2: Advantages and disadvantages of R&D option deal financing

6 Option Theory in the Valuation of Drug Development

Basic option theory stretches back to the first scientific discussions of Bachelier (1900) and Bronzin (1908) at the beginning of the last century. Since that time, numerous studies and publications have expanded financial option theory into other scientific areas. One reason for the increasing use of option valuation in other areas is the consensus that traditional valuation methods like net present value analysis are not appropriate to evaluate real life business decisions. These approaches do not consider management's flexibility to adapt strategies to changing market conditions[299]. Traditional models generally assume that once the decision on a strategy is made, it cannot be changed, which is clearly not a realistic assumption.[300] This "static" thinking can be avoided by applying option based valuation approaches.

Since the time researchers started applying option theory to real life problems, several industries are repeatedly being listed as being well suited for option thinking. According to Yeo and Qiu (2003, p. 250) these are mostly industries "where volatility and uncertainty is high and the need for flexibility is at its premium", like the oil and gas exploration industry[301], the mining industry[302], high tech R&D[303], the multimedia industry[304], real estate development[305], general manufacturing with flexible processes[306], pharmaceutical companies in general[307] and also the related individual drug development projects[308].

As for most of these industries, there is a general consensus that drug development represents a real option on future cash flows. This led to the development of a variety of studies trying to assign a value to ongoing drug development projects using some kind of adapted financial option valuation method. The following sections give a brief overview of selected financial

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[299] Hodder and Riggs (1985) criticize three main characteristics of the discounted cash flow method. First that it neglects the effect of inflation, second the different levels of uncertainty in different project phases and third the management's ability to mitigate risk.

[300] Valuable discussions demonstrating the advantages of option theory over traditional valuation methods and their application in real-life business strategy can be found at Kester (1984), Dixit and Pindyck (1995), Luehrman (1998a) or Luehrman (1998b).

[301] Compare to Paddock et al. (1988)

[302] Compare to Leslie and Michaels (1997)

[303] Compare to Copeland and Antikarov (2001, p. 301)

[304] Compare to Pennings and Lint (1997), Schwartz and Moon (2000) or Schwartz and Moon (2001)

[305] Compare to Titman (1985) or Quigg (1995)

[306] Compare to McDonald and Siegel (1985)

[307] Compare to Kellogg and Charnes (2000) or Bäcker and Hommel (2002)

[308] A general work on option theory and investments in research and development can be found at Greenberg (1992).

option valuation models[309] and how they are applied in scientific literature to evaluate drug development projects. This is done with the objective of assessing whether these valuation approaches can also be used to estimate the financing potential of the R&D option being the main focus of this study.

6.1 Tree Based Valuation Approaches

Binomial Trees

The main reason for the popularity of the binomial tree method in financial option theory is the fact that it is a very descriptive method avoiding the use of complex mathematical tools like statistical time series modeling or partial differential equations. Besides the advantage that they can be solved with basic mathematical procedures they are also valuable in modeling one-time occurrences like dividends or volatility changes[310].

Methodology

The fundamental approach of valuing options by using binomial trees received substantial attention since it was investigated by Cox et al. (1979). The intention of their work was to establish an option pricing approach that uses only basic mathematical principles instead of sophisticated mathematical tools. Instead of the assumption that stocks are traded continuously, they use a discrete time approach where option prices are only observable after specified periods of time[311].

In this approach new stock prices are determined by a simple stochastic process and can only result in one out of two specific occurrences after one time period. If a time period is related to an upward movement, the stock price S becomes uS and if it is related to a downward movement, it becomes dS. Upward movements occur with a probability q[312] while downward movements occur with a probability (1-q). To transfer this stock price movement into a valuation model Cox et al. (1979) use some of the same assumptions as Black and Scholes (1973):

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[309] This chapter is not intended to give a complete overview over all valuation techniques that exist in financial option theory but is limited to the ones that have been transferred to the valuation of pharmaceutical companies. Other approaches like the Finite Difference Method (FDM), which are established financial option valuation techniques, are not covered at this point because there are no known scientific studies applying them to pharmaceutical valuation problems. For a more complete overview on financial option theory one can refer to basic literature on financial options like Hull (2006). A detailed description of the mentioned Finite Difference Method and its applications can be found at Brennan and Schwartz (1977), Brennan and Schwartz (1978), Geske and Shastri (1985), Hull and White (1990) or Wilmott et al. (1993, p. 267).

[310] See Christoffersen et al. (2005)

[311] Leisen (1998) extend this approach by allowing time increments between occurences to be random instead of being of fixed length.

[312] $0 \leq q \leq 1$

- The risk-free interest rate is publicly available, is constant over time and is the same for all maturities.
- Markets are frictionless.
- Markets are complete.
- Markets are arbitrage free.
- With r being the risk-free rate of interest, the no-arbitrage assumption leads to the conclusion that $u>(1+r)>d$[313], otherwise arbitrage opportunities would exist.
- The underlying stock pays no dividends.
- The option represents a "European" type option.

The valuation approach builds on the main assumption that markets are free of arbitrage opportunities. Since it is possible in a complete market to duplicate the payoffs of every security by a portfolio of other securities, a portfolio of bonds and stocks is built to duplicate the payoff of a call option. By borrowing money (selling bonds) and buying a certain number of stocks for the proceeds it is possible to create a portfolio that duplicates the payoff a call option would generate at maturity. Thus, the price of the call option and the price of the portfolio containing a certain number of stock ΔS and the risk-free bond B have to be the same to eliminate arbitrage opportunities. The following section briefly summarizes the main valuation steps of Cox et al. (1979) for a one-period and for a multiple period scenario.

One period scenario[314]

In a one period scenario the value of the stock and therefore also the value of the call option C with exercise price X and the value of the portfolio can only take on two values as shown in Figure 6.1.

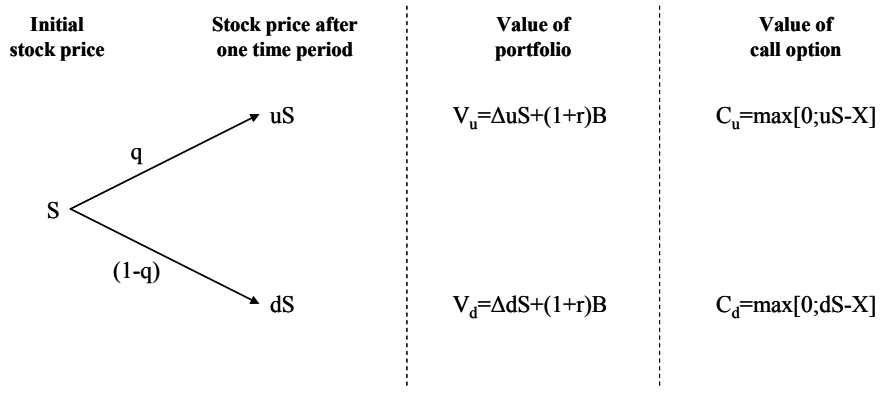

Figure 6.1: One period binomial option valuation model

[313] Compare Cox and Rubinstein (1985, p. 171)

[314] For a more detailed discussion of this scenario refer to Cox et al. (1979).

By selecting Δ and B in a way that the value V of the portfolio matches the value of the option at each of the two occurrences[315] and by knowing that today's price of the option C and the price of the portfolio ΔS+B have to be the same, it can be concluded that the value of the call today can be expressed as equation (6.1).

$$C = \frac{\left(\left(\frac{(1+r)-d}{u-d}\right)C_u + \left(\frac{u-(1+r)}{u-d}\right)C_d\right)}{(1+r)} \qquad (6.1)$$

To simplify this equation, a new parameter p is defined as (6.2).

$$p \equiv \frac{((1+r)-d)}{(u-d)} \qquad (6.2)$$

Substituting (6.2) in (6.1) simplifies the equation for the value of a call option to (6.3).

$$C = \frac{(pC_u + (1-p)C_d)}{(1+r)} \qquad (6.3)$$

Multiple n-period scenario

To more precisely specify a binomial tree model and to include a wider range of potential occurrences of the underlying asset, the number of decision points between the point of valuation and the expiration date can be increased. By doing so, the one period model is expanded into an n-period model. From a valuation standpoint the breakdown into an n-period model does not increase the mathematical complexity and can still be solved using the same basic algebra used to solve the one period example. The main advantage of the n-step tree model over the simple one-step model is the fact that for duplication purposes, cash-flows can be modeled more dynamically as opposed to the static one-step approach and can therefore consider a more comlex and changing valuation environment.

[315] Simply solving the two equations $C_u=\Delta uS+(1+r)B$ and $C_d=\Delta dS+(1+r)B$ results in

$\Delta = \frac{C_u - C_d}{(u-d)S}$ and $B = \frac{uC_d - dC_u}{(u-d)(1+r)}$.

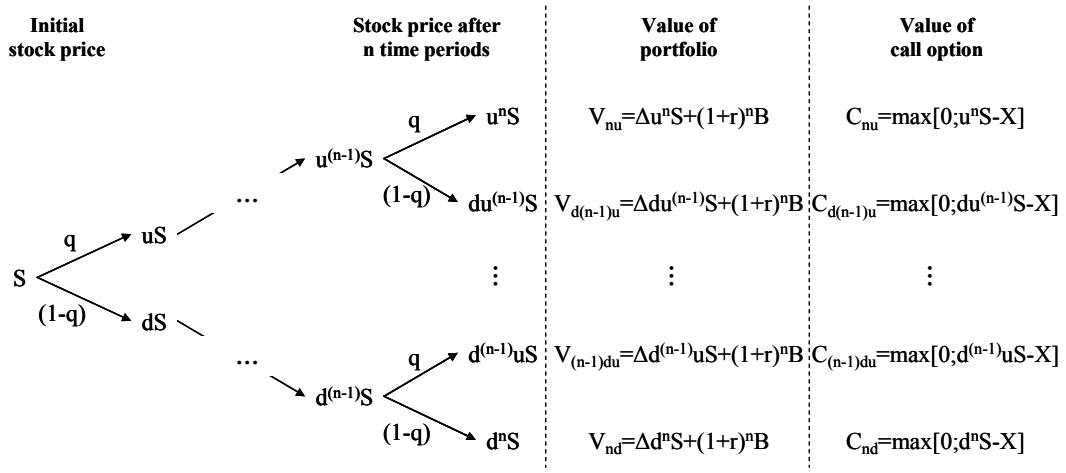

Figure 6.2: N-period binomial option valuation model

Following the same approach for the n-period model that is used to derive equation (6.1) involves solving a system of (n+1) equations and leads to the following valuation formula (6.4) for a European call option.

$$C = \frac{1}{(1+r)^n}\left[\sum_{j=0}^{n}\left(\frac{n!}{j!(n-j)!}\right)p^j(1-p)^{n-j}\max\left[0;u^j d^{n-j}S - X\right]\right] \qquad (6.4)$$

In order for MAX[0;$u^j d^{n-j}$S-X] to become greater zero, the term ($u^j d^{n-j}$S) has to exceed the exercise price X of the option. Since j represents the number of upward movements in the model this is the case if j exceeds a certain limit a. Knowing that $\left(u^j d^{n-j}S\right) \geq X$ for all $j \geq a$, (6.4) can be rewritten as equation (6.5).

$$C = \frac{1}{(1+r)^n}\left[\sum_{j=a}^{n}\left(\frac{n!}{j!(n-j)!}\right)p^j(1-p)^{n-j}\left[u^j d^{n-j}S - X\right]\right] \qquad (6.5)$$

With the binomial distribution function[316], a portion of (6.5) can be extracted and simplified using the complementary binomial distribution function (6.6).

$$\Phi[a;n;p] = \sum_{j=a}^{n}\frac{n!}{j!(n-j)!}p^j(1-p)^{n-j} \qquad (6.6)$$

Thus, equation (6.5) can be simplified into the following formula.

$$C = S\Phi[a;n;p'] - X(1+r)^{-n}\Phi[a;n;p] \qquad (6.7)$$

with

[316] Regular binomial distribution function: $F_B(k;n;p) = \sum_{i=0}^{k}\frac{n!}{i!(n-i)!}p^i q^{n-i}$

$$p = \frac{\left((1+r)-d\right)}{\left(u-d\right)},\ p' = \left(\frac{u}{(1+r)}\right)p$$

and parameter a being the smallest non-negative integer larger than

$$\frac{\log\left(\frac{X}{Sd^n}\right)}{\log\left(\frac{u}{d}\right)}$$

The above equation represents the pricing formula for a European call option on a non-dividend paying stock in an n-period binomial model.

Use in valuation of drug development projects

Shockley et al. (2003) use a binomial tree approach to evaluate an individual drug development project. They start their analysis by building a binomial tree model as if the project was completed irrespective of environmental influences. As a starting point they use the expected net present value $E(NPV_{launch})$ of the project at the time of product launch. This parameter is defined as the value of all cash flows expected from the final product during its lifetime discounted back to the point of drug approval.

Since the time of product launch occurs at some time in the future $E(NPV_{launch})$ is discounted back over the duration of the entire R&D process using a risk-adjusted corporate discount rate r_c to derive an expected net present value eNPV. If the project has i project stages and d_i represents the duration of one project stage, the resulting starting point for the analysis is calculated using equation (6.8).

$$eNPV = \frac{E\left(NPV_{launch}\right)}{\left(1+r_c\right)^{\sum_{t=1}^{i} d_t}} \qquad (6.8)$$

To include risk and uncertainty in their valuation they build a binomial tree to model the uncertainty related to the value of the project. Following a procedure described at Hull (2006, p. 394), they modify the initial value eNPV by assuming that it can change by a factor u or d during each stage of the R&D process. For the up- or downward movements of eNPV they define the jump probabilities u and d as follows using the volatility factor σ.

$$u = e^{\sigma\sqrt{t}} \qquad d = \frac{1}{u}$$

The resulting binomial tree, which is used at Shockley et al. (2003) to model the value development of the underlying project can therefore be represented as Figure 6.3.

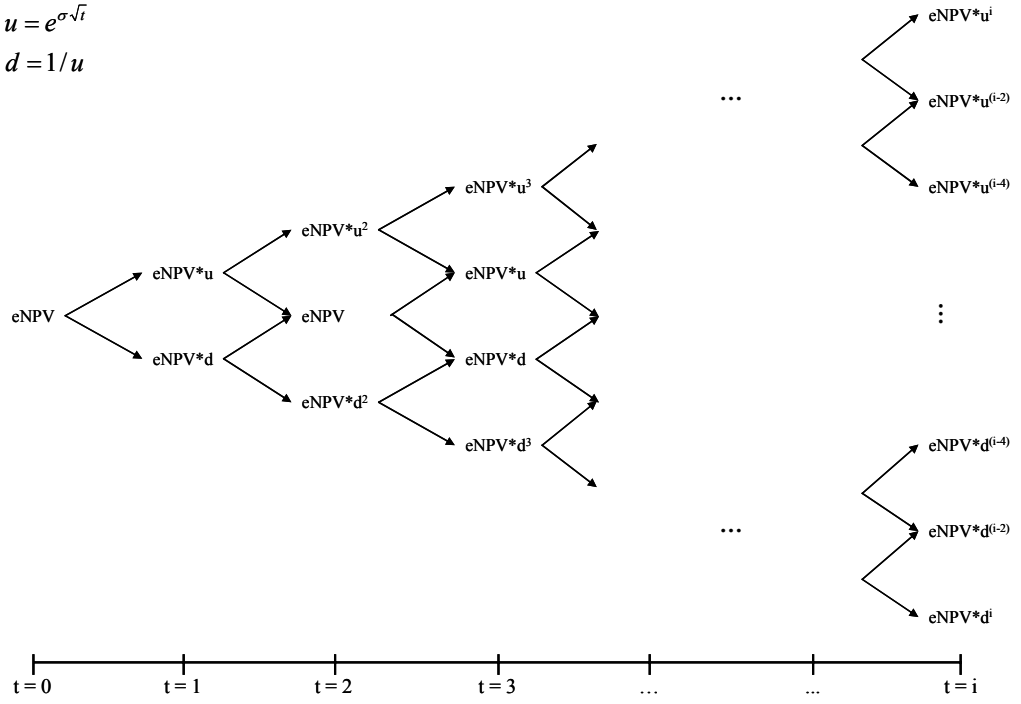

Figure 6.3: Binomial tree to evaluate drug development projects

To consider that a drug development project can economically fail during the research process they work backwards along the binomial tree to evaluate the project. The starting point for their valuation approach is the potential project launch after i time periods. Assuming rational behavior they conclude that an investment k_n to enter the next project stage n will only be invested if the project represents a positive value to the investor. This means that the expected value of the remainder of the project exceeds the required investment k_n. If this is not the case, the project will be abandoned without adding any value for the investor. At the point of final drug approval after i time periods and "a" upward movements in the binomial tree, the value V_{ia} of the project can therefore be written as (6.9).

$$V_{ia} = MAX\left[eNPVu^a d^{(i-a)} - k_i; 0\right] \qquad (6.9)^{317}$$

With equation (6.9), each node of the binomial tree at time i can receive an assigned value V_{ia} with a = 0, …, i. For all previous nodes the value of the project depends on the two scenarios that can potentially follow at the next time period. Both possible cases are weighted with their risk-neutral probabilities and then discounted back over the period under discussion using the risk-free interest rate before they are compared to the cost k necessary to conduct this project phase. The risk-neutral probability u_{rn} of an upward movement is calculated as follows:[318]

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[317] Since $d = \frac{1}{u}$ and therefore $d * u = 1$, the two factors u and d can partially offset each other.

[318] The subscript rn is used to emphasize that it represents the risk-neutral probability and not a subjective probability for an up- or downward movement along the binomial tree.

$$u_{rn} = \frac{\left(e^{rt} - d\right)}{(u-d)} = \frac{e^{\sigma\sqrt{t}+rt} - 1}{e^{2\sigma\sqrt{t}} - 1} \text{ and } d_{rn} = (1 - u_{rn})$$

With these risk-neutral probabilities u_{rn} and d_{rn} the value $V_{(i-1)a}$ of the project at the beginning of the period (i-1) with a=0, ..., (i-1) upward movements can be calculated using (6.10).

$$V_{(i-1)a} = MAX\left[\frac{u_{rn}V_{i(a+1)} + d_{rn}V_{i(a-1)}}{(1+r)} - k_{(i-1)};0\right] \qquad (6.10)$$

This methodology can be applied to all decision points of the binomial tree assigning a value to every node of the tree as shown in Figure 6.4.

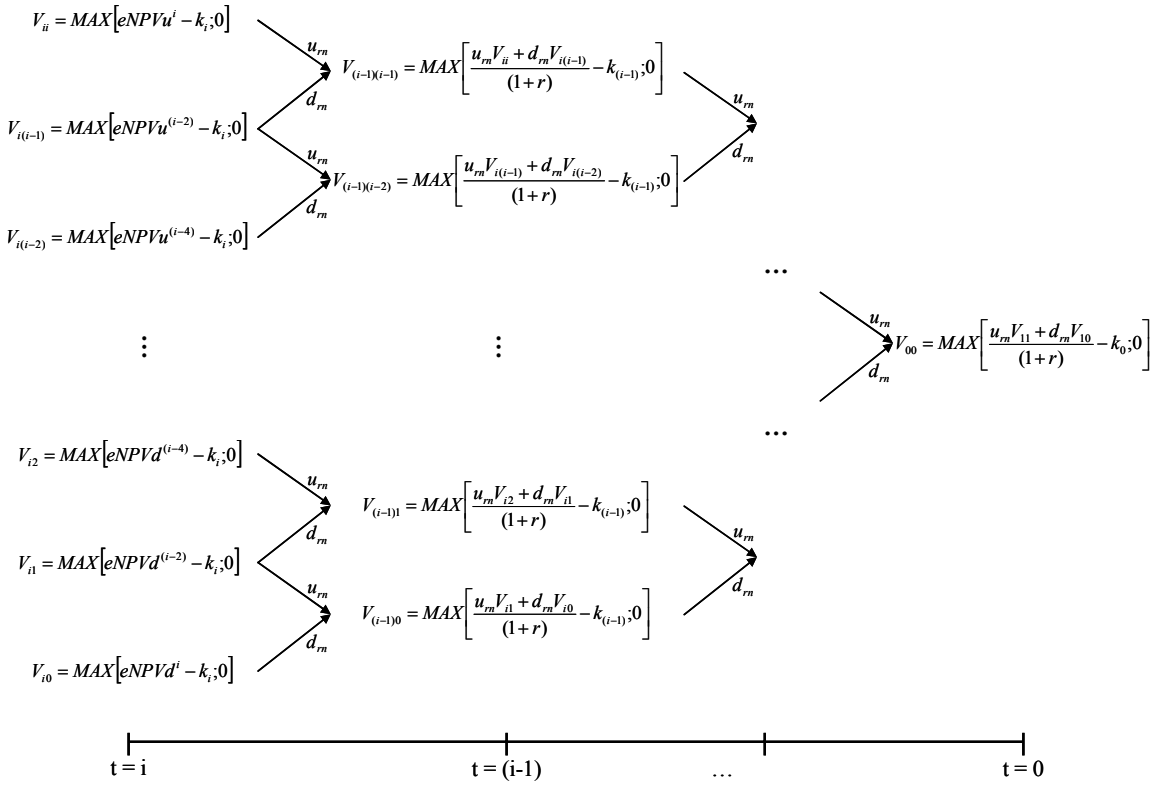

Figure 6.4: Tree based valuation approach for drug development projects

A practical application of tree analysis can be observed at SmithKline Beecham, where the approach is mainly appreciated for its transparency and its ability to capture risk factors that are specific to the drug development process.[319]

Other Tree based approaches in the valuation of pharmaceutical R&D

A similar tree based approach to evaluate a drug development project can be found at Brach (2003) who uses decision tree analysis to evaluate an individual research project. Her approach uses the specific characteristics of a drug development project and breaks it down into six individual project stages, which can clearly be separated from each other. While the

[319] Compare to Sharpe, Paul and Keelin (1998, p. 52)

commercialization of a new drug represents the very last stage of the process, each of the precedent stages represents an option to execute the following stage. Her approach is based on the steps of the pharmaceutical value chain introduced in chapter 5.3.2. Each stage requires the previous stage to be successfully completed and stage completion is also related to a cost. The factor k_i represent the cost to complete a specific stage i representing the option premium securing the right to execute the following stage. Each stage i is also related to a specific probability q_i that it can be completed successfully. If all process stages are successfully completed the final product can be a success in the marketplace resulting in a best case net present value BC at the start of the commercialization phase. Alternatively, the project can be disappointing with a worst case net present value of WC. Figure 6.5 visualizes the binomial tree approach used by Brach (2003).

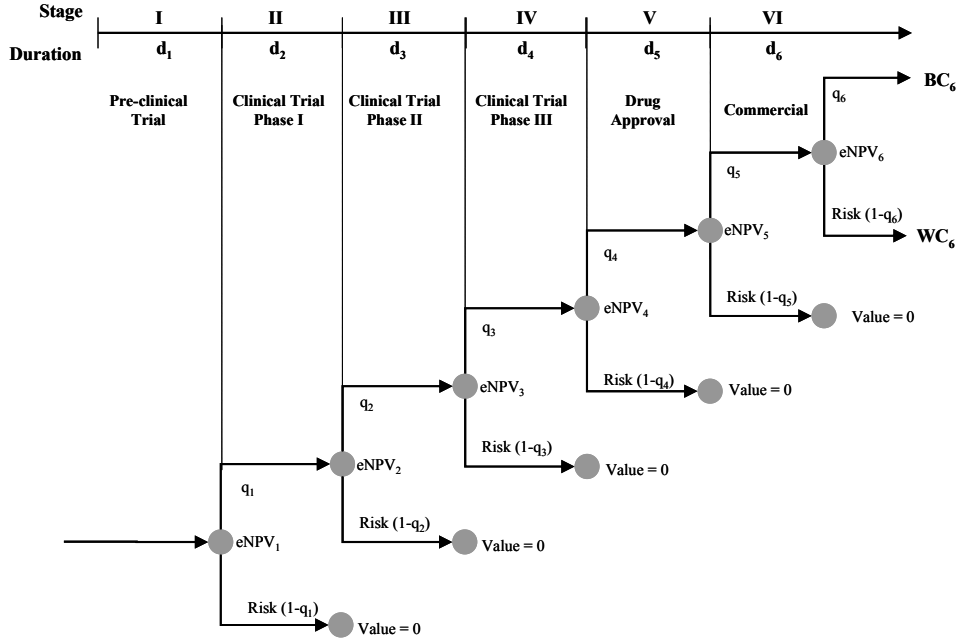

Figure 6.5: Drug development evaluation using a compound option approach

With q6 being the probability for a successful market launch resulting in the best case scenario BC, the expected net present value eNPV of the project at the time of market entry can be calculated using equation (6.11).

$$eNPV_6 = q_6 * BC_6 + (1 - q_6) * WC_6 \qquad (6.11)$$

For every preceding project stage i, the expected net present value $eNPV_i$ can be calculated using the corporate discount rate r_c, the probability for successful completion of a project stage q_i, and the duration d_i it takes to complete a specific project stage. With these input parameters $eNPV_i$ can be derived using (6.12).

$$eNPV_i = \frac{q_i * eNPV_{i+1}}{(1 + r_c)^{d_i}}; 0 < i < 6 \qquad (6.12)$$

Besides the expected value at each project stage it is also known in which range the actual value NPV_i occurs. Since BC_6 represents the best possible outcome of the project it can be concluded that this also represents the upper limit at each project stage if discounted back to

adjust for time value of money. Equation (6.13) can therefore be used to determine the upper value limit at each period i.

$$BC_i = \frac{BC_{i+1}}{(1+r_c)^{d_i}}; 0 < i < 6 \qquad (6.13)$$

As opposed to the upper limit, which varies at each stage, the lower limit for all WC_i with $0<i<6$ is zero because of the technical failure risk at each stage. After upper limits, lower limits, and expected net present values for all stages are calculated, Brach (2003) determines the risk-neutral probabilities for up- or downward movements at each stage. The approach used is similar to that of Cox et al. (1979) for financial options using the risk-free interest rate r. These risk-neutral probabilities are then determined using (6.14).

$$p_i = \frac{(1+r)^{d_i} * eNPV_i - WC_i}{BC_i - WC_i} \qquad (6.14)$$

With these risk-neutral probabilities, the real option value of the drug development project can be calculated for each of the different stages i using equation (6.15).

$$C_i = \frac{p_i * BC_i + (1-p_i) * WC_i}{(1+r)^{d_i}} - k_i \qquad (6.15)$$

With the various equations described above, Brach (2003) calculates the value of a drug development project starting in reverse order from the very last project phase to the starting point of the project as summarized in Figure 6.6.

	Project Stages i					
	I	**II**	**III**	**IV**	**V**	**VI**
Stage duration	d_1	d_2	d_3	d_4	d_5	d_6
Stage cost	k_1	k_2	k_3	k_4	k_5	k_6
Upper limit project value	$\frac{BC_2}{(1+r_c)^{d_1}}$	$\frac{BC_3}{(1+r_c)^{d_2}}$	$\frac{BC_4}{(1+r_c)^{d_3}}$	$\frac{BC_5}{(1+r_c)^{d_4}}$	$\frac{BC_6}{(1+r_c)^{d_5}}$	BC_6
Lower Limit project value	0	0	0	0	0	WC_6
Expected Net Present Value ($eNPV_i$)	$\frac{q_1 * eNPV_2}{(1+r_c)^{d_1}}$	$\frac{q_2 * eNPV_3}{(1+r_c)^{d_2}}$	$\frac{q_3 * eNPV_4}{(1+r_c)^{d_3}}$	$\frac{q_4 * eNPV_5}{(1+r_c)^{d_4}}$	$\frac{q_5 * eNPV_6}{(1+r_c)^{d_5}}$	$q_6 * BC_6 + (1-q_6) * WC_6$
Risk free probability stage i	$p_i = \frac{(1+r)^{d_i} * eNPV_i - WC_i}{BC_i - WC_i}$					
Real Option based project value starting stage i	$C_i = \frac{p_i * BC_i + (1-p_i) * WC_i}{(1+r)^{d_i}} - k_i$					

Figure 6.6: Evaluating R&D using a staged tree approach

6.2 Black-Scholes (BS) Based Valuation

Probably the most widely know method of continuous time option pricing is the one developed by Black and Scholes (1973)[320], which is described in this section.

Methodology

The option valuation approach of Black and Scholes (1973) reached its predominant status in financial option literature because it is a closed form equilibrium formula that consists of only observable and objective input parameters. Another advantage of this approach is the limited need for external information because their formula is based on only six input parameters.

S : Stock price of the stock representing the underlying asset of the option

X : Price at which the option right can be exercised

T : Expiration date

t : Current date

r : Risk-free interest rate

σ : Volatility of the price of the stock serving as the underlying asset

BS base their valuation approach on the same idea of a duplicating portfolio as Cox et al. (1979) do with their binomial tree approach described above.[321] They duplicate the payoff structure of a call option with a debt financed stock portfolio. With the payoff structure being the same, the duplicating portfolio and the sold call result in a risk-free portfolio because both payoffs offset each other. By knowing that the portfolio is risk-free it is also known that it has to generate a return equivalent to the risk-free interest rate. If it would not generate the risk free interest rate, arbitrage opportunities would exist.[322] From this thought they derive the following valuation formula for a European call option on a non-dividend paying stock[323]:

$$C = SN(d_1) - Xe^{-r(T-t)}N(d_2) \qquad (6.16)$$

with

---

[320] Selected examples of valuable discussions on the Black and Scholes equation are Black and Scholes (1973), Jarrow and Rudd (1983, p. 117), Merton (1990, p. 255), Duffie (1992, p. 77), Trigeorgis (1996, p. 89), Chriss (1997, p. 119), Korn and Korn (1999, p. 101), Bingham and Kiesel (2004, p. 131), Hull (2006, p. 281) and others.

[321] In fact, the binomial tree valuation method converges to the BS formula if the length of the discrete time steps becomes infinitesimally small.

[322] Black and Scholes (1973) describe a second way to derive the BS formula by deriving the underlying differential equation from the Capital Asset Pricing Model (CAPM) developed by Sharpe, William F. (1964).

[323] For a very detailed discussion on the stochastic calculus and probability theory underlying the work of Black-Scholes one can refer to Ikeda et al. (1996).

$$d_1 = \frac{\ln(S/X) + (r + \sigma^2/2)(T-t)}{\sigma\sqrt{T-t}}$$

and

$$d_2 = \frac{\ln(S/X) + (r - \sigma^2/2)(T-t)}{\sigma\sqrt{T-t}} = d_1 - \sigma\sqrt{T-t}$$

While (6.16) is an appealing, easy to apply closed-form equation, it only holds true under what Black and Scholes consider "ideal conditions".[324] Specific care must be taken that the following assumptions are fulfilled for the equation to be applicable:

- The risk-free rate of interest is publicly available and it is constant over time.
- Stock prices follow a stochastic process of the form $\delta S=\mu S\delta t+\sigma S\delta z$ with
  - μ: expected rate of return of the underlying stock also called "drift"[325] of S.
  - σ: volatility of the price of the underlying stock also called "diffusion"[326] of S.
  - δz: stochastic factor modeling the randomness of the stock price development.[327]
- Both the drift rate μ as well as the diffusion factor σ are constant over time.
- Markets are frictionless and complete.
- The underlying stock pays no dividends.
- The option represents a "European" type option.

Although the formula might not appear intuitive to the reader, the different components of the BS formula can be interpreted in quite a descriptive way[328]:

- $SN(d_1)$ represents the expected value of the stock at the expiration date if S exceeds the exercise price X.
- $N(d_2)$ represents the risk neutral probability that the stock price will exceed X at expiration.
- $Xe^{-r(T-t)}$ represents the net present value of the exercise price of the option.

As qualitatively described in chapter 3.1.3, the value of a call option evaluated with formula (6.16) reacts in a certain way to changes in the various input parameters with all other parameters remaining unchanged.[329]

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[324] See Black and Scholes (1973)

[325] See Duffie (1992, p. 81)

[326] See Duffie (1992, p. 81)

[327] Black Scholes assume a geometric Brownian motion for the stock price development.

[328] Compare to Amram and Kulatilaka (1999, p. 121)

Changes in price of underlying stock (Delta Δ)

If the price of the underlying stock increases, the value of the related call option increases as well because the first derivative over S is always greater than zero. This first derivative is often referred to as Delta.

$$\Delta = \frac{\partial C}{\partial S} = N(d_1) > 0 \qquad (6.17)$$

Changes in the exercise price

The higher the exercise price of an option the lower its value with all other parameters remaining the same. This can be concluded from the first derivative of the BS formula over X, which is always smaller than zero.

$$\frac{\partial C}{\partial X} = -e^{-r(T-t)} N(d_2) < 0 \qquad (6.18)$$

Changes in time to maturity (Theta Θ)

The greater the time to maturity (T-t), the greater the value of the call option resulting from the first derivative of the BS equation over the remaining time to maturity (T-t) being greater than zero. This first derivative is often referred to as Theta.

$$\Theta = \frac{\partial C}{\partial (T-t)} = -\frac{Sn(d_1)\sigma}{2\sqrt{(T-t)}} - rXe^{-r(T-t)} N(d_2) > 0 \qquad (6.19)$$

with

$$n(d_1) = \frac{1}{\sqrt{2\pi}} e^{-\frac{d_1^2}{2}}$$

Changes in the risk-free interest rate (Rho P)

Increases in the risk-free interest rate also increase the value of the European call option as can be derived from the first derivative of (6.16) over the risk-free rate of return, which is greater than zero. This parameter is often referred to as Rho.

$$\mathrm{P} = \frac{\partial C}{\partial r} = X(T-t)e^{-r(T-t)} N(d_2) > 0 \qquad (6.20)$$

Changes in stock price volatility (Lambda Λ)[330]

Increasing stock price volatility increases the value of the European call option because the first derivative over the volatility factor is always greater than zero. This first derivative is often referred to as Lambda.

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[329] Summarized at Jarrow and Rudd (1983, p. 119) and Kilka (1995, p. 52).

[330] Referred to as "Vega" at Hull (2006, p. 359) and Korn and Korn (1999, p. 104).

$$\Lambda = \frac{\partial C}{\partial \sigma} = Sn(d_1)\sqrt{(T-t)} > 0 \qquad (6.21)$$

with

$$n(d_1) = \frac{1}{\sqrt{2\pi}} e^{-\frac{d_1^2}{2}}$$

Certain assumptions regarding the Black-Scholes formula can be relaxed as Merton (1973) did to include dividend payments into the model. With δ being a constant dividend yield related to the underlying stock of an option, equation (6.16) can be rewritten to include dividend payments and calculate a call option on a dividend paying stock C_D.[331]

$$C_D = Se^{-\delta(T-t)}N(d_1) - Xe^{-r(T-t)}N(d_2) \qquad (6.22)$$

with

$$d_1 = \frac{\ln(S/X) + (r - \delta + \sigma^2/2)(T-t)}{\sigma\sqrt{T-t}}$$

and

$$d_2 = \frac{\ln(S/X) + (r - \delta - \sigma^2/2)(T-t)}{\sigma\sqrt{T-t}} = d_1 - \sigma\sqrt{T-t}$$

Equation (6.22) represents the valuation equation for a European call option on a stock paying a constant dividend yield δ.

Use in valuation of drug development projects

An early example where the BS approach is applied to the valuation of drug development is described by Nichols (1994, p. 92) and Sender (1994). The paper describes how drug developing companies can apply the defined financial option valuation framework to more appropriately evaluate their projects than by using simple net present value analysis. To obtain the input parameters for the BS formula, the conversions in Table 6.1 are used.[332]

[331] Compare also to Kilka (1995, p. 56)

[332] Derived from Sender (1994, p. 92)

Variable	Black and Scholes (1973)	Sender (1994)
Underlying asset (S)	Current stock price	Present value of expected project cash flows[333]
Exercise price (X)	Fixed stock price	Required capital investment
Maturity date (T)	One fixed date (Europ. call)	Subjective estimate for potential market entry
Risk-free interest rate (r)	Market rate for appropriate maturity	U.S. treasury rate for respective maturity
Risk/Volatility (σ)	Stock price movements	Annual standard deviation of typical industry stocks

Table 6.1: Input parameter comparison between financial and real option valuation

They found that applying the Black-Scholes option model captures the value of drug development projects better than net present value techniques. Nichols (1994) argues that by using option valuation techniques companies are able to quantify some of the intuition businesspeople have and that are not captured by net present value techniques. Another finding is related to an option to wait as described in chapter 3.2.1. Sender (1994) concludes that the value of a drug development real option becomes more valuable as its time to expiration increases because a company "would be able to collect more information and therefore make better investment decisions"[334]. While this is consistent with (6.19) of the Black-Scholes framework it might not be applicable to drug development projects as discussed in section 9.2.

Another example where the Black-Scholes model is applied to value a real option represented by a drug development project is the study by Banerjee (2003). The study attempts to evaluate two components of ongoing research projects of an Indian drug manufacturer. Banerjee (2003) uses the Black-Scholes formula (6.22) for a call option on a dividend paying stock as opposed to the simple form (6.16) used by Sender (1994) to estimate the value of these projects. In addition to the input factors of Table 6.1, Banerjee (2003) argues that a deducting factor such as the dividend yield has to be included to consider the specific situation of the drug developing industry that revenues can only be generated during the effective patent protection period.[335] By including such a factor he shows that after a component is patent protected, an increasing time to maturity does not necessarily increase the value of the option. While this is not consistent with Sender (1994) and (6.19) of the Black-Scholes model, it is intuitively understandable because the longer a company waits to bring a new drug to market, the shorter the effective patent protection period to recover R&D cost and generate profits.

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[333] This is in line with Pennings and Lint (1997, p. 85), who found that for real options the "expected value of the project value outcome equals the estimated underlying value".

[334] See Sender (1994, p. 92)

[335] It is a simplifying assumption that there are no post-patent period revenues but it can be considered appropriate because severe price pressure and competition of generic drug manufacturers sets in as soon as a drug loses its patent protection status. See also section 1.3.1 on generic drug competition.

6.3 Compound Option Based Valuation

Another breakthrough in financial option theory relevant for this study is the compound option valuation method using closed form equations. The method covers situations where options are not written on assets like a stock but rather on other options therefore representing options on options. In this approach the staged character of the investment is not evaluated by using tree algorithms but modeled with a closed form equation.

Methodology

Geske (1979) developed the first closed-form equation to value compound options by building on the established valuation approach of Black and Scholes. The assumptions Geske (1979) uses for his model are similar to the ones used by Black and Scholes.[336] Assuming that C_1 represents a call option on a stock S with an exercise price X_1 and exercise date T_1 and C_2 represents another call to acquire the initial option C_1 at time T_2[337] at a specified price X_2, Geske developed the following closed form equation to value C_2.[338]

$$C_2 = SM\left(a+\sigma\sqrt{(T_2-t)}, b+\sqrt{(T_2-t)}; \sqrt{\frac{(T_2-t)}{(T_1-t)}}\right) - X_1 e^{-r(T_1-t)} M\left(a,b; \sqrt{\frac{(T_2-t)}{(T_1-t)}}\right) - X_2 e^{-r(T_2-t)} N(a) \qquad (6.23)$$

with $a = \dfrac{\left(\ln\left(\dfrac{S}{S^*}\right)+\left(r-0{,}5\sigma^2\right)(T_2-t)\right)}{\sigma\sqrt{(T_2-t)}}$, $b = \dfrac{\left(\ln\left(\dfrac{S}{X_1}\right)+\left(r-0{,}5\sigma^2\right)(T_1-t)\right)}{\sigma\sqrt{(T_2-t)}}$,

a bivariate cumulative normal distribution function M with

$$M(a,b,\rho) = \int_{-\infty}^{a}\int_{-\infty}^{b} \frac{1}{2\pi\sqrt{\left(1-\rho^2\right)}} e^{-\frac{1}{2}\frac{\left(x^2-2\rho xy+y^2\right)}{\left(1-\rho^2\right)}} dxdy$$

and S* being the lowest stock price, at which the compound option C2 is exercised by a rational investor. The threshold S* has to fulfill requirement (6.24).

$$C_2(S^*; r, \sigma, T_1, X_1) - K = 0 \qquad (6.24)$$

Equation (6.23) represents the pricing formula for a compound call on another call. Geske's two stage model was expanded by Lin (2002), Cassimon et al. (2004) or Mölls et al. (2005) into a multiple studies to derive a closed-form solution for multi-stage compound options.

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[336] The assumptions of the Black-Scholes model are summarized in chapter 6.2.

[337] With $T_2<T_1$

[338] Geske (1979) initially did not develop his model by investigating a financial call option on another financial call option but by considering a financial call option on a stock and interpreting the stock as an option on the assets of the underlying firm. Generalizations of this approach evaluating a financial call on another financial call can be found at Jarrow and Rudd (1983, p. 143).

Use in valuation of drug development projects

Evaluating a drug development project by using a closed-form compound option approach was attempted in scientific studies by Cassimon et al. (2002) and Cassimon et al. (2004).[339]

They built their study based on the same process breakdown as Brach (2003). They separate a drug development project in the same distinct phases, each of them representing a call option on the succeeding project stage.[340] The major innovation of the Cassimon et al. (2004) study is the fact that it does not evaluate the project by working along a tree model but by establishing a closed-form equation that allows the value of the R&D project to be quantified. Cassimon et al. (2004) apply the model of Geske (1979)[341] to the real option world of drug development and extend it into a n-fold compound option model to capture the complexity of the drug development process.

As a first step the model of Geske (1979), which was described above, is transferred into a real option context changing its notation. Formula (6.23) becomes (6.25).

$$C_1(V,t) = VM\left(b_1 + \sigma\sqrt{(T_1 - t)}, b_2 + \sqrt{(T_2 - t)}); \sqrt{\frac{(T_1 - t)}{(T_2 - t)}}\right) - X_2 e^{-r(T_2 - t)} M\left(b_1, b_2; \sqrt{\frac{(T_1 - t)}{(T_2 - t)}}\right) - X_1 e^{-r(T_1 - t)} N(a) \qquad (6.25)$$

with $b_1 = \dfrac{\left(\ln\left(\dfrac{V}{\overline{V}}\right) + \left(r - \dfrac{\sigma^2}{2}\right)(T_1 - t)\right)}{\sigma\sqrt{(T_1 - t)}}$, $b_2 = \dfrac{\left(\ln\left(\dfrac{V}{X_2}\right) + \left(r - \dfrac{\sigma^2}{2}\right)(T_2 - t)\right)}{\sigma\sqrt{(T_2 - t)}}$

and M being a bivariate cumulative normal distribution function[342].

In this context, the following notations are used:

V : Current value of an asset representing the underlying of a regular call option

T_1 : Maturity date of compound call C_1

T_2 : Maturity date of a call option C_2 representing the underlying of C_1

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[339] Another good example of compound option valuation in drug development can be found at Gamba et al. (1999) who value two closely related product launches as a compound option. A similar approach can be found at Schäfer and Schässburger (2001) who try to evaluate a biotech start-up using a compound option approach.

[340] While both studies use the same project phases to break down the entire project, they do start their investigation at different stages. While Cassimon et al. (2004) use basic research activities as the first project stage, Brach (2003) does not start her investigation until the phase of pre-clinical trials.

[341] With all its underlying assumptions.

[342] $M(a;b;\rho) = \int_{-\infty}^{a}\int_{-\infty}^{b} \dfrac{1}{2\pi\sqrt{(1-\rho^2)}} e^{-\frac{1}{2}\frac{\left(x^2 - 2\rho xy + y^2\right)}{\left(1-\rho^2\right)}} dxdy$

X_1 : Exercise price of the compound call option

X_2 : Exercise price of the standard call option

r : Risk-free interest rate

σ^2 : Variance of returns on the underlying asset

N : Cumulative normal distribution function

M : Multivariate normal distribution function[343]

As S^* represented the lowest stock price, at which the compound option is exercised by a rational investor at Geske (1979), the real option threshold $\overline{V}$ has to fulfill a similar condition $C_1(\overline{V}, T_1)-X_1=0$.

During a second step, Cassimon et al. extend this view and define a series of compound options, each granting the right to acquire another option. While the 1-fold compound option is equivalent to a standard call option, the 2-fold compound option is the one described by Geske (1979). For all n>2 the n-fold compound option grants the right on a (n-1)-fold compound option. In such a series of compound options, Cassimon et al. (2004) show that the value of the highest level option C_n can be calculated using equation (6.26).

$$C_n(V,t) = VM_n\left(a_1,...,a_n;A^n\right) - \sum_{m=1}^{n} X_m e^{-r(T_m-t)} M_m\left(b_1,...,b_m;A^m\right) \qquad (6.26)$$

with

$$b_i = \frac{\ln\left(\frac{V}{\overline{V}_i}\right) + \left(r - \frac{\sigma^2}{2}\right)(T_i - t)}{\sigma\sqrt{T_i - t}}; i = 1,...,n,$$

$$a_i = b_i + \sigma\sqrt{T_i - t}; i = 1,...,n,$$

$$\rho_{ij} = \sqrt{\frac{T_i - t}{T_j - t}}; i < j,$$

$\overline{V}_i$ being the solution to the equation $C_{i+1}(V,T_i) = X_i; i = 1,...,n-1$, $\overline{V}_n = X_n$ and

$$A^{\ell} = \left(a_{ij}^{\ell}\right), i,j = 1,...,\ell, with \begin{cases} a_{ii} = 1 \\ a_{ij} = a_{ji} = \rho_{ij}, i < j \end{cases}$$

[343] In the case of a two-fold compound option M represents a bivariate cumulative normal distribution function M(a; b; ρ) with a and b representing normally distributed variables and ρ being the correlation coefficient between these two variables.

6.4 Simulation in Option Valuation

In addition to the calculation models described above there is an alternative approach to derive the value of a financial option or other derivative securities, which is known as Monte Carlo Analysis (MCA). It is an analytical technique for solving a problem by performing a large number of trial runs that simulate potential future environmental developments and inferring a solution from the collective results of these trial runs.

Methodology

In a Monte Carlo Analysis approach, Boyle (1977)[344] derives the value of an option by simulating the process generating the return of an underlying asset and uses the assumption of risk neutrality to assess the value of this option. To derive the value of a European call option he uses the stochastic process describing future stock price movements until the expiration date of the option. By simulating this process he creates a set of future stock prices for the execution date and uses these prices to estimate the option value. His approach has the advantage that it avoids solving highly sophisticated mathematical formulas or evaluating integrals with numerical methods.

Boyle (1977) bases his approach on the assumption that stocks generate the risk-free rate of return in a complete market and that the ratio S_{t+1}/S_t is log-normally distributed. The first assumption implies the following relationship (6.27).

$$E(S_{t+1}) = S_t * e^r \qquad (6.27)$$

With the additional knowledge on the properties of the lognormal distribution he derives the following formula (6.28)[345], with $\tilde{x}$ being a standard-normally distributed random variable with zero mean and one unit variance.

$$S_{t+1} = S_t e^{\left(r - \frac{\sigma^2}{2} + \sigma\tilde{x}\right)} \qquad (6.28)$$

With equation (6.28), Boyle is able to simulate a stock price development path over any number of time periods starting at S_t and resulting in a final stock price S_T at the end of the simulation path. Running this simulation n times results in final stock prices S_{Ti} with $1 \leq i \leq n$. Also knowing that the value of the European call at maturity T is given by $MAX[S_T\text{-}X;0]$, he approximates the value of a call using (6.29).

$$C_t = e^{-r(T-t)} * \frac{1}{n} \sum_{i=1}^{n} MAX[S_{Ti} - X;0] \qquad (6.29)$$

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[344] There are numerous other examples where MCA is used to value financial options. A more recent example can be found at Menn (2004, p. 111).

[345] For a more detailed description of the approach refer to Boyle (1977, p. 328) or Korn and Korn (1999, S. 205).

Use in valuation of drug development projects

According to Bode-Greuel and Greuel (2005) and Bratic et al. (1997), MCA is a methodology that can be applied to drug development valuation problems. This study refrains from presenting an individual application case of MCA in drug development because these cases are based on individual probability distributions for the relevant parameters and therefore such a presentation would not add value to the general understanding of the concept, which was already introduced above from a methodological standpoint.

The general reason why MCA appears appropriate for the valuation of drug development projects is the fact that it is a very flexible approach that allows for the incorporation of a wide range of environmental parameters. It also gives the user the opportunity to assign various kinds of individual probability distributions to the input parameters of a valuation model. This characteristic is desirable when evaluating pharmaceutical R&D recalling the various risk factors presented in chapter 5.1 that can influence the value of a drug development project. Bratic et al. (1997) expect an increasing use of Monte Carlo based and other subjective models to value drug development projects in the future. Because of the flexibility of this approach, an adapted MCA approach is used in the quantitative section of this study.

6.5 Applicability of Existing Concepts in Valuation of a R&D Option

After presenting some of the established option valuation methodologies and how they are applied to the valuation of drug development projects, this concluding section of the chapter discusses the applicability of these established models. Since it is not a key objective of this study to prove the inappropriateness of financial option models in the valuation of real options, only selected key points are highlighted.[346] Table 6.2 summarizes the main advantages and disadvantages of the major financial option valuation approaches when evaluating real options.[347]

The increasing use of financial option models to evaluate drug development projects and other real options[348] appears questionable if one investigates the basic framework assumptions that need to be fulfilled for their appropriate use. One of the main assumptions the models for financial options have in common is the concept of arbitrage free pricing. Arbitrage free pricing assumes that there is either another market traded asset or a portfolio of traded assets that exactly duplicates the payoff structure of the asset to be evaluated.

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[346] For more details on the limitations of financial option theory in real option valuation one can refer to Meise (1998, p. 82), Hilzenbecher (2000, p. 274), Lin (2002, p. 185) or Arnold and Shockley (2003) for additional information.

[347] For a detailed survey that investigates reasons why drug developing companies avoid the use of real option theory see Hartmann and Hassan (2006, p. 350).

[348] According to Dr. Christa Bähr, Leader Research Team "Life Science" at DZ Bank, in Ernst&Young (2002, p. 88).

Following the law of one price this duplicating asset or asset portfolio must trade at exactly the same price as the evaluated asset otherwise arbitrage opportunities would exist.

The problem with this concept is that market prices only consider market or shared risk factors. This is not a problem for financial options where the underlying asset is market traded but it becomes problematic for real options like pharmaceutical R&D projects where there is no market traded underlying asset. These real options contain a significant amount of private risk as discussed in chapter 5.1, which cannot be duplicated with an asset portfolio and are therefore not considered by these traditional option valuation techniques. Banerjee (2003, p. 68) already criticized the problem of underlying assets that are not market traded and Mello and Pyo (2003, p. 98) even conclude that "in the presence of private risk, the value of the option cannot be determined in a risk-neutral framework".

In an environment where private risk exists, preference-based subjective approaches must be employed to derive estimates of the value of real options. Such an approach can capture the private risk factors impacting the value of a real option. Since preference functions for individual market participants differ from each other and since there is no efficient market for real options, the value of complex real options like a drug development project is better represented by a range than by one specific value.

Lin (2002, p. 185) considers the absence of market traded assets to create a duplicating portfolio as the biggest problem in applying financial option models to real option problems. Arnold and Shockley (2003) on the other hand confirm that the absence of market traded assets is a problem in the applicability of financial option theory on real options but they also conclude that other traditional valuation models such as NPV analysis are also based on critical assumptions making the financial option approach, despite these flaws, still the superior valuation method. In addition to the problem of non-traded underlying assets of a real option, other issues also need to be mentioned.

One of these additional points is related to the sensitivity of financial option prices to changes in their input parameters. In previous chapters it was shown that the value of a European call option[349] increases as the time to maturity increases, which is not necessarily true for real options. In contrast to standard financial option pricing theory, Garner et al. (2002) concluded that the value of certain real options is inversely related to the time to maturity. The study conducted by Banerjee (2003, p. 67), which specifically covered drug development projects, also concluded that the longer the time to maturity, the higher the option value does not necessarily hold true. The main reason for this adverse behavior of real options in drug development is the issue of patent protection and effective patent protection period[350].

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[349] On a non-dividend paying stock.

[350] One of the few scientific sources that considers the effective patent protection period when valuing the launch of a new pharmaceutical product is the one of Gamba et al. (1999).

An additional point to be criticized is related to the maturity of real options. While financial options have contractually fixed maturity dates that allow a precise modeling from a time perspective, real options usually lack this precision. Instead of a given maturity date, this variable is stochastic by nature[351] making it more difficult to apply a financial option valuation methodology that is based on a fixed lifetime of the option.

It is also important to note that most of these models do not consider one individual characteristic that differentiates drug development projects as real options from financial options. This characteristic is the non-exclusivity of these options. When discussing the applicability of various valuation models it is important to recall the fact that a pharmaceutical research project does not represent an exclusive option as most financial options do[352]. This important difference between the two option types is not explicitly considered in any of the financial option models discussed above.

Besides these general points of concern regarding the applicability of financial option theory on real options, there are additional points that should be mentioned on the individual methodologies described in the previous sections. The binomial tree approach has achieved high acceptance in the industry[353] because it follows an intuitive logic and can easily be explained. Although its simplicity is widely appreciated, the technique also has certain drawbacks. One stage binomial trees can often be considered inappropriate because most real options and especially corporate investment projects are multi-staged requiring a valuation model to include multiple decision points to better reflect managerial flexibility.[354]

The use of multi-stage binomial trees on the other hand appears critical for long-term real options such as drug development projects because it does not consider new information gathered during the course of one project stage and only changes environmental factors at pre-defined decision points. Recalling that individual project stages in drug development can take multiple years to complete, this appears critical when setting up a valuation model. In a setting of ongoing information gathering, continuous time models appear more appropriate. The presented continuous time models themselves have to be criticized in certain points when it comes to real option valuation. When recalling the requirements for the applicability of the Black-Scholes formula, it becomes clear that an application for real options is critical. This results from the fact that the underlying of a real option is generally not market traded on a continuous basis, the value of the underlying does not necessarily follow a geometric

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[351] Compare to Fischer, Kay M. (1996, p. 142)

[352] The difference between exclusive financial options and shared real option rights was extensively discussed in chapter 3.2.2.

[353] Compare to Mun (2002, p. 100)

[354] See also Copeland and Tufano (2004)

Brownian motion[355], uncertainty over time is not constant and the relevant markets are neither frictionless nor complete.

The mentioned uncertainty in the BS model is expressed by the volatility factor, which is assumed to be constant over time[356]. This is unrealistic uncertainty often changes over time and therefore it seems impossible to determine a single correct standard deviation for the valuation of real option. This is criticized by Pennings and Lint (1997, p. 92). Brach (2003, p. 48) considers the task of deriving the correct volatility as challenging, "if not impossible". Pennings and Lint (1997, p. 92) considered this such a critical issue that they abandon BS approaches altogether while other studies use the volatility of stock prices of comparable companies or even industry indices as estimators for the volatility. Examples of figures used for this market volatility in the pharmaceutical industry are 40 to 60 per cent at Nichols (1994), 25 per cent at Perlitz et al. (1999), 26 per cent at Kellogg and Charnes (2000), 36 per cent at Banerjee (2003) and 102 per cent at Cassimon et al. (2004). Considering the broad range of estimates observed, this emphasizes the difficulties when applying a closed-form valuation equation to a real option problem.[357]

[355] See also Gamba et al. (1999)

[356] For a detailed discussion on valuation using stochastic project volatility see Nagel (2001).

[357] A comprehensive study investigating the impact of stochastic volatility in financial option valuation can be found at Nagel (2001).

	Main Advantages	Main Application Problems
Tree based valuation approach	• Easy to understand approach with simple step model • Only basic math skills required • Intuitive logic of iterative solution	• Constant risk within a project stage • Fixed duration of project steps • Potential misjudgment in subjective input parameters
Black-Scholes (BS) based valuation	• Objective valuation • Closed form approach • Few input parameters	• Underlying has to be market traded • Value of underlying has to follow Geometric Brownian Motion • Does not consider private risk • Constant volatility • Does not consider project stages • Uses fixed time to maturity
Closed form compound option approach	• Objective valuation • Closed form approach • More realistic approach compared to BS for most real life situations	• Underlying has to be market traded • Value of underlying has to follow Geometric Brownian Motion • Does not consider private risk • Constant volatility • Uses fixed time to maturity
Monte Carlo Analysis (MCA)	• Complex input parameter dependencies can be modeled • Flexible approach regarding distribution assumptions of input parameters • Well suited to consider subjective input parameter estimates	• Detailed understanding of dependencies between input parameters necessary • Requires knowledge about distribution of input factors • Can be complex to model • Can be time consuming because of large number of simulation runs

Table 6.2: Applicability of financial option theory in real option valuation

As a bottom-line, it can be concluded that valuation methods that treat drug development projects as real options and apply existing financial option theory for their valuation do have significant drawbacks. The main issue is the fact that by adopting these valuation methodologies, the specific market environment and risk factors of the industry are not sufficiently considered. This point has already been criticized by Bahuguna (2000) who states that "option pricing – fine for the stock and oil exploration, option pricing models don't work in valuing life science research" and was already indicated on Table 3.3 where risk-neutral valuation techniques were only considered appropriate for Type 0 Real Options. Copeland and Tufano (2004, p. 90) come to the same conclusion that environmental factors influencing real option values are not sufficiently considered in traditional financial option valuation models. They conclude that "it would be dangerous to try to reduce those complexities into standard option models, such as the Black-Scholes model"[358]. This view is supported by Hilzenbecher (2000, p. 274) who concludes that especially for complex option valuation problems with a mixture of private and market risk factors, subjective valuation approaches are the only feasible approach.

[358] Copeland and Tufano (2004, p. 90)

To take this criticism into account a subjective model to value a R&D option is developed in the following part III of this study. This model considers that the underlying of the R&D option is not market traded, that a R&D option does not have a fixed time to maturity, that the value of the underlying does not necessarily follow a Geometric Brownian Motion and that R&D options do not represent exclusive option rights. With the developed model representing a subjective model its results, as for all models of this type, heavily depend on the quality of the input parameters used. Since a discussion regarding approaches on how to select correct input parameters for a subjective model represents a comprehensive study on its own, this is not within the scope of this study and the following part III. Instead, the model is developed step by step and its application is explained for the practitioner using an illustrative case example.

PART III: Quantitative Concept Assessment

7 Fund Raising Potential of R&D Option in Idealistic Environment

Within the drug developing industry it is important that a round of financing allows a company to either reach breakeven or to achieve the next project milestone, which opens the door to additional sources of financing.[359] This chapter investigates the financing potential that resides in a R&D option in an idealistic market environment. It represents the base for the subsequent chapter where some of these assumptions are relaxed to assess the financing potential in a more realistic environment.

7.1 Basic Assumptions of the Idealistic Market Environment

In the context of this study the term idealistic market environment is used to describe an artificial environment, which is characterized by certain simplifying assumptions. These assumptions are made to reduce modeling complexity and to better describe the thought process when assessing the fund raising potential of a R&D option.

The first assumption is related to the market potential of a drug candidate under development. In reality, no company knows with exact certainty which revenues or profits a new drug can generate until the development process is finalized and the drug is physically introduced into the market. This future market potential depends on multiple external factors that can vary over time and that are highly complex if not impossible to model. To avoid this problem during this assessment phase, it is assumed that in an idealistic market environment the future market potential of a new drug is known and constant over time.[360]

The second assumption is related to a new drug introduction on the market. In reality there is a chance that regulatory market approval of new drugs will be revoked even after they have been introduced on the market[361]. For simplification reasons this additional risk is excluded from the analysis. The assumption is therefore that a new drug, once approved by regulatory authorities, maintains its approval status at least until the related patents expire.

An additional factor related to the market potential of a new drug is the field of competition in the drug developing industry. In this first valuation step an assumption is made that is

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[359] This point is emphasized by Ernst&Young (2003, p. 83).

[360] Working with a constant market potential represents a simplifying assumption because in reality product sales and in return total contribution margins generally increase over the lifetime of a pharmaceutical product until the end of the patent protection period as shown in Grabowski and Vernon (2000a), Banerjee (2003), Brach (2003), Shockley et al. (2003) and multiple others.

[361] Recent examples include the 2001 case, which received large public attention, where Bayer had to take its blockbuster Lipobay® from the market. Other cases of recalls of approved drugs include Redux®, Vioxx®, Bextra® and Tysabri®. On recent drug recalls see also Kutter et al. (2004), Handelsblatt (2004a), Handelsblatt (2004b), Handelsblatt (2005), Süddeutsche Zeitung (2005) or Lindner (2005).

frequently used in scientific literature[362]. It is assumed that real options represent exclusive option rights because it significantly reduces modeling complexity. Knowing that this assumption is an artificial one and does not represent reality, this assumption is relaxed in section 8.1.4. Until then, the idealistic assumption is used that competition does not exist and that a drug development project represents an exclusive right on future cash flows until a granted patent expires.

There is one more assumption related to competition that is made at this point. This assumption is related to the competitive situation after the patent of a drug has expired and generic drug manufacturers are allowed to enter the market. The average sales profile in section 2.3 demonstrates the immediate sales drop for branded products after patent expiration and therefore it is assumed that the company that initially developed a product loses all its sales and profits at the point of patent expiration. In addition it is assumed that the company neither has the opportunity to expand the product lifetime through patent extensions nor to establish a new patent by expanding into new therapeutic areas or by developing new application formats.

Summarizing these assumptions related to the patent protection period it can be concluded that the life cycle of a drug ends exactly twenty years after a patent was filed with regulatory authorities. At the end of this life cycle, revenues and profits immediately decrease to zero and the value of the project also drops to zero because of the lack of related future revenue streams and business opportunities.

With the assumptions above, the idealistic market environment is characterized by:

- Known and constant market potential over time
- No competition
- No technical failure risk after initial regulatory approval of a new drug
- Immediate total loss of revenues and profits at the end of the patent protection period
- No opportunity to extend product lifecycle beyond 20-year patent protection period
- Salvage value of zero at the end of patent protection period

7.2 Potential R&D Option Buyer Classification

In chapter 6.5 it is discussed that there is no complete market for drug development projects and therefore the value of a project depends on the individual judgment of the market participants. If the R&D project itself does not have one specific value the same holds true for the R&D option with the project as the underlying asset. In the absence of a complete

[362] These studies generally do not assume option exclusivity in an explicit way but rather neglect the opportunity of others to exercise a similar option right and therefore implicitly assume that the option is exclusive by nature. An example of treating real options that way can be found at Cassimon et al. (2004).

market, the price and at the same time the related financing potential of the R&D option is always negotiated between two parties and depends on their personal expectations. Lin (2002, p. 186) argues that for real option valuation problems where the underlying asset is not market traded and investors cannot be assumed to be risk neutral, individual risk preferences need to be subjectively considered in the valuation approach.

For this reason, this section classifies potential buyers of a R&D option into categories to identify investors that are potentially willing to pay the highest and the lowest price for such an option right. The classification is carried out along two dimensions. One dimension is the buyers' ability to diversify unsystematic risk and the second one is the availability of financial resources on buyers' side.

7.2.1 Buyers' Ability to Diversify Risk

Before entering into any risky investment, investors assess their own personal willingness to tolerate risk. They do so to estimate if the expected return justifies taking on the risk associated with a specific investment. The reason for this behavior is the fact that investors are generally risk-avers[363], which means that they avoid acquiring risky assets unless those assets have a higher expected return than assets without risk. In particular, a risk averse investor always prefers a less risky asset over a risky one if they are expected to yield the same return. The assumption that investors are risk avers is generally accepted and widely used in economic literature[364].

In an economy with incomplete markets and risk averse investors, one needs to be aware of the risk exposure of the individual investor. This is necessary to draw conclusions about the return an investor expects and therefore the price he is willing to pay to enter a specific investment. Taking a closer look at risk itself reveals that there are two different types of risks as described above, where the two components private and market risk are introduced. With these two types of risk, the common total risk definition can be used:

$$\text{Total Risk} = \text{Market Risk} + \text{Private Risk}$$

Based on portfolio theory it is known that the combination of two investments, unless their risk is perfectly positively correlated, results in a portfolio that is less risky than the weighted risk average of the two investments. Since all investments are somehow influenced by market forces, it is impossible to find two investments that are perfectly negatively correlated and therefore diversification can reduce some but cannot eliminate all risk associated with an investment[365]. The theoretical maximum diversification can be achieved by investing in all

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[363] For a more detailed discussion on risk aversion refer to Perridon and Steiner (2002, p. 107).

[364] According to Brigham et al. (1999, p. 168)

[365] Risk diversification in drug develoment is investigated by Ding and Eliashberg (2002) who build a model that allows optimizing the chance of a research development portfolio to contain at least one successful product.

opportunities in the market that are not perfectly correlated[366]. Since this study focuses on the drug developing industry, players in this industry are expected to only consider investments in the same industry and therefore the maximum theoretical diversification is represented by an investment in all ongoing drug development projects.

The remaining risk after establishing such a complete portfolio is the general market risk of the drug developing industry. The risk that is diversified on the other hand is the project risk related to the individual drug development projects. Figure 7.1 illustrates how an increasing number of investment projects can reduce the total risk of an investment portfolio. In chapter 5.2 it is described, which risk components in drug development can be considered private risk that can be diversified and which components can be considered market risk.

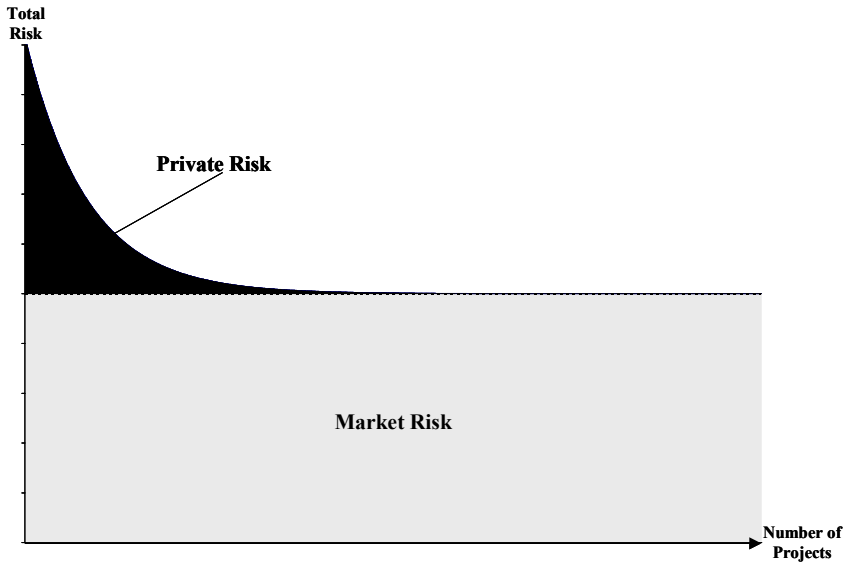

Figure 7.1: Risk reduction through diversification

With the described diversification in mind it can be said that the more investment projects an individual or a company holds[367], the smaller the total risk to which this entity is exposed[368]. Because of investors' risk aversion it can also be said that the more investments an entity holds, the smaller the total return it expects from these investments relative to the weighted risk advantage. Since the return of an investment decreases as its price increases it follows that a well diversified investor is willing to pay a higher price for an investment than one who is not able to diversify risk over a multitude of different projects. An investor fully diversified within the industry therefore not only requires the risk-free interest as a return on his investment but also a premium to be compensated for the remaining general industry risk.

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[366] This is called the market portfolio.

[367] Assuming their risk is not perfectly correlated.

[368] This is heavily supported by Hodder and Riggs (1985) who state that "the risk of a particular project appears lower from a portfolio perspective than from the perspective of an analyst looking at the project itself".

The described risk-value relationship is in line with recent real option literature. One example is the study of Lin (2002) who finds that the higher the diversification in an investor's portfolio, the higher the subjective value of a real option this investor holds[369].

7.2.2 Availability of Financial Resources on the Buyer's Side

The second dimension impacting the outcome of price negotiations between a seller of a R&D option and a potential buyer is the availability of financial resources. This point needs to be considered because in reality financial resources are limited. One of the assumptions used in a wide range of scientific studies that financial resources are available to an unlimited extent therefore does not hold true[370].

Most studies on option pricing are based on risk-neutral valuation and use a risk-free interest rate for the valuation. This approach might be applicable in situations where a general market view is applied but not for the purpose of this study. Kellogg and Charnes (2000, p. 81) justify the use of risk-neutral pricing by saying "furthermore, because we are interested in the market (rather than a subjective or private) value of the project […] the use of risk-neutral pricing is justified by the same arguments made by Cox et al. (1979) for pricing financial assets that are traded directly in the market." For this study, exactly this subjective or private value of an individual R&D project is of key interest and therefore it is essential to take a closer look at the applicable interest rates if the use of risk-free rates is not appropriate.

When considering an investment in a R&D option, a potential buyer compares the investment opportunity with other investment alternatives and they are therefore in direct competition for available funds. It follows that a risk averse investor makes his first investment into the opportunity promising the highest return with all other factors being comparable. Once the first investment opportunity with an expected return of r_{max} is completed, the investor uses his remaining funds to pursue the second best investment alternative with an expected return r_{exp} below r_{max} but above the return of all other remaining investment opportunities available.

In this situation it becomes clear that the more financial resources an investor has available, the more promising investment projects can be completed and the lower r_{exp}. In case there are sufficient resources available to pursue all promising investment opportunities, the investor is still able to invest remaining funds in the capital market and to buy investments such as governmental bonds, which are always available to an investor[371]. The expected

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[369] Which is caused by the risk reduction effect achieved through risk diversification.

[370] This is also one of the basic assumptions of the fundamental paper on option pricing of Black and Scholes (1973) who assume that "it is possible to borrow any fraction of the price of a security to buy it or hold it, at the short-term interest rate", which is not a realistic assumption in a real business environment.

[371] Because of the size of this segment of financial markets today, it represents an unlimited investment opportunity to the individual investor. In addition, the investor does not have to be concerned about influencing market conditions with his own individual investment because the relative size of this investment compared to the market size can always be neglected. To support

return of these investments can therefore be considered the minimum return achievable because if an investment is not expected to reach this minimum return r_{min}, it is not considered a viable alternative. Instead, available funds are directed to the financial market. Figure 7.2 shows this relationship between availability of financial resources and the expected return of a new investment.

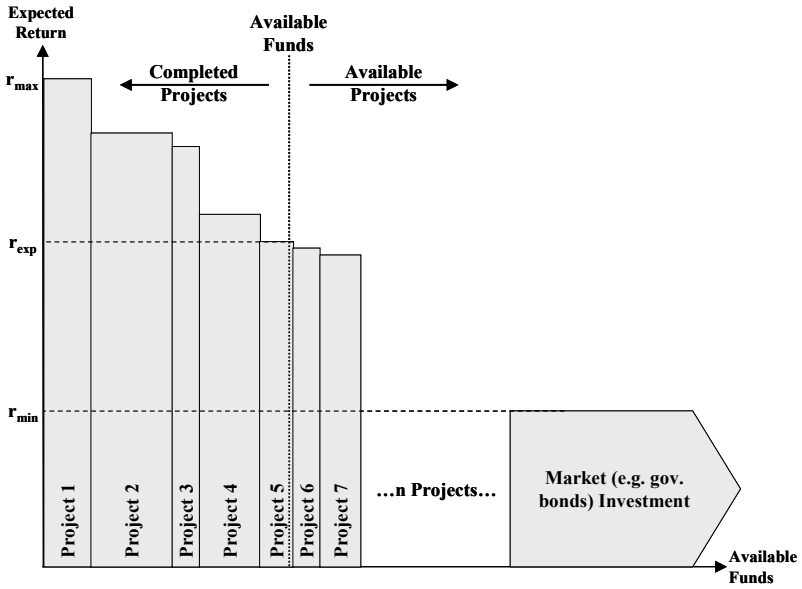

Figure 7.2: Relationship between availability of funds and expected return

If an investor has the opportunity to invest funds into a R&D option, this investment competes with the next investment he could alternatively pursue. It is known that the expected return r_{exp} of this next investment opportunity fulfills $r_{max} \geq r_{exp} \geq r_{min}$ and is also referred to as opportunity cost r_{opp} because it is the cost for not pursuing the next investment opportunity.

With the above explanations it follows that the more financial resources an investor has available, the more projects can be completed and therefore the lower r_{opp} becomes[372]. With these lower return expectations, an investor with more financial resources is willing to invest more into a R&D option than an investor with very limited financial resources. This is caused by the fact that a higher initial investment reduces the expected return of an investment with all other factors remaining unchanged.

7.2.3 Buyer Classification Matrix

Above, two dimensions are discussed that influence the price investors are willing to pay for a R&D option and two relations are identified:

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this point one should consider that the US Government alone had US$4,580 billion in treasury securities outstanding to the public in July 2005 according to BPD (2005) and average daily trading of these securities reached a volume of US$535 billion according to the Federal Reserve Bank of New York FEDNY (2005).

[372] Assuming all available projects are of similar risk.

- The more research projects a potential investor pursues, the lower his total private risk exposure[373] due to diversification effects. This reduces the total risk this investor associates with an additional R&D project and therefore the higher the price he is willing to pay for this investment or a call option on it.
- The more financial resources a buyer of a R&D option has available, the higher the price he is willing to pay because the lower his expected return.

Based on these findings, potential buyers of a R&D option can be classified along the two dimensions investment structure and availability of financial resources to determine the classes of investors that finally determine the financing potential of a R&D option. Figure 7.3 illustrates this classification of potential R&D option buyers. It can be derived, which investors are willing to pay the lowest price for a R&D option and which ones are willing to only pay the highest price. With this information, a pricing range can be determined, which is limited by these two extreme types of investors.

With all other environmental factors being the same, an investor with very limited financial resources and without other ongoing projects to diversify unsystematic risk exposure is only willing to pay a reduced amount of money to acquire a R&D option. This is caused by the fact that this investor is exposed to general market risk and all project-specific risks because he does not benefit from diversification effects. In addition, this type of investor has the highest return expectations because the investment competes with a multitude of alternative investment opportunities that cannot be pursued if the R&D option is acquired. An example of this type of investor is a small drug developing company with very limited financial resources that has to decide between buying a R&D option or to invest the same amount of money in internal research to pursue a promising internal research project.

At the other end of the spectrum one can find an investor who owns a portfolio of a large number of different research projects and who still has significant financial resources available to be invested. Such an investor has diversified most or all project-specific private risk and is only exposed to general market risk. This in combination with his financial ability to pursue a wide variety of new projects makes him the type of investor who is willing to pay the highest price for a R&D option or any other investment.

Pharmaceutical companies with large research portfolios[374] and significant accrued reserves to be invested[375] are potential buyers of a R&D option that fall into this category. Bäcker and Hommel (2002, p. 510) follow this point of view with their finding that technical or project

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[373] Compared to the weighted risk advantage of the individual investments.

[374] On the strategic importance and management of research portfolios refer to MacMillan and McGrath (2002).

[375] Compare to Lichtenberg (2001, p. 221) who states that "it also seems unlikely that "big pharma" firms such as Pfizer and Glaxo SmithKline are constrained in their liquidity".

specific risk is completely uncorrelated with market risk and a fully diversified investor does not expect to be compensated for this type of risk.

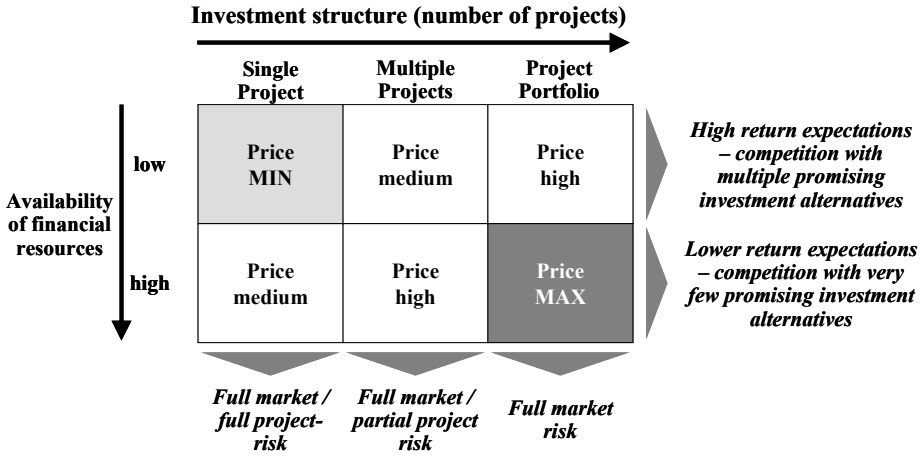

Figure 7.3: Potential R&D option buyer classification matrix

With these explanations it can be said that the financing potential of a R&D option is not a fixed number but rather a range, which is limited to both sides by the two types of investors described. In the remainder of this study these two cases are investigated to determine an upper and a lower limit of this financing range. Since all other types of option buyers fall into this range, an additional investigation of their investment preferences does not add value to this study and therefore only the two most extreme cases are considered.

7.2.4 Expected Investors' Return

To determine the financing range of the R&D option using a subjective valuation approach it is necessary to have knowledge of the return investors expect from their investment and therefore the discount factor to be applied. Following Dixit and Pindyck (1995, p. 107), the use of opportunity cost as a discount factor would theoretically produce meaningful results for the lower pricing limit because it incorporates all the systematic or non-diversifiable risk associated with an individual project in the calculations. In reality, opportunity cost can hardly be used as a discount factor because of the criticism mentioned at Perridon and Steiner (2002, p. 87) who describe opportunity cost as a waste product of a result rather than an input parameter to generate a result and because this factor is extremely difficult to measure. Dixit and Pindyck (1995, p. 107) state that it is appropriate to substitute opportunity cost with the weighted average cost of capital of a company as long as a company's projects are exposed to a similar non-diversifiable risk. For projects with significant private risk, adjustments are necessary to appropriately consider these risk factors.

As shown above, drug development projects do include a significant amount of private risk and therefore the unadjusted use of weighted average cost of capital (WACC) appears critical. In addition, Loch and Bode-Greuel (2001, p. 232) limit the appropriate use of WACC to cases where funds for R&D are not scarce. As discussed above, the availability of financial resources is one of the factors impacting the willingness to invest in a R&D option and therefore the requirements for the use of WACC as a discount factor in the valuation approach are not fulfilled to derive the lower financing limit of the R&D option.

For the case of the upper financing limit the availability of financial resources is, by definition, not critical. In addition the upper limit is defined by an investor with fully diversified private risk. As long as this type of investor operates within one industry the involved non-diversifiable risk appears the same for all investment projects, being equivalent to the general industry risk. To determine the upper financing range of a R&D option the use of WACC therefore appears appropriate because it fulfills the requirement of unlimited financial resources as well as comparable systematic risk over all investments.

Nevertheless, WACC represents a factor, which is specific to an individual company and is affected by its capital structure[376]. To apply a more general view, the expected return of an abstract investor determining the upper financing limit of a R&D option is broken down into two components. The first component is represented by the risk-free rate of return applicable to any investor. In addition, an investor fully diversified within the industry requires a return premium for the systematic industry risk, which cannot be diversified. For the purpose of this study the following notation is used to describe the two return components.

r_{rf} - Risk-free rate of interest

α - Return premium for general market risk

As discussed above, the described expected return ($r_{rf}+\alpha$) is also relevant for the investor representing the lower end of the financing range. In addition, this type of investor expects to be compensated for private risk he is unable to diversify and therefore a risk premium is introduced to consider this inability to diversify risk. The risk premiums are selected in accordance with the risk factors involved in drug development projects as described in section 5.1. The following parameters are introduced for the quantitative assessment.

β - Return premium for the risk of competition

ε - Return premium for potential project failure

ρ - Return premium for uncertain project timing

To reduce modeling complexity throughout the remainder of this work it is assumed that the introduced additional risk premiums consider the financial situation of a potential investor as opposed to introducing an additional factor to model a premium for the availability of financial resources. With all these premiums being subjective by nature this appears an appropriate simplification. For an investor A with better access to financial resources compared to an investor B, this simplification implies that $\beta_A<\beta_B$, $\varepsilon_A<\varepsilon_B$ and $\rho_A<\rho_B$.

[376] The calculation of a firm's WACC includes the financing cost of all corporate capital sources - common stock, preferred stock, bonds and any other long-term debt. WACC is calculated by multiplying the cost of each capital component by its proportional weight and then adding all components up to derive the corporate WACC.

7.3 Upper Pricing Limit of a R&D Option

This section investigates the maximum amount a seller can expect to receive when offering a R&D option. In chapter 7.2 it is described that potential buyers with an opportunity to diversify unsystematic risk and unlimited financial resources are the type of buyer that can be expected to pay the highest price for a R&D option. Modeling the price expectations of this buyer therefore results in the upper limit of the pricing range of a R&D option. The condition of a fully diversified investor[377] is best fulfilled by large pharmaceutical companies holding extensive and diverse product and research portfolios.

Initially this upper pricing case was intended to be modeled using a risk-neutral valuation model because such an approach by definition eliminates unsystematic risk. While this allows a much simpler valuation model, it creates a market view on the situation and does not result in a subjective view of the project, which is the relevant perspective in an incomplete market. The price of the R&D option is a result of individual price negotiations because of the absence of a liquid market. Kellogg and Charnes (2000, p. 81) already claim that the use of risk-neutral pricing is only appropriate "for pricing financial assets that are traded directly in the market".

On the other hand, Loch and Bode-Greuel (2001) support the view that large diversified companies are the type of investors that can be described as being risk-neutral when making an investment[378]. While this might be a valid point of view for investments in market traded assets, it is not applicable to this study because the requirement of a complete market is not fulfilled. Pennings and Lint (1997, p. 84) discuss this issue in their evaluation of options in the high-tech industry.

To consider a more private and subjective view, a new model for the upper pricing limit is developed instead of building a model based on existing risk-neutral valuation approaches.

7.3.1 Underlying Assumptions

In addition to the underlying assumption of an idealistic market environment there are several points to be clarified before the model to assess the fund raising potential of a R&D option is built. The most important assumptions are related to the drug development project representing the underlying asset of the R&D option.

For the purpose of this study the variable Drug Approval Value (DAV) is introduced. The DAV represents the value of a new drug at the time it is approved by regulatory authorities. The point of final drug approval is noted as T_A and is measured relative to the point patent protection status is requested. The DAV of an approved new drug at time T_A is equal to the

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[377] Fully diversified in this context always refers to being fully diversified within the industry and not across the entire economy as described above.

[378] "A large company […] is typically risk-neutral, as the projects under discussion are small relative to the company's business" Loch and Bode-Greuel (2001).

sum of its discounted contribution margins CM(t) being revenues less all running cost such as production, marketing and distribution costs over the effective patent protection period. In addition, a drug potentially has a terminal value TV at time T_X when the patent expires. With this in mind, the drug approval value can be defined as equation (7.1).

$$DAV = \int_{T_A}^{T_X} CM(t) * e^{-r(t-T_A)} dt + TV_{T_X} * e^{-r(T_X-T_A)} \qquad (7.1)$$

DAV : Drug Approval Value at the point of drug approval T_A

CM(t) : Contribution margins from sales of the approved new drug in period t

T_A : Time of final drug approval relative to the point when the application for patent protection status is filed with regulatory authorities

T_X : Time of patent expiration relative to the point when the application for patent protection status is filed with regulatory authorities

TV_{TX} : Terminal Value of a drug at the end of the patent protection period

r : Applied discount factor

It is defined for the idealistic market environment that the market potential measured in total contribution margins[379] is constant over time and that a project has no salvage value once the related patent expires[380]. From these assumptions it can be concluded that CM(t)=MP, with MP being a constant and TV_{TX}=0. In combination with the knowledge that patent expiration occurs exactly twenty years after the application for patent protection status and therefore T_X=20, equation (7.1) can be simplified to equation (7.2).

$$DAV = \int_{0}^{20-T_A} MP * e^{-rt} dt \qquad (7.2)$$

Solving the integral leads to formula (7.3) for the valuation of the drug approval value DAV.

$$DAV = \frac{MP}{r} * (1 - e^{-r(20-T_A)}) \qquad (7.3)$$

From (7.3) it becomes clear that the drug approval value significantly depends on the discount factor r used in the calculation. Finding the appropriate discount factor for valuation problems is a challenging task and it is not uncommon in the context of drug development to find companies using a wide range[381] of discount rates from as low as 8%[382] up to 30%[383].

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[379] Banerjee (2003, p. 70) estimate the cash operating margin in the pharmaceutical industry during the patent protection period to be around thirty per cent of revenues in a free market environment while it is around twenty five per cent of revenues in a price regulated environment.

[380] This is consistent to the drug development valuation approach of Banerjee (2003, p. 68) who does not consider revenues from the post-patent protection area for his study.

[381] For the upper range of discount factors the findings of Hodder and Riggs (1985, p. 135) can be stated who found that excessive risk adjustments lead to a systematic bias against R&D projects.

The widely respected work of DiMasi et al. (2003, p. 164) on drug development cost uses a real discount rate of 11.9% for a fully diversified investor[384]. With finding the correct discount factor for valuation problems being a study in itself, this work uses generic placeholders throughout the discussion. For demonstration purposes these placeholders are filled with exemplary figures. The assumed magnitude for the risk-free rate of interest and the introduced risk premiums are shown in Table 7.1. For detailed valuable discussions on discount rates used in corporate investment decisions one can refer to Schwarz, Horst (1967), Brandt (1970), Krause (1973), Brealey and Myers (2000) or Perridon and Steiner (2002).

Risk free rate of interest	r_{rf}	=	**4%**
Return premium for general market risk	α	=	**7%**
Return premium for the risk of competition	β	=	**5%**
Return premium for potential project failure	ε	=	**5%**
Return premium for uncertain project timing	ρ	=	**5%**

Table 7.1: Assumptions on magnitude of discount factors for valuation examples

In addition, an exemplary drug development project is introduced to demonstrate the various valuation steps presented in this study. Table 7.2 summarizes the main characteristics of this illustrative case example.

Fixed market potential as total contribution margin per annum	MP	=	**100**
Upper limit of market potential expectations as total contribution margin per annum (95% confidence)	MP_u	=	**120**
Lower limit of market potential expectations as total contribution margin per annum (95% confidence)	MP_l	=	**80**
Initial expected project termination date from time of patent application	$E(T_A)$	=	**11**
Initial uncertainty related to log-normally distributed project duration	$\sigma_{ln(TA)}$	=	**0.20**
Initial lower 95% confidence interval for log-normally distributed project duration	$LoL_{95\%}(T_A)$	=	**7.4**
Initial upper 95% confidence interval for log-normally distributed project duration	$UpL_{95\%}(T_A)$	=	**16.4**
Minimum initial project termination date for exp. distributed project delay	$T_{Amin}(0)$	=	**11**
Initial 95% confidence interval for exponentially distributed project delay	$T_{Amax}(0)$	=	**16.4**

Table 7.2: Underlying assumptions for illustrative case example

For demonstration purposes, a R&D option on this case example is defined that allows the owner to acquire the outcome of the project for 400 mil. monetary units at the time of final drug approval. Additional details on the case example are introduced in the individual sections of this work when they become relevant for the presented valuation approach.

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[382] See Dixit and Pindyck (1995, p. 108)

[383] See Loch and Bode-Greuel (2001, p. 233)

[384] "These technical risks can be diversified away by investors", DiMasi et al. (2003, p. 170).

7.3.2 Time Discrete One Step Binomial Assessment

This section is intended to summarize some points on option theory and apply them to the specific valuation problem of this study. In the tree based valuation approaches for R&D projects, described in chapter 6.1, a company conducting internal R&D is confronted with multiple decision points to abandon a project. While this might be the case for the research conducting company itself, it is not the case for a company buying a R&D option. The owner of such a R&D option has exactly one decision point where he can execute his right or can let it expire unexercised. By definition this point is fixed relative to the value chain and always occurs at the time a new drug is approved by regulatory authorities. Should the project fail before this point it does not reach this final decision point and also expires unexercised.

While a research conducting company holds a real compound call option with uncertain time to maturity, a R&D option owner holds a European style call option with uncertain time to maturity. This reduces the complexity of the valuation problem as visualized in Figure 7.4 where the differences between decision points in internal research are directly compared to the decision points of a R&D option.

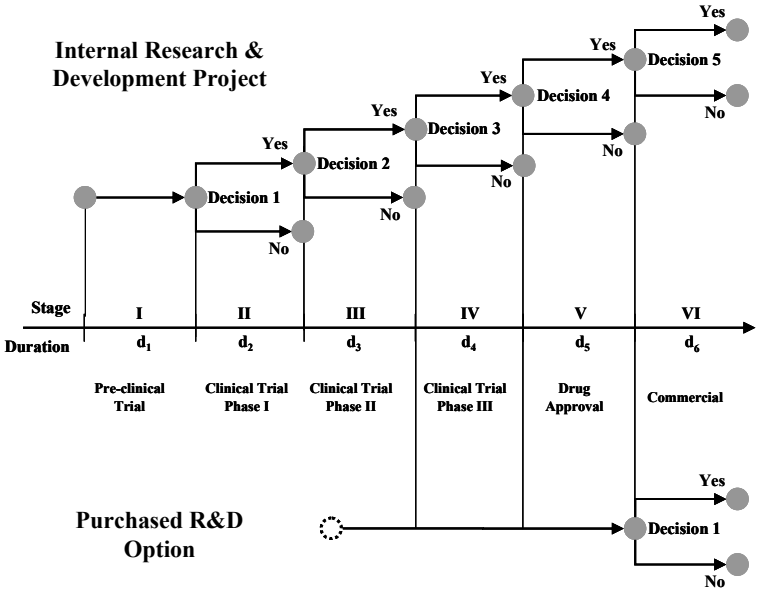

Figure 7.4: Number of decision points for internal R&D and a R&D option

The decision rule for the R&D option owner is the same as for a financial call option. If the value of the underlying asset, in this case the research project, exceeds the agreed exercise price X at maturity the option is exercised. In all other cases the option expires unexercised. With the value of the project at drug approval being the defined drug approval value DAV, the value of the R&D option C at the final decision point can be written as follows.

$$C(T_A) = MAX\left[DAV - X;0\right] \qquad (7.4)$$

Figure 7.5 illustrates the R&D option exercise decision rule. It also shows that irrespective of t_1 the option is bought, the decision rule at T_A remains unchanged.

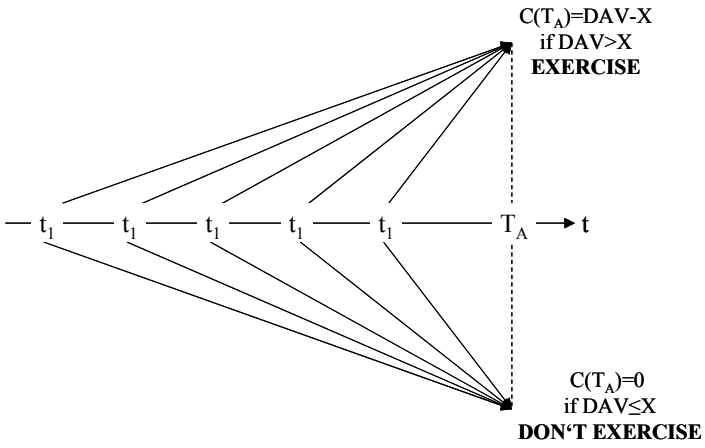

Figure 7.5: Decision rule for exercising R&D option

At this point, all parameters to determine DAV are known and not related to uncertainty therefore the exercise decision only depends on the exercise price X of the option. If the exercise price is set too high, the option expires unexercised with a value of zero at T_A. In cases where X is fixed low enough for the option to be exercised at T_A, the option has a known value of $C(T_A)$=DAV-X at the time of expiration. This relationship always holds true at the time of drug approval T_A, no matter at which time t_1 the R&D option is acquired.

As defined in chapter 5.3.2, the R&D option can be written any time t_1 between the time the application for patent protection is filed and the time of final drug approval. If the process of developing a new drug was without additional risk, the R&D option would guarantee an amount of MAX[DAV-X;0] at time T_A to the option owner. To have the same amount at his disposal at time T_A the investor has to invest an unknown amount of money at any time $t_1<T_A$ in an alternative investment that guarantees an equivalent payout at time T_A. Since the payout can be predetermined with a given exercise price X the unknown amount of money can be quantified. In cases where X is set high enough to let the R&D option expire unexercised the known payout is zero and therefore the value of the option at any time t_1 is also zero. For all cases where X is set low enough for the option to be exercised, the know value at T_A is DAV-X and therefore the value of the R&D option can be expressed as (7.5).

$$\left.\begin{array}{lll} C(t)=0 & if & X \geq \dfrac{MP}{r_{rf}} * \left(1-e^{-r_{rf}(20-T_A)}\right) \\ C(t)=\left(\dfrac{MP}{r_{rf}} * \left(1-e^{-r_{rf}(20-T_A)}\right)-X\right) * e^{-r_{rf}(T_A-t)} & if & X < \dfrac{MP}{r_{rf}} * \left(1-e^{-r_{rf}(20-T_A)}\right) \end{array}\right\} \qquad (7.5)$$

This represents the value of the R&D option at time t if there is no uncertainty[385] and the exercise decision can be predetermined by selecting an appropriate value for the exercise price X above or below the exercise threshold DAV. Without any type of uncertainty at this

[385] Except the basic market uncertainty discussed in section 7.3.1 and the related risk premium α.

stage of building the valuation model the applicable risk-free rate of interest represents the correct discount factor to be applied otherwise arbitrage opportunities would exist.

7.3.3 Introduction of Continuous Project Failure Risk

As described in chapter 5.1 the drug development process is far from being free of uncertainties. The first and most important factor of uncertainty investors are exposed to is related to the potential failure of a project before a new drug is approved or that final approval is not granted by regulatory authorities. This potential risk is generally modeled from the perspective of the research conducting company with a tree structure as indicated in Figure 7.4. This implies that at the end of each project phase a decision is made to either continue the project and enter the next project phase or to abandon the project altogether[386].

Such a view is not appropriate from the perspective of the R&D option owner because he neither has control over the failure of the project nor does he know when decision points occur[387]. With this in mind, it appears more appropriate to model the risk of project failure as a continuous function of time. For this purpose a function is introduced that quantifies the failure risk of a standard drug development project. This failure rate function is referred to as $FR(t_S)$ with t_s being the time relative to the start of a new research project.

$FR(t_S)$ = Failure Rate at time t_S relative to the start of a development project

The function to model a project's failure risk has to fulfill multiple criteria:

1. The function has to be defined for all t_S from the start of the project until final approval. If the R&D project starts at $t_S=0$ and ends at $t_S=T_{AS}$, $FR(t_S)$ needs to be defined for all $t_S \in D_{ts}$ with $D_{ts}=[0;T_{AS}]$.
2. It can be assumed that the risk of technical failure of a drug development project decreases the more information is acquired over time[388]. Since relevant information is continuously generated, $FR(t_S)$ is a strictly monotonic decreasing function in D_{ts}. This means for all t_{Sa}, $t_{Sb} \in D_{ts}$ with $t_{Sa}<t_{Sb}$ that $FR(t_{Sa})>FR(t_{Sb})$.

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[386] One can argue about the appropriateness of this modeling approach because in reality, a company involved in R&D activities not only has the option to abandon a project at the end of a project phase but can rather do so at any time. Information about the prospectives of a project is generated on a continuous basis and therefore it appears more appropriate, even from the perspective of the research conducting company, to use a model considering potential project termination as a continuous function rather than using a few distinct decision points. This appears even more important if one considers that the individual project phases between decision points can take multiple years to complete.

[387] This was one of the framework assumptions defined in chapter 5.3.2. In reality a research conducting company will not be able to discontinue a project without a discussion and extensive information exchange with the option owner.

[388] Also refer to Boer (2003, p. 52) who states "in a well-managed project, the overall level of risk typically decreases".

3. Before any research activities are started, the risk of failure is 100% therefore $\lim_{t_S \to 0} FR(t_S) = 1$.

4. For this study it is assumed that at the time of final drug approval, all risk of technical failure is removed and therefore $\lim_{t_S \to T_{AS}} FR(t_S) = 0$.[389]

5. Applying the intermediate value theorem it can be concluded that the domain W_{FR} for $FR(t_S)$ for all $t_S \in D_{ts}$ is $W_{FR}=[0;1]$.

The function $FR(t_S)$ has to approximate the experiences from previous studies shown in Table 5.1 and therefore should match the data as closely as possible. Plotting these failure rates against the timing of an average development project results in Figure 7.6.

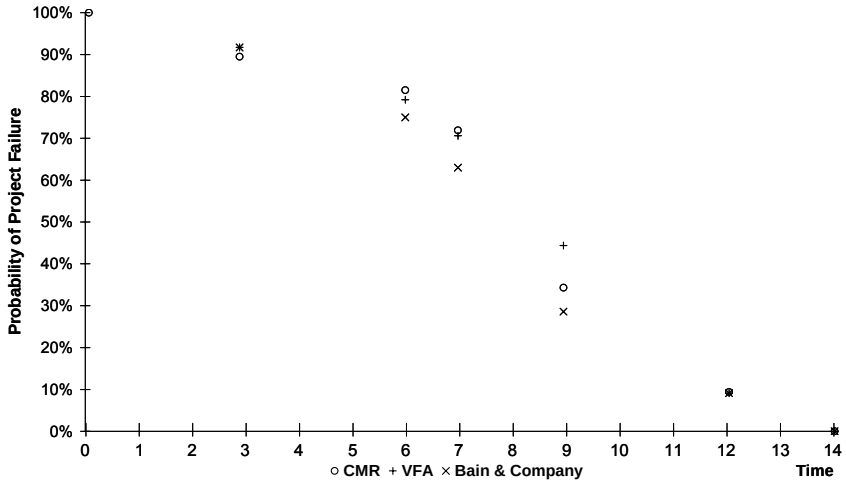

Figure 7.6: Results of recent studies on technical failure risk

A function that fulfills criteria 1-5 and can be adjusted to approximate the plot in Figure 7.6 is a shifted and compressed cosine function with one exponent of the form (7.6). This type of function is used for the standard failure risk with $t_S \in D_{ts}$, $D_{ts}=[0;T_{AS}]$ and $\gamma \in R_+^*$.

$$FR(t_S) = \left(\frac{\cos \frac{t_S}{T_{AS}} \pi + 1}{2} \right)^{\gamma} \qquad (7.6)$$

Using $T_{AS}=14$ for the standard drug development project as shown on Table 2.1, equation (7.6) becomes (7.7) with $t_S \in D_{ts}$, $D_{ts}=[0;14]$ and $\gamma \in R_+^*$.

[389] The rational behind this point is the assumption that no approved drug is discontinued during its effective patent protection period. In reality, a fraction of projects are discontinued even after final drug approval therefore setting $\lim(FR(t_S))=0$ with $t_S \to T_{AS}$ represents a simplifying assumption.

$$FR(t_S) = \left(\frac{\cos\frac{t_S}{14}\pi + 1}{2} \right)^{\gamma} \tag{7.7}$$

To select a factor $\gamma \in R_+^*$ that most appropriately fits function (7.7) into the plot of Figure 7.6, the method of relative least squares is used. With this method $\gamma \in R_+^*$ is selected in a way that the following relative error function (7.8), with i=[1;15] being the 15 points in Figure 7.6 and $\gamma \in R_+^*$, is minimized with $\overline{FR}(t_{Si})$ being the actual observed failure rates listed in Table 5.1 and displayed in Figure 7.6.

$$Q(\gamma) = \sum_{i=1}^{15} \left(\frac{\overline{FR}(t_{S_i}) - FR(t_{S_i})}{\overline{FR}(t_{S_i})} \right)^2 = \sum_{i=1}^{15} \left(\frac{\overline{FR}(t_{S_i}) - \left(\frac{\cos\frac{t_{S_i}}{14}\pi + 1}{2} \right)^{\gamma}}{\overline{FR}(t_{S_i})} \right)^2 \tag{7.8}$$

The relationship between γ and Q(γ) is displayed in Figure 7.7, showing a local minimum for the relative squared error at γ=0.79 with Q(0.79)=0.26.

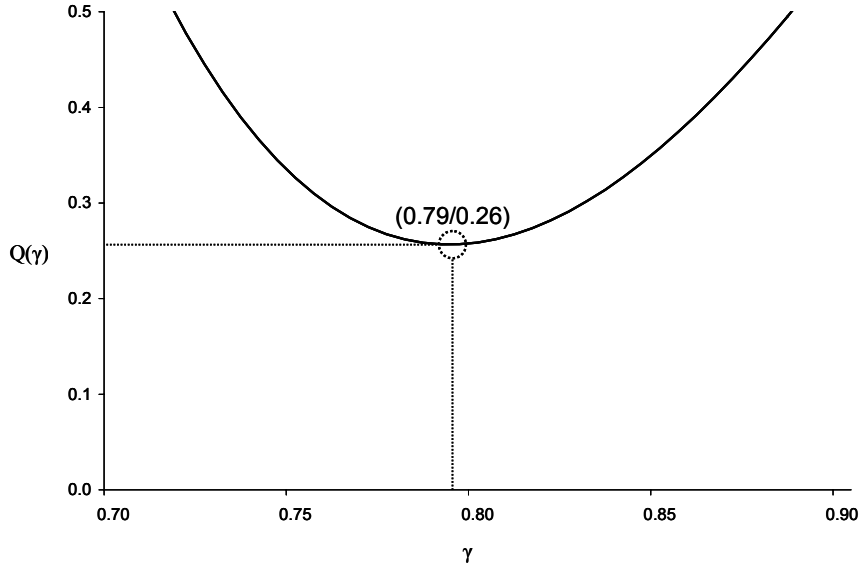

Figure 7.7: Relative error function of one exponent failure risk approximation

For this study the rounded figure of γ=0.8 is used. With the optimized value for γ, equation (7.6) can be transferred into the standardized failure risk function (7.9) quantifying the risk of technical failure during a drug development project with $t_S \in D_{ts}$, and $D_{ts}=[0;T_{AS}]$.

$$FR(t_S) = \left(\frac{\cos \frac{t_S}{T_{AS}} \pi + 1}{2} \right)^{\frac{4}{5}} \tag{7.9}$$

Figure 7.8 shows the derived failure risk function in comparison to the other historical studies on risk of technical failure in drug development.

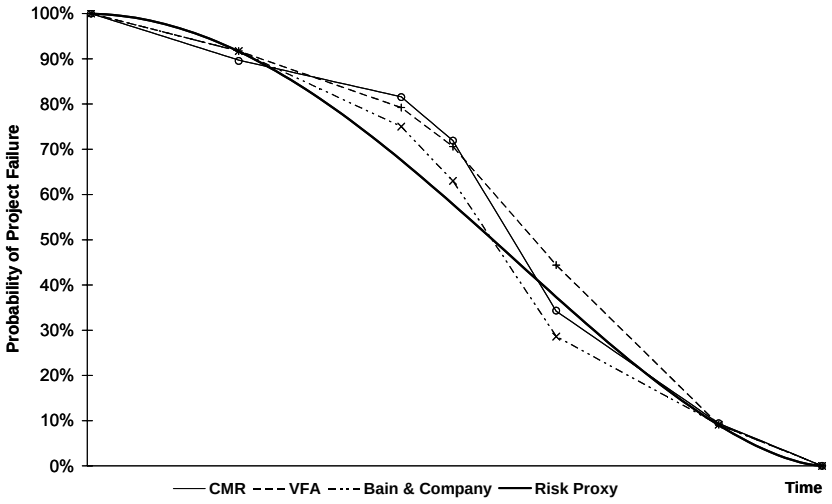

Figure 7.8: Technical failure risk approximation function

To ensure a direct comparison between these studies, Table 7.3 shows the expected failure rates when entering a new stage of drug development. For the purpose of this study it is not distinguished between different failure reasons because an outside view is applied. In case drug development projects are evaluated internally, Villinger and Bogdan (2005) show that it is necessary to distinguish between economic failure[390] and safety or efficacy related failure.

[390] According to Villinger and Bogdan (2005), around 30% of all project abandonments are for economic reasons.

	CMR International[391]	VFA[392]	Bain & Company[393]	**Failure Risk Proxy FR(t_S)**
Pre-clinical Test	89.7%	91.7%	91.7%	**91.2%**
Clinical Phase I	81.6%	79.2%	75.0%	**67.4%**
Clinical Phase II	71.9%	70.6%	63.0%	**57.4%**
Clinical Phase III	34.2%	44.4%	28.6%	**36.4%**
Approval Process	9.4%	9.1%	9.1%	**9.0%**

Table 7.3: Approx. failure risk entering various stages of drug development

Although equation (7.9) is suited to approximate the risk of technical failure during a drug development project, it needs an additional adjustment. The adjustment is necessary because of the time factor t_s, which models the failure risk relative to the start of the project and not relative to the time the application for patent protection is filed. Since this point is defined as the reference point of this study, the following section transfers the failure risk function relative to t_s to a new function relative to the starting point t.

7.3.3.1 Approximation of a Standard Technical Risk Function

In chapter 5.3.2 it is assumed that the first time an option can be written on a drug development project is the time an application for patent protection is filed and an intangible asset is created. To take this assumption into account the function $FR(t_S)$ is adapted to a technical risk function TR(t) with t=0 being the time of patent application, which is equal to t_S=3 considering the standardized base research period shown in Table 2.1. This transformation is based on the following criteria.

- TR(t) is independent from the time before filing for patent protection. The point TR(0) marks the end of the base research phase irrespective of its duration.
- TR(t) is dependent on the time of expected final approval for a new drug $E(T_A)$.
- TR(t) has to be defined for all $t \in D_t$ and $D_t=[0;E(T_A)]$.
- TR(t) has to be strictly monotonic decreasing in D_t. This means for all $t_a, t_b \in D_t$ with $t_a<t_b$ that $TR(t_a)>TR(t_b)$.
- Technical risk at the time patent protection is requested is the same for all drug development projects therefore TR(0)=FR(3).
- For this study it is assumed that at the time of final approval all risk of technical failure is removed and therefore $\lim_{t \to T_A} TR(t) = 0$.
- Applying the intermediate value theorem it can be concluded that the domain W_{TR} for TR(t) for all $t \in D_t$ is $W_{TR}=[0;FR(3)]$.

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[391] Source: PAREXEL (2003, p. 184)

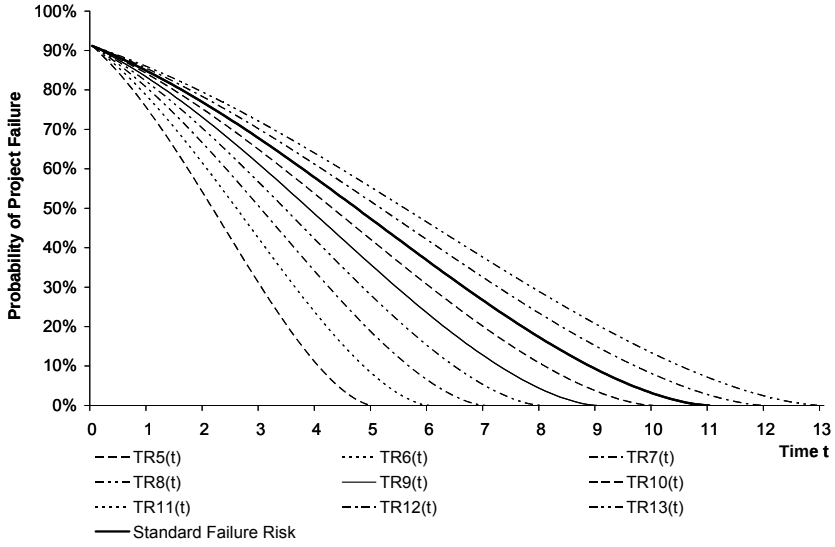
[392] Source: FDA (2004, p. 5)

[393] Source: PAREXEL (2003, p. 170)

Equation (7.10) shows the derived[394] function with T_{SS} being the time period between the initiation of a project and the time of patent application of the averaged research project.

$$TR(t) = \left(\frac{\cos\left(\frac{\frac{(T_{AS} - T_{SS})}{E(T_A)} t + T_{SS}}{T_{AS}} \right) \pi + 1}{2} \right)^{\frac{4}{5}} = \left(\frac{\cos\left(\frac{\frac{11}{E(T_A)} t + 3}{14} \right) \pi + 1}{2} \right)^{\frac{4}{5}} \qquad (7.10)$$

The technical risk function TR(t) with $t \in D_t$, $D_t=[0;E(T_A)]$ and $E(T_A)=11$ matches exactly the path of the standardized failure risk function $FR(t_S)$ with $t_S \in D_{ts}$, $D_{ts}=[0;T_{AS}]$ and $T_{AS}=14$ from $t_S=3$ to $t_S=14$. Figure 7.9 shows various technical risk functions $TR_i(t)$ with different selected $E(T_A)$ compared to the path of the standardized failure risk function.[395]



$TR_i(t)$	$TR_5(t)$	$TR_6(t)$	$TR_7(t)$	$TR_8(t)$	$TR_9(t)$	$TR_{10}(t)$	$TR_{11}(t)$	$TR_{12}(t)$	$TR_{13}(t)$
$E(T_A)$	5	6	7	8	9	10	11	12	13

Figure 7.9: Illustrative examples of various technical risk functions

[394] Appendix A describes the transformation from the standardized failure risk function $FR(t_S)$ to the standardized technical risk function TR(t) in detail.

[395] While the technical risk function TR(t) defined by equation (7.10) is expressed relative to t, being the time an application for patent protection is filed, it can also be adapted to any later point in time during the research process. This changes TR(t) to $TR(t_*)$ with t* being the new reference point expressed in time relative to the standard development project. With this type of referencing TR(t) is equivalent to $TR_3(t_3)$ but as the main formula used in this study, it is kept as TR(t) for readability purposes. Since the derivation of $TR(t_*)$ does not add value to the main body of this work, one can refer to Appendix C for adjustments to the technical risk function.

To quantify the probability of completion during a research project as opposed to the risk of technical failure, a new measure is derived from the standardized technical risk function (7.10). This new function for the expected completion rate CR of a project is defined as

(7.11). Alternative approaches to estimate technical risk can be found at Roberts and Weitzman (1981)[396], Reinhardt (1997, p. 197) and DiMasi (2001b)[397].

$$CR(t) = 1 - TR(t) = 1 - \left(\frac{\cos\left(\frac{\frac{11}{E(T_A)} t + 3}{14} \right) \pi + 1}{2} \right)^{\frac{4}{5}} \qquad (7.11)$$

Figure 7.10 illustrates[398] the difference between continuous information arrival and an approach considering new information arrival at discrete decision points. The graph shows that at times before a decision point the discrepancy between the two approaches is large.

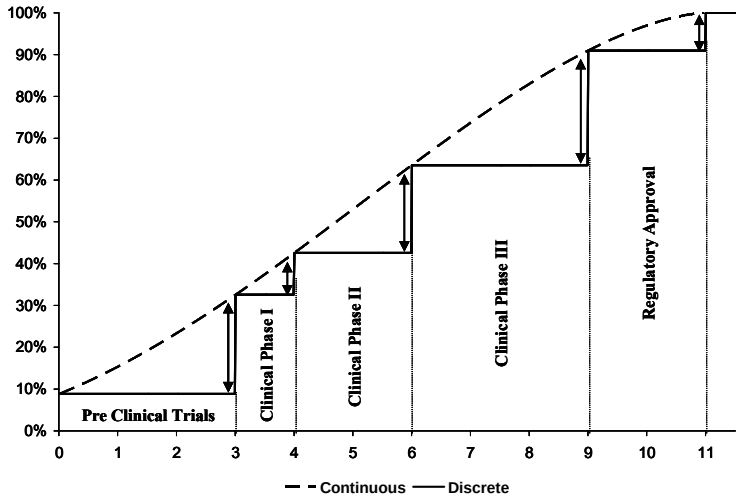


Figure 7.10: R&D success rates of discrete vs. continuous information arrival

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[396] The approach of Roberts and Weitzman (1981) is based on the idea that development cost are paid to obtain additional information about the outcome of a R&D project. In their model, uncertainty is a function of the remaining cost necessary to complete a project.

[397] DiMasi (2001) indicates in his study that the success rate of drug development projects can be predicted with a combination of two probability functions. He suggests combining a probability for project survival with a probability of final drug approval.

[398] The graph is based on the standardized project stage durations defined in Table 2.1 and the failure risk proxy shown in Table 7.3.

7.3.3.2 Continuous Technical Risk Adjusted Assessment

Above, the value of a R&D option in an idealistic market environment with known market potential and certain time to maturity is quantified. It is discussed that in such an environment the exercise decision only depends on the exercise price and if it is set above or below a certain exercise threshold. This threshold X_{Thres} is equal to the drug approval value DAV of a drug.

$$X_{Thres} = DAV = \frac{MP}{r_{rf}} * \left(1 - e^{-r_{rf}(20-T_A)}\right) \tag{7.12}$$

At this point it is assumed that X is set below the exercise threshold X_{Thres} and the R&D option is therefore exercised by the option owner if the drug development process is completed. From (7.5) it can be seen that the value of the option at time t can be quantified using (7.13) with $X<X_{Thres}$[399].

$$C(t) = \left(\frac{MP}{r_{rf}} * \left(1 - e^{-r_{rf}(20-T_A)}\right) - X \right) * e^{-r_{rf}(T_A - t)} \tag{7.13}$$

It is known from the discussion on risk in drug development that it is necessary to consider the project-specific risk of technical failure in the valuation model. Recalling the assumption that X is set in a way that the option represents a valuable right if the point of final approval is reached, the option value is only zero to the owner in those cases where the investigated drug proves to be ineffective or dangerous before T_A is reached. This can happen any time during the course of the research project. The probability that it happens is defined as the technical risk TR(t), which varies during the project and reflects the risk of technical failure throughout the drug development process. To consider this potential loss of investment, the owner of the option is only willing to pay a price to acquire the option that is adjusted by a factor representing technical risk. This risk adjusted upper pricing limit C_U at time t can be calculated by weighting (7.13) with the expected success rate

(7.11). In addition the discount factor is changed to a level appropriate for the investigated type of investor. As discussed above all market participants are exposed to general market risk and therefore the risk-free interest rate r_{rf} is supplemented by the premium for general, non-diversifiable market risk α. This results in a technical failure risk adjusted R&D option value (7.14) at time t.

$$C_U(t) = \left(\frac{MP}{(r_{rf} + \alpha)} * (1 - e^{-(r_{rf}+\alpha)(20-T_A)}) - X \right) * e^{-(r_{rf}+\alpha)(T_A - t)} * \left(1 - TR(t)\right) \tag{7.14}$$

In full detail it can be expressed as equation (7.15).

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[399] The opposite case with $X \geq X_{Thres}$ does not require special attention and can easily be explained. For all $X \geq X_{Thres}$ the project value always stays below the agreed exercise price and therefore C(t)=0.

$$C_U(t) = \left(\frac{MP}{(r_{rf} + \alpha)} * \left(1 - e^{-(r_{rf}+\alpha)(20-T_A)}\right) - X \right) * e^{-(r_{rf}+\alpha)(T_A - t)} * \left(1 - \left(\frac{\cos\left(\frac{\frac{11}{T_A}t + 3}{14} \right)\pi + 1}{2} \right)^{\frac{4}{5}} \right) \qquad (7.15)$$

Figure 7.11 illustrates the upper R&D option value over time considering the risk of technical failure in an idealistic market environment.

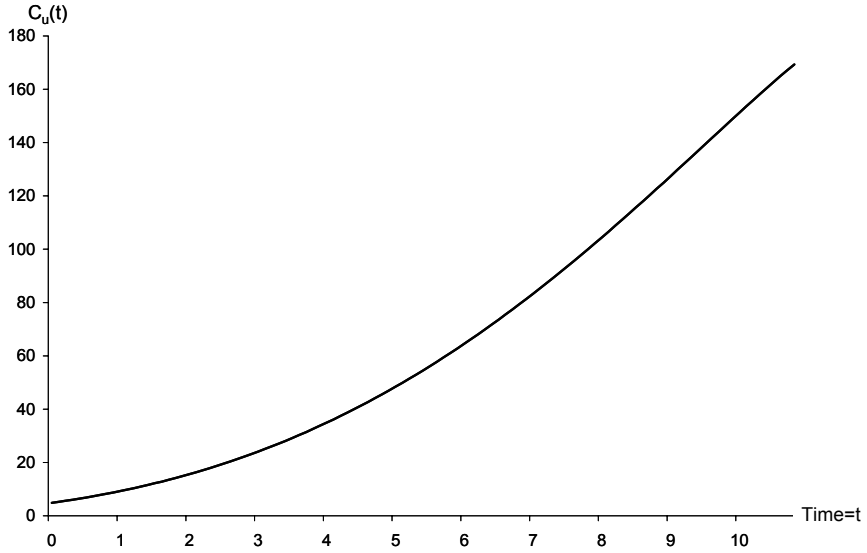

Figure 7.11: R&D option value considering continuous failure risk[400]

Equation (7.15) only represents a first step in estimating the upper limit of the fund raising potential of a R&D option because it still does not consider uncertain project timing.

7.3.4 Introduction of Uncertain Time to Maturity

Equation (7.15) shows the value of the R&D option assuming known market potential and a known product development time being equivalent to a fixed maturity date of the R&D option. In this chapter the assumption of a fixed maturity date is relaxed to consider the risk of uncertain development progress and uncertain market entry timing. At the same time, this represents a characteristic that differentiates a R&D option from most financial options. While financial options generally have fixed maturity dates it is unclear when a project representing the underlying asset of a R&D option can b finalized. The uncertain maturity

[400] The plot in the graph is based on the illustrative drug development example defined in Table 7.2.

date of a R&D option affects its value through two main levers both impacting the future potential of the drug under development.

The first lever is based on the fact that drug development options are not exclusive. The longer the time to maturity the higher the risk that other companies enter the market for a specific indication with a competing product. The risk of competition is not covered in this section because of the assumption that there is no competition in an idealistic market environment and the market potential is know and constant over time.

The second lever is the impact time to maturity has on the total market potential of a new drug because of its direct relationship to the effective patent protection period, which is essential for profitable sales in the marketplace[401]. The relationship between maturity date of the R&D option and the effective patent protection period is visualized in Figure 5.5.

7.3.4.1 Introduction of Uncertain Time to Maturity

In the previous sections it is assumed that time to maturity is fixed at T_A and that technical risk is the only type of risk explicitly considered in the valuation model of the R&D option. At this point the assumption is relaxed and the Drug Approval Value is redefined as a variable directly depending on the time of final drug approval. Treating the time of final drug approval as a variable parameter, DAV is adjusted to a function dependent on this time of final drug approval T_A as represented by (7.16).

$$DAV(T_A) = \frac{MP}{\left(r_{rf} + \alpha\right)} * \left(1 - e^{-\left(r_{rf}+\alpha\right)\left(20-T_A\right)}\right) \qquad (7.16)$$

With $T_A \in D_2$, $D_2 =]0;20]$ and MP representing the constant annual market potential in terms of total annual contribution. The first derivative (7.17) of this function shows a negative relationship between final drug approval and the value of the research project at the time of final approval because it only takes on negative values in the relevant range $0 < T_A \leq 20$.

$$\frac{\partial DAV(T_A)}{\partial T_A} = -MP * e^{-\left(r_{rf}+\alpha\right)\left(20-T_A\right)} < 0 \qquad (7.17)$$

The risk for the R&D option owner is now two-fold, even in an environment with constant market potential. Not only can the project fail to generate any marketable drug at all, the development process can also take such a long time that the reduced drug approval value does not justify executing the option.

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[401] Recall the discussion around the sales profile of a new drug introduction in chapter 2.3.

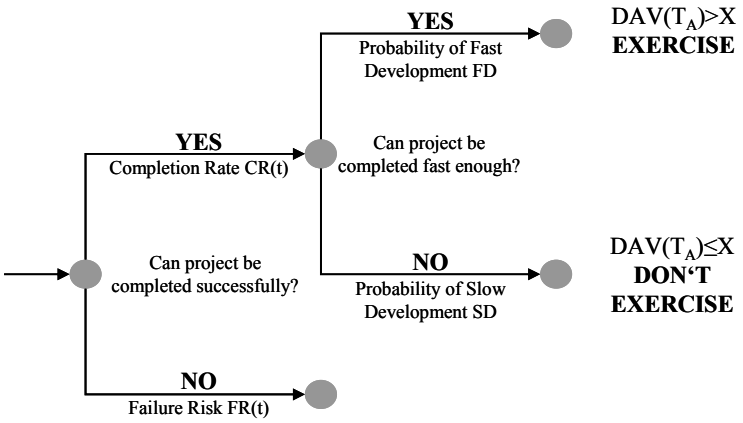

Figure 7.12: R&D option decision tree considering two risk dimensions

Figure 7.12 visualizes this situation by illustrating the two risk factors as consecutive steps in a decision tree. While the first decision point considers the risk of technical failure, the second decision point represents the choice to exercise the R&D option if the project is completed successfully but takes too long to justify execution economically. The decision rule if final approval is reached remains unchanged.

From the exercise requirement $DAV(T_A)>X$ a threshold for T_A can be derived that represents the limit for the option owner when to exercise the option right. Recalling (7.16), setting $DAV(T_A)=X$ and solving this equation for the relevant value for T_A allows the derivation of this threshold, which is labeled the execution limit EL. It can now be said that the option owner exercises his option right at maturity if T_A does not exceed the execution limit EL expressed by (7.18).

$$EL: T_A < 20 + \frac{1}{(r_{rf} + \alpha)} \ln\left(1 - \frac{(r_{rf} + \alpha)X}{MP}\right) \qquad (7.18)$$

As a first requirement for executing the option the project has to be completed successfully with the probability of the introduced completion rate

(7.11). The second requirement is that the project has to be completed faster than the execution limit EL. For this requirement the probability for fast development FD is introduced. FD represents the probability that a research project can be completed faster than the exercise limit EL and therefore the R&D option represents a positive value to the owner at T_A and is exercised. Figure 7.13 shows the adapted two step decision tree.

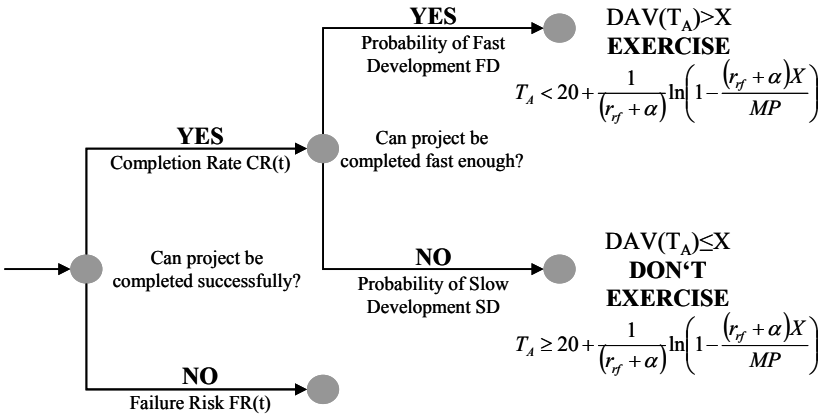

Figure 7.13: Decision rule of two-step R&D option decision tree

To quantify the value the R&D option represents to the owner it is necessary to quantify this probability of fast development FD and include it into the valuation model. To achieve this, one has to gather information on the expected termination date of the project and the distribution of possible alternative distribution dates. The next section includes timing risk into the valuation model by working with a log-normally distributed project duration and alternatively working with an exponentially distributed project duration.

7.3.4.2 Assessment using a Log-normally Distributed Project Duration

For every R&D project management has an expectation as to when the development process of a new drug will be finalized. This is generally a figure documented in business plans and other profitability calculations. The final approval date is subject to uncertainty until approval is physically granted because it is unclear how long it takes to complete the individual development steps. It is also unclear how much time regulatory authorities need for the final review process of a new drug.

Theoretically the time until final approval can take on any value between zero and infinity. While it is highly uncertain that a project can be finalized within a very short period of time it is also highly uncertain that a project is completed more than twenty years after filing for patent protection because this results in no effective patent protection time for the research conducting company[402]. This risk of non-completion is captured with the introduced function FR(t). With these limitations it is assumed that the time of final drug approval T_A follows a lognormal distribution. This means that the natural logarithm of T_A is normally distributed. Using a log-normal distribution function requires a conservative planning approach because the final approval date can take place earlier than expected but can also be delayed.

[402] In the idealistic market environment it is abandoned because it is assumed that the market potential after patent expiration is equal to zero.

Following the approach of modeling project duration with a log-normal distribution implies the following relationship (7.19) for T_A.

$$\ln(T_A) \sim N\left(E\left(\ln(T_A)\right); \sigma_{\ln(T_A)}\right) \qquad (7.19)$$

The two variables $E(\ln(T_A))$ and $\sigma_{\ln(TA)}$ are project and company-specific variables and are therefore subject to managerial estimations. While $E(\ln(T_A))$ is generally available from company internal strategic planning activities, $\sigma_{\ln(TA)}$ is more difficult to estimate. Depending on the project to be evaluated and the data available from previous projects, one of three main sources of data can be used[403]. The value for $\sigma_{\ln(TA)}$ can be calculated from a set of other internal projects of similar kind, can be estimated from industry average figures or can be derived using scenario analysis[404]. It is important to state that $\sigma_{\ln(TA)}$ as a measure for planning uncertainty is not constant during the course of the project as assumed at this point. It can be expected decrease over time with $\lim_{t \to T_A} \sigma_{\ln(TA)}(t)=0$. The assumption of constant $\sigma_{\ln(TA)}$ is relaxed later in this study. Figure 7.14 visualizes the dependency of the decision to exercise the R&D option at maturity on the log-normal distribution function of T_A.

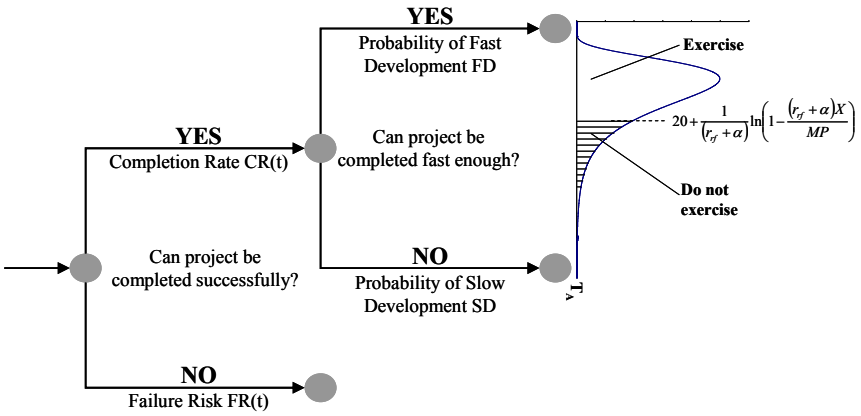

Figure 7.14: Log-normal project duration in a two-step R&D option decision tree

With the assumption that T_A follows a lognormal distribution, a density function for T_A can be derived to estimate the probability of fast development FD. This density function is denoted as (7.20) with $T_A \in D_3$ and $D_3=[0;\infty[$.

$$f(T_A) = \frac{1}{\sigma_{\ln(T_A)}\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{\ln(T_A)-E(\ln(T_A))}{\sigma_{\ln(T_A)}}\right)^2} \qquad (7.20)$$

---

[403] There is no source that allows the extraction of an objectively correct value for $\sigma_{\ln(TA)}$. Its value is related to subjectivity and therefore it is recommended to conduct a sensitivity analysis on all results derived from calculations involving σ to gain an impression over the impact a potentially inappropriate value for σ might have on the outcome of the valuation process.

[404] A characteristic of the normal distribution is that 95% of all possible observations fall within a range of 2 times its standard deviation. Since $\ln(T_A)$ is assumed to be normally distributed, this rule can be used to derive a potential value for $\sigma_{\ln(TA)}$ through a scenario analysis.

If $\ln(T_A)$ follows a normal distribution $N(\mu;\sigma)$ with $\mu=E(\ln(T_A))$ and $\sigma=\sigma_{\ln(TA)}$ it is known that the standardized variable $Z=\frac{\ln(T_A)-E(\ln(T_A))}{\sigma_{\ln(T_A)}}$ follows the standardized normal distribution N(0;1) with density function (7.21) and $-\infty<z<\infty$

$$\varphi(z)=\frac{1}{\sqrt{2\pi}}e^{-\frac{1}{2}z^2} \qquad (7.21)$$

Knowing the execution limit (7.18), the density function (7.21) and the Drug Approval Value, a preliminary value estimate of the R&D option at time t can be established, which is denoted as PV(t). In addition it has to be noted that it is unrealistic to consider potential project termination dates T_A in the valuation that are smaller than the reference time t and therefore the lower integration limit is set at t instead of zero. Equation (7.22) represents this preliminary valuation formula for PV(t).

$$PV(t)=\int_{t}^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)}\left(\frac{MP}{(r_{rf}+\alpha)}*\left(1-e^{-(r_{rf}+\alpha)(20-T_A)}\right)-X\right)*e^{-(r_{rf}+\alpha)(T_A-t)}*\varphi\left(\frac{\ln(T_A)-E(\ln(T_A))}{\sigma_{\ln(T_A)}}\right)dT_A \qquad (7.22)$$

Setting the lower integration limit from 0 to t generates a problem with the probability function included in the valuation formula. As indicated above it is not realistic to allow values for T_A that occur in the past and even though the correction of the lower integration limit to t excludes them explicitly from the formula, they are still part of the probability distribution function and are therefore implicitly considered.

Especially with progressing t there are occurrences of T_A, which occur in the past with $t>T_A$ but do have a probability value assigned to them. It is explained above that the correct probability for these occurrences would be zero. Excluding them from the integration interval does not solve this issue but leads to a violation of the basic requirement (7.23).

$$\int_{\text{lowest occurance of } z}^{\text{highest occurance of } z}\varphi(z)\partial z=1 \qquad (7.23)$$

Instead, by explicitly excluding the lower potential occurrences of TA, this requirement is violated because with progressing t the cumulated probabilities do not add up to the required value of one as shown in equation (7.24).

$$\int_{t}^{\infty}\frac{1}{\sigma_{\ln(T_A)}\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{\ln(T_A)-E(\ln(T_A))}{\sigma_{\ln(T_A)}}\right)^2}\partial T_A<1 \qquad (7.24)$$

From equation (7.24) it can be concluded that the probabilities for values for T_A are underestimated and therefore underestimates the preliminary option value at time t. Figure 7.15 visualizes the described problem for the illustrative case example at time t=8.

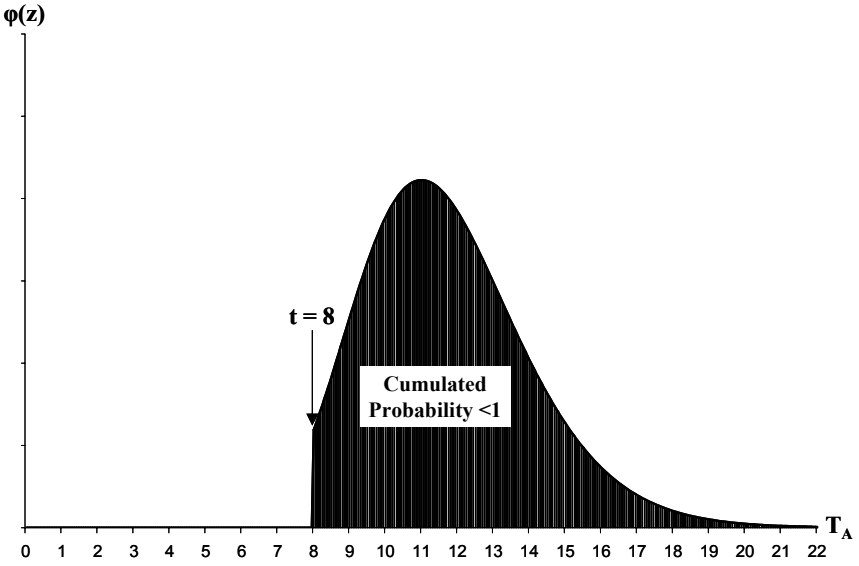

Figure 7.15: Probability underestimation with constant lognormal project timing

This systematic underestimation of PV requires an adjustment to the probability density function to satisfy (7.23). For this adjustment the probability term in equation (7.22) is substituted using the probability term $p(T_A)$ expressed by (7.25) for the probabilities related to the potential project termination timing.

$$p(T_A) = \frac{\varphi\left(\frac{\ln(T_A) - E(\ln(T_A))}{\sigma_{\ln(T_A)}}\right)}{\left(1 - \int_0^t \varphi\left(\frac{\ln(T_A) - E(\ln(T_A))}{\sigma_{\ln(T_A)}}\right)\partial T_A\right)} \qquad (7.25)$$

Using this adjusted probability term ensures that the requirement (7.23) is fulfilled and the cumulated probability over all theoretically possible T_A is equal to one[405]. Figure 7.16 visualizes the impact of this adjustment on the probability density function of the illustrative case example at t=8 and t=10. The probability functions on the right hand side of the figure after adjustment do satisfy the basic requirement (7.23). As indicated, the adjustment becomes more important with increasing t because more potential occurrences of T_A are excluded by the requirement T_A>t.

[405] $\int_t^\infty p(T_A)\partial T_A = 1$

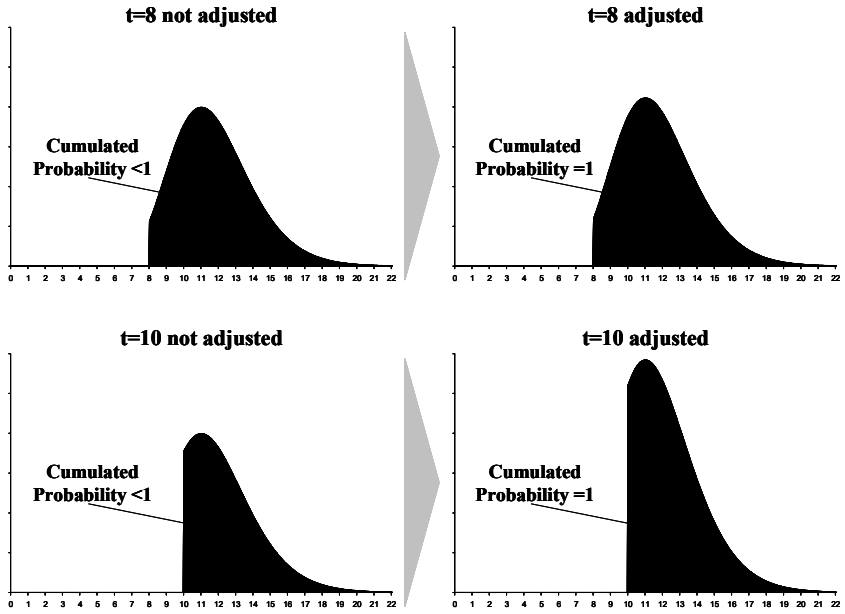

Figure 7.16: Probability adjustment for log-normal timing distribution

Using the adjusted term $p(T_A)$ changes the preliminary upper limit of the option value PV(t) to (7.26).

$$PV(t) = \int_{t}^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)} \left(\frac{MP}{(r_{rf}+\alpha)} * \left(1-e^{-(r_{rf}+\alpha)(20-T_A)}\right) - X\right) * e^{-(r_{rf}+\alpha)(T_A-t)} * p(T_A)dT_A \qquad (7.26)$$

The significance of the described probability adjustment becomes clear directly comparing the preliminary option value in its previous form with the probability adjusted equation (7.26). Figure 7.17 visualizes the impact of the two different probability functions for expected drug approval on the illustrative case example.

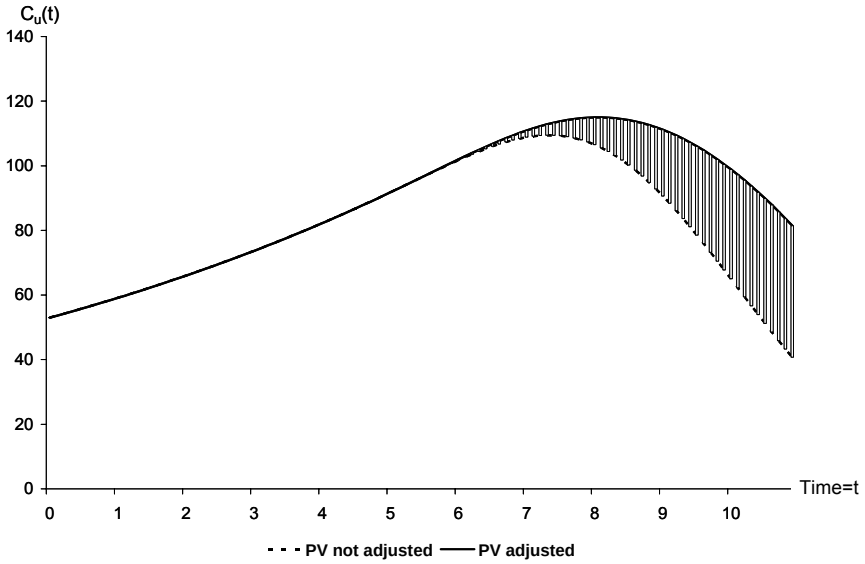

Figure 7.17: Probability adjustment for preliminary option value

Although both methods generate the same results during early project stages the graph demonstrates the importance of using the adjusted formula for later stages of the project because the indicated undervaluation of the option value becomes larger as t approaches $E(T_A)$. In addition, both graphs show a maximum during the last third of the expected research period before the option value decreases towards the end of the expected research period. This phenomenon can be explained by the reduced opportunity that the research project is completed ahead of schedule. Early during the project there is a chance that the project is completed significantly before $E(T_A)$ and therefore the value of the project is increased in those cases. As t progresses and approaches $E(T_A)$ there is less chance to complete the project ahead of schedule and therefore this additional element of value to the option owner is reduced. As t reaches $E(T_A)$, the opportunity of faster project completion is eliminated entirely.

What is classified as the preliminary value above and expressed by (7.26) is the value a R&D option represents to the owner in cases where he does not have to be concerned about technical failure of the research project. This risk needs to be considered when estimating the upper pricing limit of the R&D option. This adjustment can be made by including the completion rate function

(7.11) and substituting the constant $E(T_A)$ with the variable parameter T_A. The resulting upper pricing limit of the R&D option can be written as (7.27).

$$C_U(t) = \int_t^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)} e^{-(r_{rf}+\alpha)(T_A-t)} * \left(1-\left(\frac{\cos\left(\frac{\frac{11}{T_A}t+3}{14}\right)\pi+1}{2}\right)^{\frac{4}{5}}\right) * \left(\frac{MP}{(r_{rf}+\alpha)} * \left(1-e^{-(r_{rf}+\alpha)(20-T_A)}\right) - X\right) * p(T_A)\partial T_A \tag{7.27}$$

With the probability function $p(T_A)$ being defined as (7.25).

$$p(T_A) = \frac{\varphi\left(\frac{\ln(T_A)-E(\ln(T_A))}{\sigma_{\ln(T_A)}}\right)}{\left(1-\int_0^t \varphi\left(\frac{\ln(T_A)-E(\ln(T_A))}{\sigma_{\ln(T_A)}}\right)\partial T_A\right)} \tag{7.25}$$

7.3.4.3 Approx. using fixed Log-normal Timing Risk

In this section, the developed model is applied to the illustrative case example to demonstrate its implementation and to investigate characteristics of the resulting pricing limit. As a first step it is necessary to model the density function $f(T_A)$ represented by (7.20). To achieve this, an understanding of the two parameters $\sigma_{\ln(TA)}$ and $E(\ln(T_A))$ needs to be developed. In cases where a research conducting company has completed multiple similar projects and

captured the data related to development times, the two parameters can be estimated based on historical data. Assuming a company has completed n similar projects with corresponding development times $T_{Ai,}$ the required parameters can be estimated using the natural log of the individual development times T_{Ai} and their arithmetic average (7.28).

$$E(\ln T_A) = \frac{1}{n}\sum_{i=1}^{n} \ln(T_{Ai}) \qquad (7.28)$$

With the natural logarithm of the historical development times and the calculated average, the variance of the distribution function can be derived.

$$(\sigma_{\ln(T_A)})^2 = \frac{1}{n}\sum_{i=1}^{n} [\ln(T_{Ai}) - E(\ln(T_A))]^2 \qquad (7.29)$$

Using fundamental characteristics of a normal distribution function[406] $N(\mu_u;\sigma_u)$, ranges can be defined that include a random observation u_x with a certain probability P. Expressing this range in multiples of σ_u around μ_u it is known that a random observation u_x falls with probability P into an interval $[\mu_u\text{-}k\sigma_u;\mu_u+k\sigma_u)]$. The probability P for a specific observation range can be defined using

$$P(k) = P(\mu_u - k\sigma_u \le u_x \le \mu_u + k\sigma_u) = 2\Phi(k) - 1 \qquad (7.30)$$

For a basic understanding of a normal distribution function it is helpful to calculate the probability ranges for k=1, k=2 and k=3 that represent the P ranges 68.3%, 95.5%, and 99.7% respectively.[407]

$$P(k) = P(\mu_u - k\sigma_u \le u_x \le \mu_u + k\sigma_u) = 2\Phi(k) - 1 = \begin{cases} 0.683 & if \quad k = 1 \\ 0.955 & if \quad k = 2 \\ 0.997 & if \quad k = 3 \end{cases}$$

To illustrate the characteristics of log-normally distributed project durations, an illustrative sample D of 25 random drug development times T_{ADi} with $i \in [1;25]$ is used.[408] Based on the assumption that development times follow a lognormal distribution it can be derived that the values $\ln(T_{AD})$ in this example are normally $N_D(\mu_D;\sigma_D)$ distributed with $\mu_D = E(\ln(T_{AD})) = 2.4$ and $\sigma_D = \sigma_{\ln(TAD)} = 0.2$. Figure 7.18 shows the shape of the function $N_D(2.4; 0.2)$ for $\ln(T_{AD})$ including the probability range P(2)=95%.

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[406] More details on the normal distribution function can be found at Bamberg and Baur (1993, p. 109).

[407] For the explanations and illustrative figures in this study the k=2 range for P = 95% is displayed unless otherwise specified.

[408] The illustrative sample contains 25 random development times T_{Ai} = (9.9; 8.6; 7.5; 11.3; 12.2; 13.3; 9.9; 11.8; 11.5; 10.3; 8.5; 6.9; 8.9; 13.1; 10.9; 15.3; 13.1; 11.7; 14.3; 10.7; 14.9; 9.2; 10.7; 11.6; 14.7)

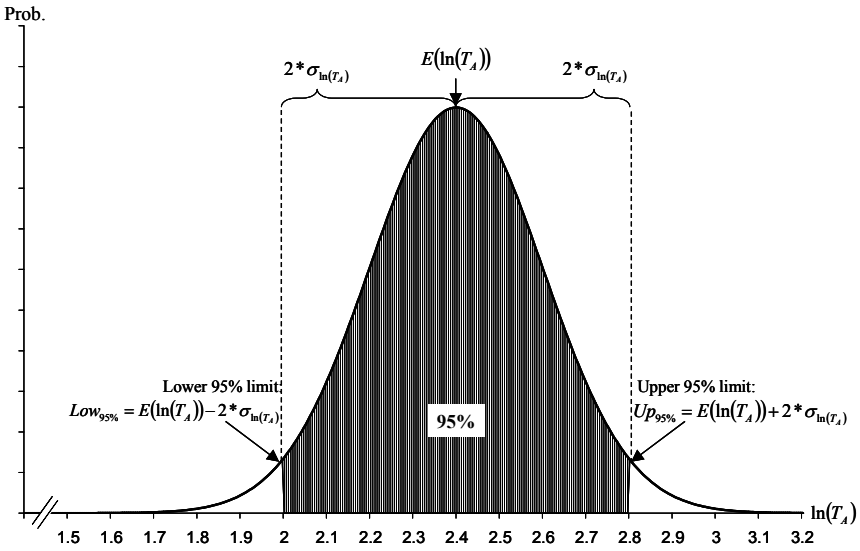

Figure 7.18: Example of normal dist. of natural log of drug development times

The corresponding lognormal distribution function for T_{AD} can be derived with $E(T_{AD}) = e^{E(\ln(T_{AD}))}$ and a 95% P(2) interval as represented by (7.31).

$$P(2) = \left[e^{\left(E(\ln(T_{AD})) - 2*\sigma_{\ln(T_{AD})}\right)}; e^{\left(E(\ln(T_{AD})) + 2*\sigma_{\ln(T_{AD})}\right)}\right] \qquad (7.31)$$

Figure 7.19 represents the lognormal distribution for the random drug development time sample D with $E(T_{AD})=11.0$ and a 95% interval [7.4; 16.4].

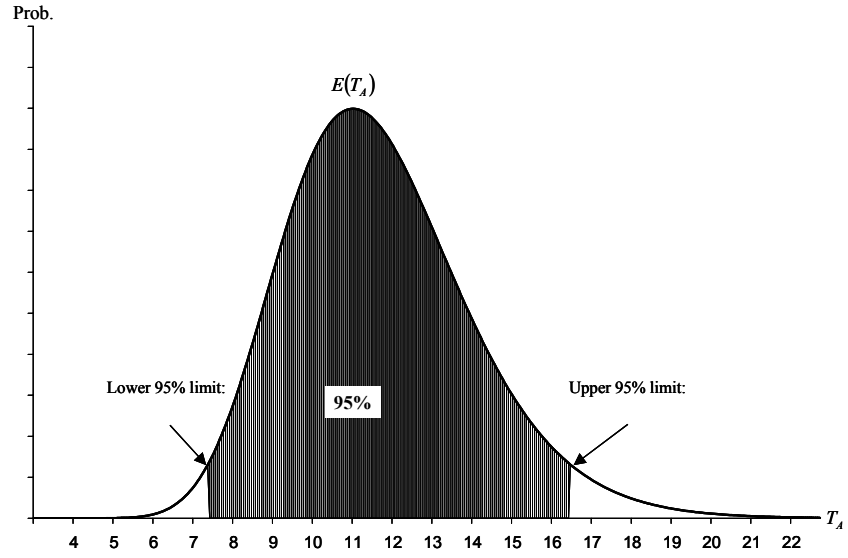

Figure 7.19: Example of log-normally distributed drug development times

In real-life applications it is difficult to obtain estimates for the variables σ_u and μ_u. The variables contain a certain amount of subjectivity because only a few drug developing

companies[409] are in the situation to own databases of historical projects that allow deriving statistically valid results. Such a database not only has to be sufficient in terms of number of entries but also has to contain projects that are comparable in terms of scope and objective to a project to be evaluated. This is the case because there are differences in the development times of certain drugs. Depending on the therapeutic area, average development times can differ by more than three years.[410] Especially for young companies it is not an opportunity to estimate the parameters based on historically completed projects because their R&D activities are generally related to their first generation of drug development projects.

Using the two parameters $\sigma_{\ln(TA)}$=0.20 and $E(T_A)$ = 11.0 derived from the illustrative sample above, the probability term (7.25) becomes the following equation (7.32).

$$p(T_A) = \frac{\varphi\left(\frac{\ln(T_A)-2.4}{0.2}\right)}{\left(1-\int_0^t \varphi\left(\frac{\ln(T_A)-2.4}{0.2}\right)\partial T_A\right)} \qquad (7.32)$$

Using (7.32) and including the figures of the illustrative example, equation (7.27) can be completed to the following valuation formula (7.33) for the upper pricing limit of the R&D option value on the illustrative case example over time.

$$C_U(t) = \int_t^{14.7} e^{-0.11(T_A-t)} * \left(1-\left(\frac{\cos\left(\frac{\frac{11}{T_A}t+3}{14}\right)\pi+1}{2}\right)^{\frac{4}{5}}\right) * \left(\frac{100}{0.11} * \left(1-e^{-0.11(20-T_A)}\right)-400\right) * p(T_A)dT_A$$

(7.33)

It is difficult to find an analytical solution to the integration problem (7.33) therefore an alternative method to estimate the upper pricing limit is applied. The approach used in this study to approximate a solution for the previous and other upcoming complex integration problems is the method of discrete summation. The continuous variable T_A is for this purpose transferred into a discrete variable with increments of size ΔT_A=0.1. Applying discrete summation to equation (7.33) for the illustrative case results in Figure 7.20. It shows

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[409] In an interview summarized by Nichols (1994, p. 90), Merck´s CFO Judy Lewent stated that Merck possesses a database that allows the company to estimate risk and volatility of their research projects.

[410] PAREXEL (2003, p. 134) shows that a sample of NCEs in the area of Immunology had a time from IND filing to FDA approval of only 5.5 years while NCEs affecting the Central Nervous System took on average 9.0 years to go through the same process.

the approximation for $C_U(t)$ of the illustrative R&D option deal[411] compared to the same case but without uncertainty in project timing. For this purpose the factor $\sigma_{ln(TA)}$ is set to 0.00001.

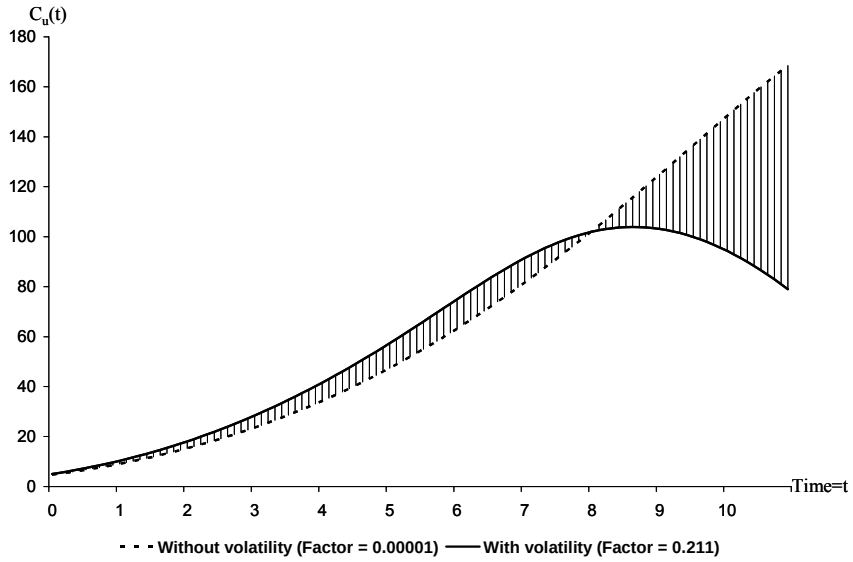

Figure 7.20: Upper pricing limit with tech. risk and stochastic development times

For the interpretation of Figure 7.20 it is essential to distinguish between three price effects. The first effect is represented by the impact of the risk of technical failure, the second one being the time value of money and the third one being the uncertainty in project timing.

The technical risk reduces the value and therefore the upper pricing limit of the R&D option because it represents a one-sided risk. One-sided in this context means that it can only drive the value of the option down without a corresponding opportunity to increase its value. This downward risk is the total failure of the project leading to a zero value of the related project. This is the reason why a higher failure risk reduces the value of the R&D option. Recalling the technical risk function from section 7.3.3.1 reveals that especially in early phases of the drug development process this type of risk is high and therefore both curves in Figure 7.20 are negatively impacted early in the project progress on the left hand side of the graph.

The second factor determining the shape of the graph in Figure 7.20 is the basic economic principle of time value of money. It concludes that money received today is worth more than the same amount received in the future and therefore the longer an expected payout occurs in the future the lower its value today with all other factors remaining unchanged.[412]

As opposed to technical risk, the third component represented by the uncertainty in project timing increases the value of the R&D option because it includes not only a risk but also a

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[411] The graph is based on the standard assumptions defined in chapter 7.3.1 with $E(T_A)=11$, MP=100, X=400, and $(r_{rf}+\alpha)=11\%$.

[412] Since this represents a fundamental principle of finance it is not explained in more detail. Background information on this principle can be found in introductory literature to financial theory and management like Brealey and Myers (2000), Brigham et al. (1999) or various other sources.

potential upside to the owner. In cases where approval of the new drug turns out to occur later than expected, the effective patent protection period is reduced and also the resulting total value of the drug development project. On the other hand there is an opportunity that the project is completed faster than expected. In this case the project value increases because of the increasing effective patent protection period. Since the R&D option owner has the opportunity to participate in such a favorable development without having to participate in the unfavorable movement, he is willing to pay an additional premium to acquire the option.

With timing uncertainty being the only difference between the two graphs in Figure 7.20, the interpretation of the shape difference between them becomes straightforward. Early during the project the R&D option with the higher uncertainty in project timing is of higher value to the owner because it includes the potential that the project is completed significantly ahead of time and the owner can benefit from an extended effective patent protection period. The other case with known time to maturity and therefore known effective patent protection period is less valuable during that time of the project.

The situation changes if t approaches $E(T_A)$. Now the opportunity for the option owner in case of high timing volatility decreases because the risk of delay still exists while the upside of the option disappears. This effect causes the upper pricing limit in case of high timing volatility to decrease significantly as t approaches $E(T_A)$. This effect does not occur in the case of certain project timing because there is still neither an up- nor a downside potential related to the project timing in the valuation formula.

This can serve as an argument as to why an option owner would prefer certainty in project timing later during the research project while he would be willing to pay a premium for the opportunity related to this uncertainty during early stages of a project. At this point one could argue that the use of a constant risk factor σ for the timing volatility even with the conducted probability adjustment is not a realistic assumption. To account for this criticism timing uncertainty is modeled in an alternative way in the following section.

7.3.4.4 Status Dependent Log-Normal Timing Risk

It is an unrealistic assumption that the uncertainty of the final approval timing of a new drug remains constant over the expected course of a drug development project. A more realistic view is to model this uncertainty as a decreasing function relative to the progress of the project. To achieve this objective, the constant parameter $\sigma_{\ln(TA)}$ is transformed into a time dependent variable $\sigma_{\ln(TA)}(t)$. The characteristic of decreasing $\sigma_{\ln(TA)}(t)$ depending on the progress of the project is achieved by multiplying the $\sigma_{\ln(TA)}$ with a factor expressing the expected remaining project development time in relation to the entire expected drug development time. The following equation (7.34) is used to model this relationship.

$$\sigma_{\ln(T_A)}(t) = \sigma_{\ln(T_A)} * \frac{E(\ln(T_A)) - \ln(t)}{E(\ln(T_A))} \qquad (7.34)$$

Figure 7.21 visualizes the impact progress dependent timing uncertainty has on the 95% probability range of possible approval dates. It can be seen that the size of the probability range is decreasing as the project progresses and approaches zero as t approaches $E(T_A)$.[413]

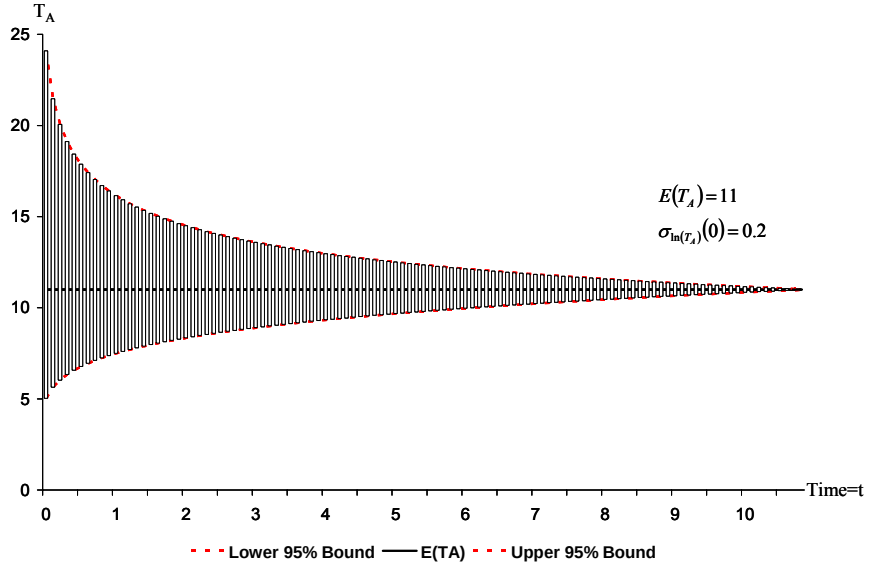

Figure 7.21: 95% range of approval date with progress dependent uncertainty

To include progress dependent timing uncertainty into the model, parameter $\sigma_{\ln(TA)}$ is substituted with $\sigma_{\ln(TA)}$ and the valuation formula can be rewritten as (7.35)[414].

$$C_U(t) = \int_t^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)} e^{-(r_{rf}+\alpha)(T_A-t)} * \left(1-\left(\frac{\cos\left(\frac{11}{T_A}t+3\right)\pi+1}{2}\right)^{\frac{4}{5}}\right) * \left(\frac{MP}{(r_{rf}+\alpha)} * \left(1-e^{-(r_{rf}+\alpha)(20-T_A)}\right)-X\right) * \varphi\left(\frac{\ln(T_A)-\ln(E(T_A))}{\sigma_{\ln(T_A)} * \frac{\ln(E(T_A))-\ln(t)}{\ln(E(T_A))}}\right) dT_A \quad (7.35)$$

To demonstrate the impact of this change the illustrative example is adapted from constant to progress dependent timing risk and (7.33) is adapted to the following equation (7.36).

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[413] In this situation where an „ex ante“ view is applied, $E(T_A)$ is kept constant over time because it represents the best estimator for project completion.

[414] In this case it is not necessary to include a probability adjustment as required in the previous section. Setting the lower integration limit to time t does not cause a significant bias because the probability that $T_A<t$ can be neglected for the demonstrated case. This can be seen in Figure 7.21 where the 95% confidence interval is visualized over time. The line $T_A=t$ is for any time instances t far below the illustrated 95% probability range and therefore no adjustment is necessary.

$$C_U(t) = \int_t^{14.7} e^{-0.11(T_A - t)} * \left(1 - \left(\frac{\cos\left(\frac{\frac{11}{T_A} t + 3}{14} \right) \pi + 1}{2} \right)^{\frac{4}{5}} \right) * \left(\frac{100}{0.11} * \left(1 - e^{-0.11(20 - T_A)} \right) - 400 \right) * \varphi \left(\frac{\ln(T_A) - 2.4}{0.2 * \frac{2.4 - \ln(t)}{2.4}} \right) dT_A \qquad (7.36)$$

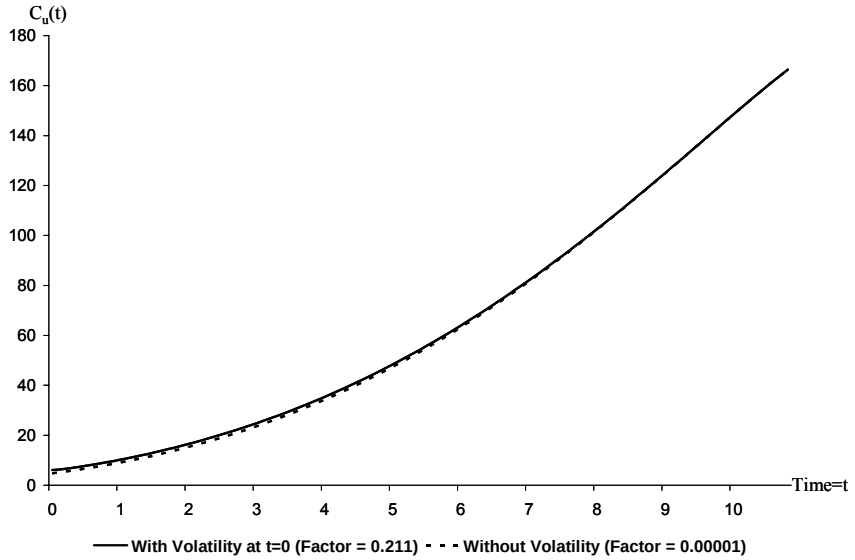

Figure 7.22: R&D option value with progress dependent timing risk

Figure 7.22 visualizes the upper pricing limit based on the adapted valuation formula using the illustrative example compared to a case without timing uncertainty. It also reveals an interesting finding. It is intuitively clear that the two cases with and without initial timing risk converge over time as time reaches the expected project termination date $E(T_A)$ because of the following relationship (7.37).

$$\lim_{t \to E(T_A)} \left(\sigma_{\ln(T_A)} * \frac{\ln(E(T_A)) - \ln(t)}{\ln(E(T_A))} \right) = 0 \qquad (7.37)$$

The more interesting finding from this analysis is the fact that the two graphs do not differ significantly during any stage of the project. The rational explanation for this behavior is the dominance of the technical failure risk and the time value of money effect during the early part of the analysis. During times when timing uncertainty does represent an additional value to the option owner the value is discounted significantly to adjust for the risk of technical failure and the time value of money. As technical risk and discount period decrease over time, the positive opportunity related to timing uncertainty decreases as well therefore these two opposite developments eliminate each other, resulting in a timing risk adjusted pricing level that is close to the one not considering timing uncertainty.

To take a closer look at the impact of progress dependent timing risk, a second case example is calculated using an extreme value of 1.25 for the initial timing uncertainty $\sigma_{ln(TA)}(0)$.

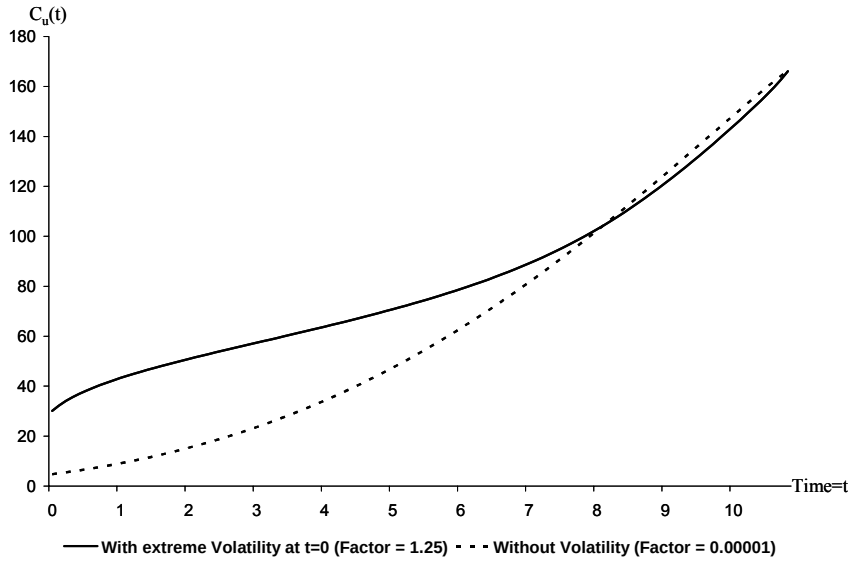

Figure 7.23: R&D option with progress dependent extreme timing risk

Figure 7.23 illustrates more descriptively that uncertainty adds value to the R&D option owner and therefore increases the price of the option during early stages of a project. With the selected extreme uncertainty the option price early during the project is significantly higher than for the other case due to the higher chance of completing the project ahead of schedule. With timing uncertainty being time dependant this effect decreases over time and therefore the graphs merge towards the end of the expected project duration.[415]

7.3.4.5 Assessment using Exponentially Distributed Project Delay

During the previous sections timing uncertainty is modeled using a log-normal distribution allowing project delays as well as earlier than expected project termination dates. Such a two-sided uncertainty occurs if initial project planning is done carefully following a conservative planning approach. Historical observations and expert interviews show that research planning is rather carried out aggressively from a timing perspective with very little if any chance of projects being completed ahead of schedule[416]. This planning approach is

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[415] The reason why the graph of the additional case with extreme uncertainty is below the initial case towards the end of the expected project duration is the missing adjustment in the probabiliy term for potential $T_A<t$. As discussed in chapter 7.3.4.2 for the case of constant uncertainty over time an adjustment in the probability function has to be made to eliminate value underestimations resulting from eliminating irrealistic cases with $T_A<t$. Since it does not add conceptual value to the study, this adjustment is not presented for time dependent project uncertainty. In addition it also has to be stated that such an adjustment is only necessary for extremely high uncertainty factors.

[416] This view is supported by Brach (2003, p. 113) who concludes that "bumps that delay the development are likely, and potentially less likely are "eureka" moments that advance and speed up the development".

modeled by replacing the log-normally distributed project termination with a function considering exponentially distributed project delay.

Drug development projects have to go through clearly defined project stages having minimum timing requirements that have to be extended depending on individual project needs. The sum of these minimum requirements can be considered a lower limit for the total project duration. A log-normal distribution does not consider any lower limit and allows values between zero and infinity, which is not appropriate for the case described.

A more realistic representation of risk in project duration is a model that fixes a minimum project duration T_{Amin} and considers the difference between the minimum timing requirement and the actual project termination date as a stochastic variable. This difference $[T_A\text{-}T_{Amin}]$ represents the project delay and can be modeled using an exponential distribution function. The assumption that a project is never completed before its minimum timing requirement T_{Amin} and that project delay follows an exponential distribution implies the relationship $T_A \geq T_{Amin}$ and $[T_A\text{-}T_{Amin}] \sim \text{ExpDist}(\lambda)$. Equation (7.38) shows the probability density function of the project delay $[T_A\text{-}T_{Amin}]$ with parameter λ and with $T_A \in D_4$ and $D_4=[T_{Amin};\infty[$.

$$f(T_A) = \lambda e^{-\lambda(T_A - T_{A\min})} \qquad (7.38)$$

Figure 7.24 shows an illustrative example of two exponentially distributed probability density functions. One function shows an exponentially distributed project delay while the second one shows the resulting probability for the duration of the illustrative case example. This second example with its minimum project duration being fixed and the potential delay being exponentially distributed with parameter λ, represents a delay as defined by (7.38).

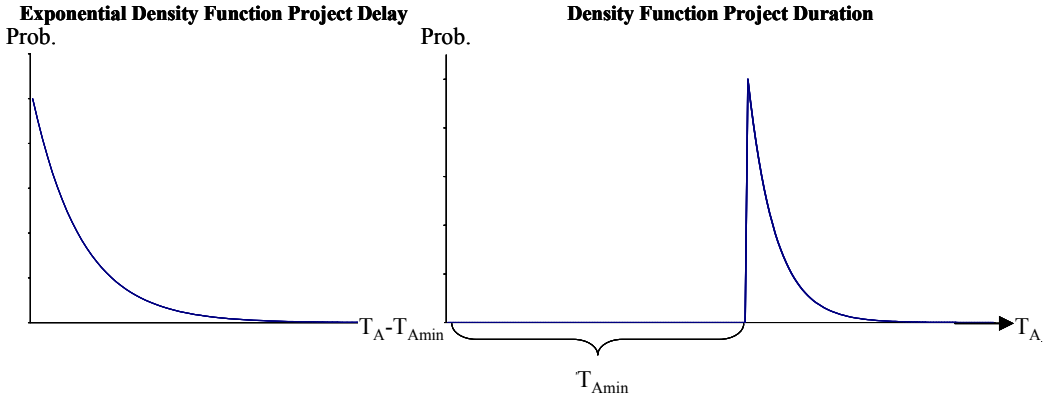

Figure 7.24: Probability function of exponentially distributed project delay

For the probability density function of the duration of the entire project, (7.38) can be expanded to become equation (7.39).

$$f(T_A) = \begin{cases} 0 & T_A < T_{A\min} \\ \lambda e^{-\lambda(T_A - T_{A\min})} & T_A \geq T_{A\min} \end{cases} \qquad (7.39)$$

At this point, λ is treated as being constant over the course of the project, which represents a simplifying assumption. This assumption is relaxed later to account for the fact that

uncertainty decreases over time and therefore λ is more accurately represented by a monotonously decreasing function λ(t).

The existence of an execution limit for an investor holding a research option remains independent from the way project durations are distributed. As for the log-normally distributed case with constant market potential, equation (7.18) to derive the execution limit is also valid for the exponentially distributed case with constant market potential.

With the defined technical risk function it is clear that the research option is only exercised in those cases where the project is successful and also completed in a timeframe that does not exceed the execution limit EL. Figure 7.25 visualized this relationship similar to Figure 7.14 but assuming a different distribution function for the final project termination date.

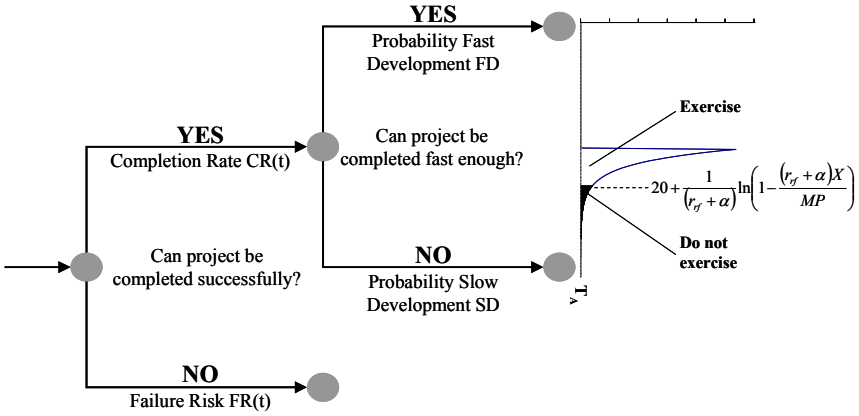

Figure 7.25: Exponential project delay in two-step R&D option decision tree

With these similarities in the execution tree from the perspective of the option owner the case under investigation can build on the discussion above and uses equation (7.27) as a starting point. This equation is adapted to the exponentially distributed case by carrying out two adjustments. The first change is a replacement of the distribution for project timing and the second is a change of the lower limit of the relevant observation period for T_A from zero to T_{Amin}. This change is justified by (7.39), which eliminates all $T_A<T_{Amin}$ by setting their probability to zero by definition. The equation for the upper limit therefore becomes (7.40).

$$C_U(t)=\int_{T_{A\min}}^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)} e^{-(r_{rf}+\alpha)(T_A-t)}*\left(1-\left(\frac{\cos\left(\frac{\frac{11}{T_A}t+3}{14}\right)\pi+1}{2}\right)^{\frac{4}{5}}\right)*\left(\frac{MP}{(r_{rf}+\alpha)}*\left(1-e^{-(r_{rf}+\alpha)(20-T_A)}\right)-X\right)*\lambda e^{-\lambda(T_A-T_{A\min})}\partial T_A \quad (7.40)$$

7.3.4.6 Approximation using Constant Exp. Distributed Timing Risk

For a practical approximation of the upper pricing limit of a R&D option with exponentially distributed development timing uncertainty the case is investigated where risk of delay is constant over the course of the project. This simplifying assumption is relaxed in the next section. Recalling (7.39) it becomes clear that it is necessary to estimate the two parameters T_{Amin} and λ that define the density distribution for project durations.

$$f(T_A) = \begin{cases} 0 & T_A < T_{A\min} \\ \lambda e^{-\lambda(T_A - T_{A\min})} & T_A \geq T_{A\min} \end{cases} \qquad (7.39)$$

As in chapter 7.3.4.2 for the case of log-normal project durations, the parameters characterizing the distribution function of the expected development times cannot be observed objectively and are subject to managerial expectations. While T_{Amin} is generally available as a best case planning scenario, the parameter λ is more difficult to estimate. It can be interpreted as a measure for planning accuracy and reliability of a company's R&D departments. The parameter for planning accuracy has to be estimated based on historical evidence and experiences.

An approach similar to that used for estimating the parameters of the lognormal distribution above can be used where a 95% confidence interval is estimated to derive the necessary distribution parameters. If management can agree on an interval $[T_{Amin};T_{Amax}]$, in which the project can be completed with 95% certainty then the missing distribution parameter can be derived from the probability function (7.41).

$$P(T_A \leq T_{A\max}) = 1 - e^{-\lambda(T_{A\max} - T_{A\min})} = 0.95 \qquad (7.41)$$

With this relationship λ can be derived using (7.42).

$$\lambda = \frac{1}{(T_{A\min} - T_{A\max})} * \ln 0.05 \qquad (7.42)$$

With the knowledge of an expected 95% interval, the distribution density function for T_A can be rewritten as (7.43).

$$f(T_A) = \begin{cases} 0 & T_A < T_{A\min} \\ \dfrac{\ln 0.05}{(T_{A\min} - T_{A\max})} e^{\frac{(T_A - T_{A\min})}{(T_{A\max} - T_{A\min})} * \ln 0.05} & T_A \geq T_{A\min} \end{cases} \qquad (7.43)$$

Figure 7.26 shows an example of a distribution density function with T_{Amin}=11.0 and the assumption that in 95% of all cases a project is terminated until T_{Amax}=16.4.

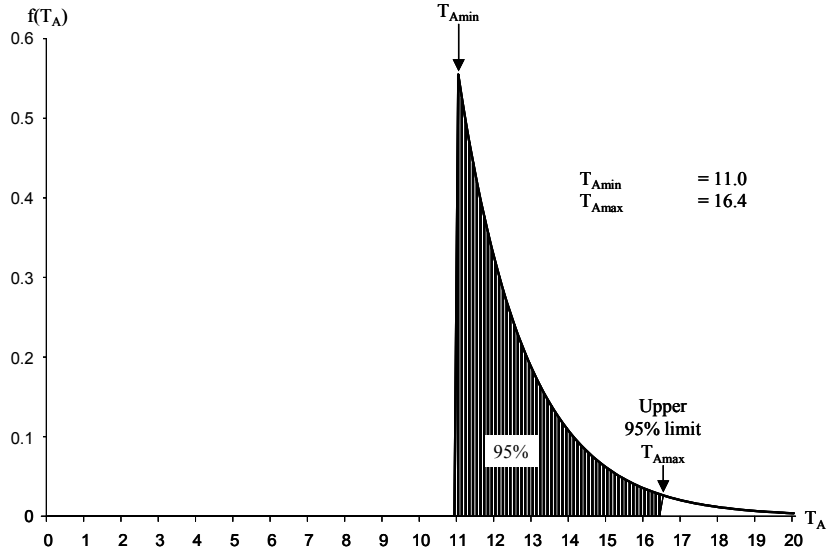

Figure 7.26: Example of exponentially distributed project delay

If such an agreement on the 95%-interval for project completion can be reached, the model for the upper pricing limit of the R&D option becomes (7.44).

$$C_U(t) = \int_{T_{A\min}}^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)} e^{-(r_{rf}+\alpha)(T_A-t)} * \left(1-\left(\frac{\cos\left(\frac{\frac{11}{T_A}t+3}{14}\right)\pi+1}{2}\right)^{\frac{4}{5}}\right) * \left(\frac{MP}{(r_{rf}+\alpha)} * \left(1-e^{-(r_{rf}+\alpha)(20-T_A)}\right) - X\right) * \frac{\ln 0.05}{(T_{A\min}-T_{A\max})} e^{\frac{(T_A-T_{A\min})}{(T_{A\max}-T_{A\min})}*\ln 0.05} \partial T_A \qquad (7.44)$$

For the illustrative case displayed in Figure 7.26, λ takes on the value 0.55 and equation (7.44) becomes (7.45).

$$C_U(t) = \int_{11}^{14.7} e^{-0.11(T_A-t)} * \left(1-\left(\frac{\cos\left(\frac{\frac{11}{T_A}t+3}{14}\right)\pi+1}{2}\right)^{\frac{4}{5}}\right) * \left(\frac{100}{0.11} * \left(1-e^{-0.11*(20-T_A)}\right) - 400\right) * 0.55e^{-0.11*(T_A-11)} \partial T_A \qquad (7.45)$$

For the approximation of function (7.45) one encounters the problem of an integral that cannot be solved numerically and therefore the method of discrete summation is used to approximate the solution to this integration problem. Figure 7.27 visualizes the result of a discrete summation with steps for T_A of size ΔT_A=0.1. Displayed are the illustrative case

with λ=0.55 and an additional case without volatility around the same expected value $E(T_A)$, which in the illustrative case is represented by $E(T_A)=T_{Amin}+(1/\lambda)=12.8$.

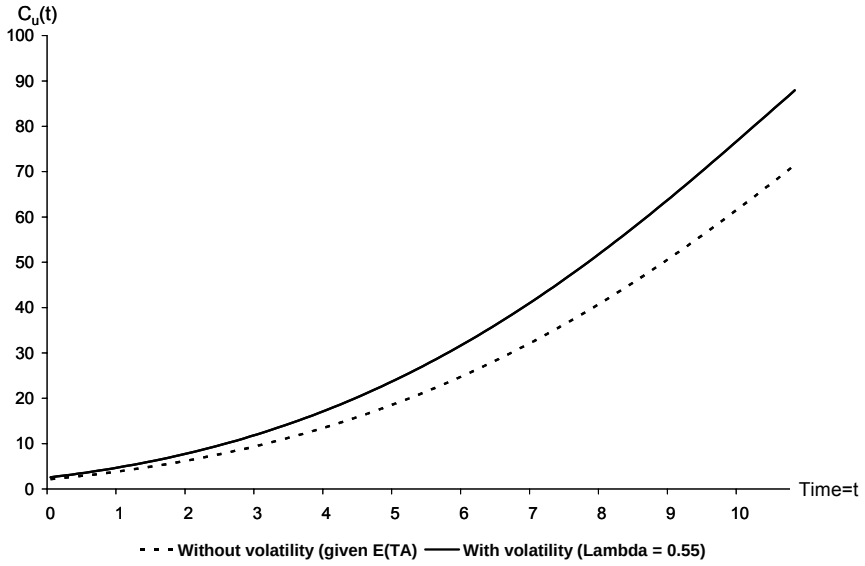

Figure 7.27: Upper pricing limit considering exponential timing risk

There is an intuitive explanation as to why the value of the R&D option for the case involving volatility exceeds the value of the other R&D option especially as time approaches T_{Amin}. Uncertainty in this case includes the opportunity for the option owner that a project is terminated ahead of schedule with $E(T_A)>T_A>T_{Amin}$. Those occurrences are very valuable for the option owner because they are related to a longer effective patent protection period. In the case of known project duration $E(T_A)$ this opportunity to participate in a longer effective patent protection period does not exist and therefore, the owner cannot benefit from a positive development and assigns no value to it.

Realistically there is also a potential downside related to uncertainty because the project can also be delayed as opposed to the case with known project duration. With the option owner not being required to participate in this downside, the value of the opportunity exceeds the value of the potential risk. This results in the graph with the case including uncertainty being above the one with known project duration although both cases have the same $E(T_A)$.

7.3.4.7 Status Dependent Exponential Timing Risk

As for the discussion on log-normally distributed project durations it also holds true for the exponentially distributed project delay that uncertainty in a real-life project is not a constant parameter. It is safe to assume that with project progress and the generation of additional information, this type of uncertainty decreases. Considering this, timing risk is more appropriately modeled using a risk factor that is monotonously decreasing over time. In this section the assumption of constant planning accuracy is relaxed and the constant λ is replaced by a time dependent variable $\lambda(t)$.

The expectation on the range, in which there is a 95% chance of project completion is subject to a large degree of managerial subjectivity and cannot be measured objectively. This does

not prevent the use of this parameter for valuation purposes but should be kept in mind. In addition, it emphasizes the necessity for sensitivity analysis to check the impact of potentially incorrect factor estimates.[417]

The management estimate for the initial confidence interval at time t=0, during which there is a 95% chance of project completion, is denoted as $[T_{Amin}(0);T_{Amax}(0)]$. With this initial confidence interval an expected project duration $E(T_A)$ can be derived using (7.46). At an "ex ante" investigation of a drug development project, $E(T_A)$ represents the constant best estimator for the completion date of the project and is therefore treated as a constant factor.

$$E(T_A) = T_{A\min}(0) + \frac{T_{A\min}(0) - T_{A\max}(0)}{\ln 0.05} \qquad (7.46)$$

In addition, there is remaining uncertainty at the time of expected drug approval when production and marketing can start[418]. This remaining 95% range, which in a best case scenario could be close to zero, is denoted as $[T_{Amin}(E(T_A));T_{Amax}(E(T_A))]$.

At this point it is assumed that the boundaries of the confidence interval $[T_{Amin}(t);T_{Amax}(t)]$ from t=0 to $t=E(T_A)$ are linear decreasing functions of time. With a final expected potential delay of $FD=[T_{Amax}(E(T_A))-T_{Amin}(E(T_A))]$ and the estimated constant $E(T_A)$, the decreasing 95% probability range can be derived using the following equations.

$$\lambda(0) = \frac{1}{(E(T_A) - T_{A\min}(0))}; \qquad \lambda(E(T_A)) = \frac{\ln 20}{FD}$$

$$T_{A\min}(E(T_A)) = E(T_A) + \frac{FD}{\ln 0.05}; \qquad T_{A\max}(E(T_A)) = E(T_A) + \frac{FD}{\ln 0.05} + FD$$

$$T_{A\min}(t) = T_{A\min}(0) + \frac{t}{E(T_A)} * \left[\frac{T_{A\min}(0) - T_{A\max}(0) + FD}{\ln 0.05}\right]$$

$$T_{A\max}(t) = T_{A\max}(0) - \frac{t}{E(T_A)} * \left[(T_{A\max}(0) - T_{A\min}(0) - FD) * \left(1 + \frac{1}{\ln 0.05}\right)\right]$$

Figure 7.28 shows the decreasing 95% probability interval of project delay over the expected lifetime $E(T_A)$ of the illustrative project[419].

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[417] Detailed sensitivity analyses are conducted in chapter 9 after a valuation model in realistic market environment has been developed.

[418] This is related to potential additional requirements from regulatory authorities that have to be fulfilled before a product can be sold in the market even though it is technically approved.

[419] With $T_{Amin}(0)=11$, $E(T_A)=12.8$, $T_{Amax}(0)=16.4$ and $FD=0.25$

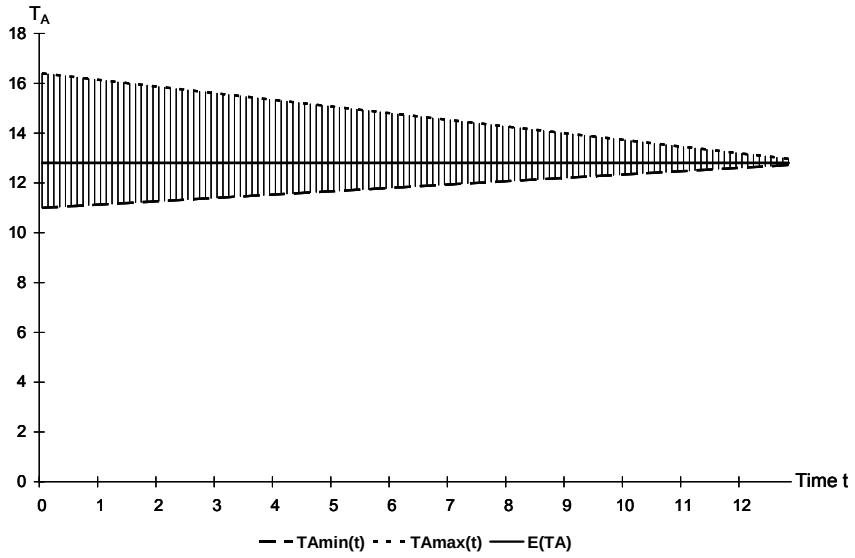

Figure 7.28: Linear decreasing timing risk over project duration

With the established relationships, one can change the previously constant parameter λ into a time dependent parameter λ(t) defined as (7.47).

$$\lambda(t) = \frac{1}{E(T_A) - T_{A\min}(t)} \tag{7.47}$$

Using the initial expected probability interval ID=[$T_{Amin}(0)$,$T_{Amax}(0)$] and the expected FD, λ(t) can be rewritten as (7.48).

$$\lambda(t) = \frac{1}{\frac{ID}{\ln 20} - \left[\frac{ID - FD}{(\ln 20 * T_{A\min}(0)) + ID} * t\right]} \tag{7.48}$$

For the valuation of the R&D option in this framework with exponentially distributed project delay and linear decreasing 95% probability range, adjustments to the valuation equation are necessary. Substituting the constant parameter λ with a time dependent variable λ(t) changes (7.40) to equation (7.49) with the probability function p(t;T_A) being represented by (7.50).

$$C_U(t) = \int_{T_{A\min}}^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)} e^{-(r_{rf}+\alpha)(T_A-t)} * \left(1 - \left(\frac{\cos\left(\frac{\frac{11}{T_A}t+3}{14}\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * \left(\frac{MP}{(r_{rf}+\alpha)} * \left(1 - e^{-(r_{rf}+\alpha)(20-T_A)}\right) - X\right) * p(t;T_A)\partial T_A \tag{7.49}$$

$$p(t;T_A)=\left(\frac{1}{\frac{ID}{\ln 20}-\left[\frac{ID-FD}{(\ln 20*T_{A\min}(0))+ID}*t\right]}\right)*e^{-\left(\frac{1}{\frac{ID}{\ln 20}-\left[\frac{ID-FD}{(\ln 20*T_{A\min}(0))+ID}*t\right]}\right)(T_A-T_{A\min}(t))} \quad (7.50)$$

Reapplying discrete summation to the upper pricing limit (7.49) results in Figure 7.29. It illustrates the upper R&D option value in case of exponentially distributed project delay with linear decreasing 95% interval in comparison to a scenario without timing uncertainty.

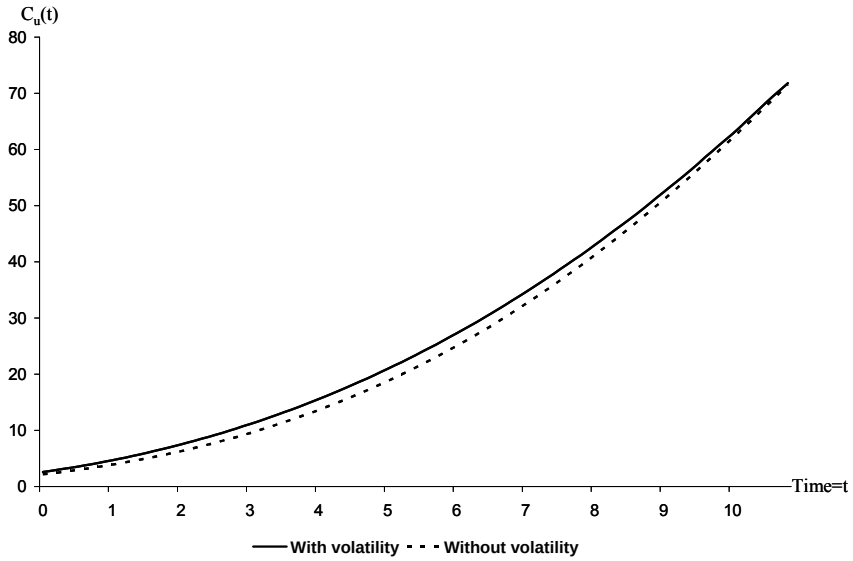

Figure 7.29: Upper pricing limit R&D option - linear decreasing timing risk

The figure shows that uncertainty in project timing increases the upper pricing limit of the R&D option. This effect is relatively small in absolute terms early during the drug development period because technical failure risk and the time value of money represent the predominant valuation criteria during that stage of the process. As the risk of technical failure and the discounting for TVM decreases over time, the potential benefit of early project termination becomes more significant and the absolute gap between the two data plots in the graph widens. As project progress approaches the expected termination date T_{Amin} of the project, this difference continuously decreases as the chance for early project termination becomes very slight.

While modeling uncertainty in project timing as a decreasing function of time can be considered a realistic assumption one could criticize that using a linear decreasing 95% probability range is not realistic. The drug development process consists of a series of activities that contribute differently to the elimination of timing uncertainty.

To consider this aspect of non-linear reduction of timing uncertainty, this section uses an alternative approach to model it. This approach allows overweighting certain parts of the value chain that contribute most to the reduction of timing uncertainty. This is done by introducing a parameter κ, which is referred to as the learning factor. To avoid an

investigation as to which processes realistically are the ones that contribute most to the elimination of timing uncertainty, the model is kept in a general form.

Starting point of this approach is the previous situation where management fixes assumptions "ex ante" on the 95% probability range for project delay at the start of the project and at the expected project termination date represented by ID=[$T_{Amin}(0),T_{Amax}(0)$] and FD=[$T_{Amin}(E(T_A)),T_{Amax}(E(T_A))$] respectively. Based on these 95% probability ranges the corresponding time dependant lambda parameters $\lambda(0)$ and $\lambda(E(T_A))$ are calculated using (7.47). With the introduction of the learning factor κ, the time dependant factor $\lambda(t)$ for the exponential distribution function is introduced by the following relationship (7.51) with $t \in D_5$, $D_5=]0;E(T_A)[$ and $\kappa \in R_+^*$.

$$\lambda(t) = \lambda_0 + \left(\frac{t}{E(T_A)}\right)^{\kappa} * \left(\lambda_{E(T_A)} - \lambda_0\right) \qquad (7.51)$$

$$T_{A\max}(t) = E(T_A) - \frac{1+\ln 0.05}{\lambda(t)}$$

$$T_{A\min}(t) = E(T_A) - \frac{1}{\lambda(t)}$$

To visualize the impact of this learning factor on the probability expectations for project timing, equation (7.47) is solved for $T_{Amax}(t)$ and the required factor $\lambda(t)$ is replaced by (7.51). The resulting equation for the upper range for the expected project delay $T_{Amax}(t)$ at time t is therefore represented by formula (7.52).

$$T_{A\max}(t) = \frac{\ln(20)}{\lambda_0 + \left(\frac{t}{E(T_A)}\right)^{\kappa} * \left(\lambda_{E(T_A)} - \lambda_0\right)} + E(T_A) \qquad (7.52)$$

Figure 7.30 illustrates the impact of the learning factor κ on the 95% range of project completion over the expected course of a project. The three cases for different values of κ represent conceptually different situations. The case with a low value for κ represents the case where learning about project timing takes place early during the project and therefore the width of the 95% probability range becomes smaller during the first third of the process. In the second illustrative case where κ is set at a value of five, learning about project termination predominantly takes place around half-way trough the development process[420]. The last case with κ=15 considers learning effects about project timing predominantly at the very end of the drug development process.

[420] In the average drug development project this corresponds to the project stage of clinical trial II. Compare to Figure 2.1 on page 23.

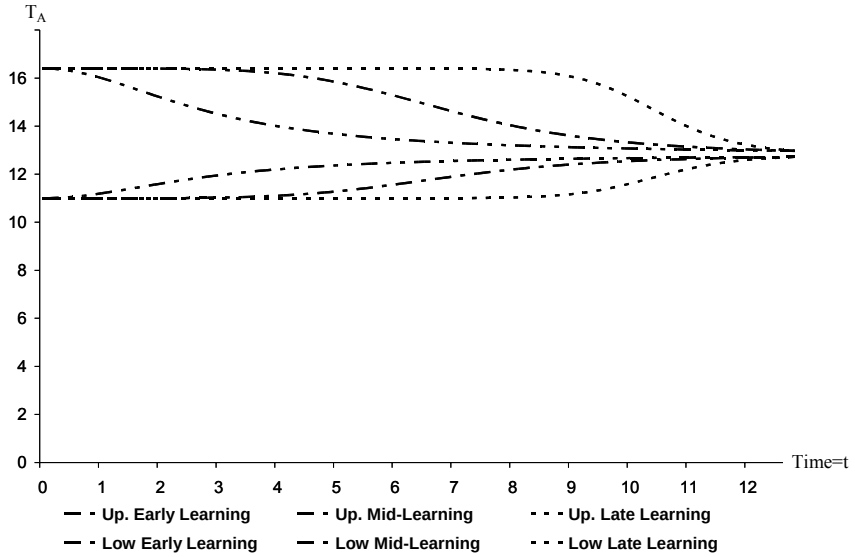

Figure 7.30: Impact of learning factor κ on project timing risk

To investigate the impact of this learning factor κ on the upper pricing limit of the R&D option it is necessary to adjust the valuation formula $C_U(t)$. In the first part of the valuation formula represented by (7.49), only the probability part $p(t; T_A)$ is affected by the introduction of κ and therefore only the relevant parts using $\lambda(t)$ in the equation for the probability distribution (7.50) are adjusted to (7.53).

$$p(t;T_A)=\left[\left(\frac{\ln(20)}{T_{A\max}(0)-E(T_A)}\right)+\left(\frac{t}{E(T_A)}\right)^{\kappa}*\left(\frac{\ln(20)}{T_{A\max}(E(T_A))-E(T_A)}-\frac{\ln(20)}{T_{A\max}(0)-E(T_A)}\right)\right]*e^{-\left[\left(\frac{\ln(20)}{T_{A\max}(0)-E(T_A)}\right)+\left(\frac{t}{E(T_A)}\right)^{\kappa}*\left(\frac{\ln(20)}{T_{A\max}(E(T_A))-E(T_A)}-\frac{\ln(20)}{T_{A\max}(0)-E(T_A)}\right)\right](T_A-E(T_A))} \tag{7.53}$$

Figure 7.30 illustrates the impact learning about project timing has on the upper limit of the R&D option pricing range. Displayed are the three illustrative cases with early-, mid- and late-stage learning from t=0 to $t=T_{Amin}(0)=11$.

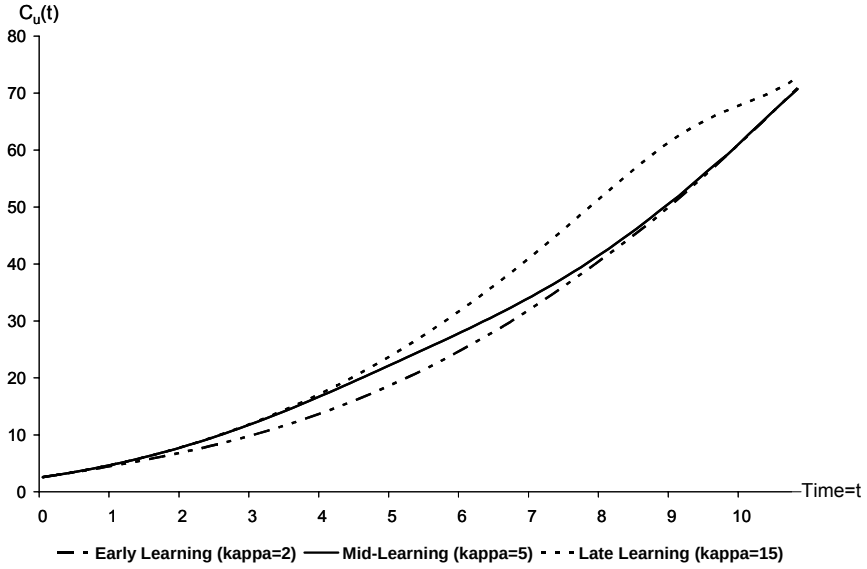

Figure 7.31: Upper pricing limit – various exp. timing uncertainty scenarios

Learning in this context represents the reduction of possible project termination dates earlier and after the expected $E(T_A)$. Since all analyses are conducted "ex ante" this value is kept constant for all three scenarios over the course of the project as the best estimator for project completion. With all three functions having the same initial 95% confidence interval and the same $E(T_A)$ it is intuitively clear that the three graphs have the same starting point at t=0 and converge to the same value as t approaches $E(T_A)$. However, learning about project termination timing reduces the value of the R&D option. This is the case because learning deprives the option owner of the valuable chance to take advantage of earlier than expected project completion dates. Although at the same time the risk is reduced that the project is delayed this is not of comparable relevance because as with all option rights, the owner is not required to participate in these negative developments.

The longer the chance exists that a project is completed before the expected $E(T_A)$ the longer the seller of the R&D option can expect to raise a financial premium with the sale of the R&D option compared to a scenario where this opportunity is already eliminated. Comparing the upper pricing limit where timing risk is reduced in a linear way with the case where intense learning occurs half way through the project[421] results in the scenario presented in Figure 7.32. Although starting and ending point of both graphs displayed are the same, the characteristics over the expected course of the project differ slightly.

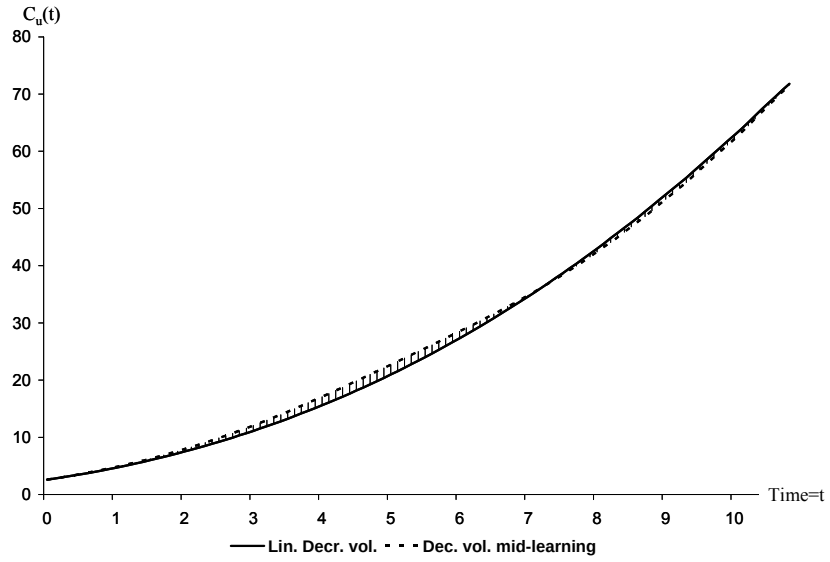

Figure 7.32: Upper pricing limit R&D option – linear vs. non linear timing risk

Rational for this slight difference is the same as discussed above. During the early project stage the scenario with intense learning longer includes the opportunity for early project termination therefore the financing potential in this case exceeds the case with linear uncertainty reduction. The situation changes towards the end of the expected timing when intense learning about project timing has eliminated most of the opportunities favorable for

[421] Learning factor being set at $\kappa=5$.

the option owner. This is why the linear scenario holds greater financing potential during later project stages.

7.3.5 Approximation of Upper Financing Potential

Over the previous sections a model has been developed to assess the upper pricing limit of a R&D option over the expected course of a drug development project. The model is based on the idea of an idealistic market environment and on certain underlying assumptions defined in section 7.3.1. All specific calculations and examples are based on the illustrative drug development project defined in Table 7.2.

The model represents the case if a R&D option is sold to a company or to an investor who is able to diversify all private risk involved in drug development. This investor does not require compensation for this risk and is therefore willing to pay the highest price of any market participant. In addition, the model is based on constant market potential over time but includes monotonously decreasing risk of project failure. Finally, uncertainty in project duration is represented by an exponentially distributed project delay function with an expected intense learning phase about mid-way through the project[422]. Figure 7.33 represents the approximated result of the final valuation model for the illustrative project example.

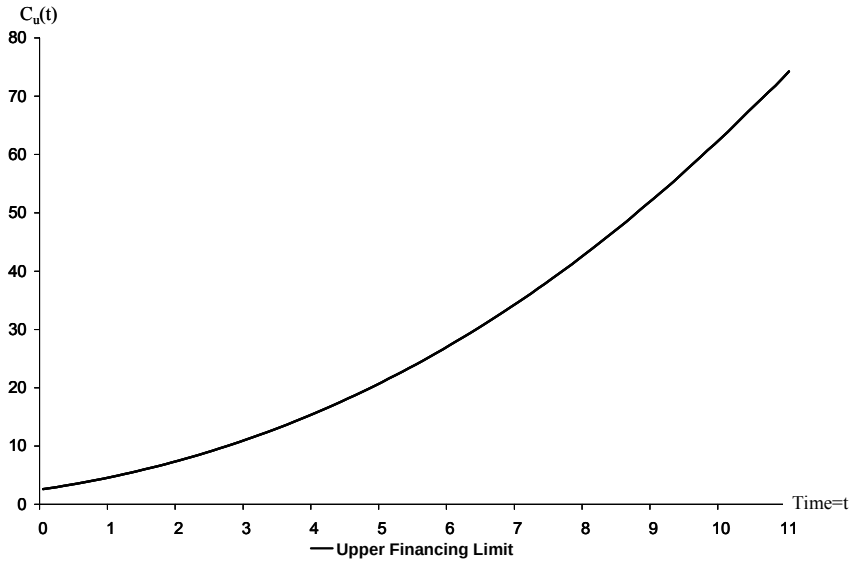

Figure 7.33: Upper financing limit of R&D option during illustrative project

The results illustrate some interesting characteristics of a R&D option sale, which are discussed in detail after the lower pricing limit of a R&D option has been investigated and therefore the financing range of a R&D option deal can be assessed.

[422] Being about the time period of clinical trial II studies.

7.4 Lower Pricing Limit of a R&D Option

From the discussion on investors' classification in chapter 7.2 it can be said that the pricing limit established in the previous section only applies to one specific group of investors representing one extreme end of the potential pricing range. This section investigates the price expectations of the other extreme group of investors who are not able to diversify private risk and therefore require a higher expected return.[423]

Because of these increased return expectations this second extreme group of investors is willing to pay the lowest price and therefore limits the pricing range to the lower end. Combined with the results from the previous chapter the outcome of this section is a pricing range for a R&D option that represents the "ex ante" financing potential of the R&D option in an idealistic market environment.

7.4.1 Starting Point to Assess Lower Pricing Limit

The starting point to assess the lower pricing limit of the R&D option is represented by the valuation approach for the upper pricing limit described in equations (7.49) and (7.53). With the risk exposure of potential investors being the key price determining factor it is first discussed how different exposure to technical risk, uncertain market entry timing, uncertain product lifetime[424], general market uncertainty and potential competition change in the scenario investigated. While competition is excluded by definition in the idealistic market environment, this point does not require further investigation in this chapter.

During the discussion above it is shown that general market uncertainty is a risk factor, which is systematic by nature and cannot be diversified. In addition, no industry player accepts any return lower than the risk-free rate of interest plus the premium for general market risk. With this in mind the two risk premiums r_{rf} and α introduced above are as relevant for the quantification of the lower pricing limit as they are for the upper pricing limit.

7.4.2 Model Adjustment to Include Private Risk Premium

This section discusses differences in private risk exposure of potential investors in a R&D option deal. In the case of the idealistic market environment there are two risk factors remaining, which fall into this category. These two factors are the risk of potential project failure and the uncertainty related to project timing. Because these two risk factors represent private risk factors, the above model for the upper pricing limit does not consider any risk compensation for these types of risk.

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[423] In addition, their general return expecations are higher following the opportunity cost approach described in section 7.2.2. To limit modeling complexitiy this effect is assumed to include the magnitude of the risk premium factors applied.

[424] Implicitly covered when discussing uncertain market entry timing because these two types of uncertainty are directly linked over the known twenty year patent protection period and the resulting effective patent protection period. This relationship is discussed in section 5.1.3.

Adjusting the model to consider the related private risk compensation is a simple step that requires additional risk premiums to be included in the model. As a notation for these risk premiums the Greek symbols ε and ρ are introduced in section 7.2.4. These symbols represent the premium for the risk of potential project failure and the risk of uncertain project timing. Since these types of uncertainty are only relevant for the time period preceding the point of drug approval T_A, ε and ρ are only considered in the discounting factor affecting the drug development period but not the marketing period following T_A. As discussed, the introduced risk premium α for general market uncertainty as well as the risk-free rate of interest r_{rf} still remain relevant for the adapted model. The resulting formula for the lower pricing limit of the R&D option over the expected course of a project in an idealistic market environment is therefore represented by (7.54). The exponentially distributed probability function (7.53) is not affected by this adjustment and remains unchanged.

$$C_L(t) = \int_{T_{A\min}}^{20+\frac{1}{(r_{rf}+\alpha)}\ln\left(1-\frac{(r_{rf}+\alpha)X}{MP}\right)} e^{-(r_{rf}+\alpha+\varepsilon+\rho)(T_A-t)} * \left(1-\left(\frac{\cos\left(\frac{11}{T_A}t+3\right)\pi+1}{2}\right)^{\frac{4}{5}}\right) * \left(\frac{MP}{(r_{rf}+\alpha)} * \left(1-e^{-(r_{rf}+\alpha)(20-T_A)}\right)-X\right) * p(t;T_A)\partial T_A \qquad (7.54)$$

As for the integration model of the upper pricing limit this equation cannot be solved numerically but can be approximated using discrete summation.

7.4.3 Approximation of Lower Financing Potential of R&D Option

By introducing the risk premium for a project's potential technical failure and for the uncertainty related to an unknown project termination date, the resulting lower pricing limit of a R&D option can be assessed.

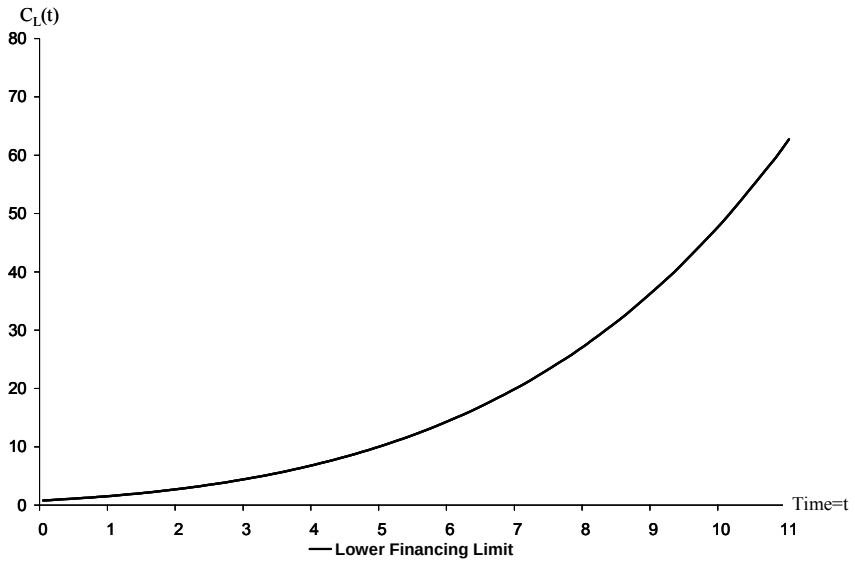

Figure 7.34: Lower pricing limit of a R&D option

Solving the valuation equation (7.54) using discrete summation results in Figure 7.34 for the illustrative case example. Basically, the resulting lower pricing limit of the R&D option is of similar shape but on a lower level compared to the final upper pricing limit as shown in Figure 7.33.

7.5 Quantification of R&D Option Financing Range

A direct comparison between the two pricing limits is displayed in Figure 7.35 for the time period $t<T_{Amin}=11$. The upper and the lower pricing limits model the price expectations of extreme types of investors that cannot be found in the market. It is extreme to assume that there is an investor who is diversified to an extent that he can entirely eliminate the impact of private risk. In reality, investors can diversify risk to some degree and therefore the price a company can achieve by selling a R&D option can be expected to reside within the displayed financing range. If the final price and therefore the short-term financing potential lies at the upper or the lower end of the range depends on the type of investor representing the buying side of a R&D option deal.

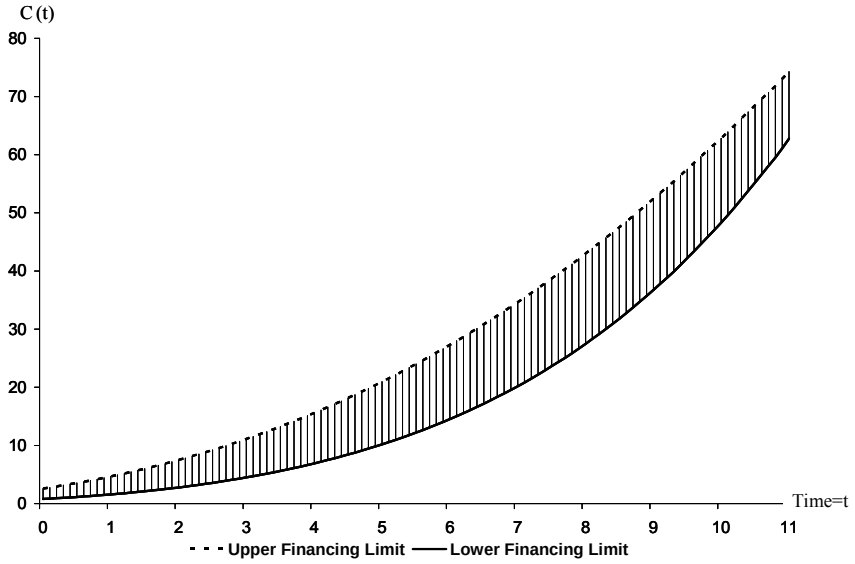

Figure 7.35: R&D option pricing range – idealistic market environment

The graph visualizes that the gap between the upper and the lower financing limit and therefore the bidding advantage of a fully diversified investor is not constant during the expected course of the drug development project. To visualize this finding, Figure 7.36 displays the absolute magnitude of this pricing gap for the illustrative case example.

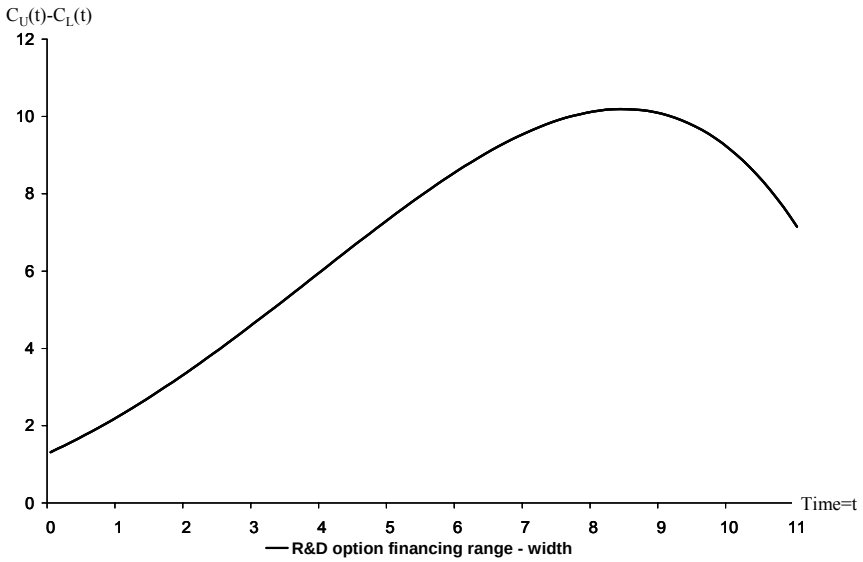

Figure 7.36: Width of expected R&D pricing range – idealistic environment

The graph shows that the pricing spread $C_U(t)-C_L(t)$ in the illustrative case example increases over the early stage of the expected project duration until it reaches a maximum about two-thirds through the project. During this period, the bidding advantage of a large diversified investor with unlimited financial resources is the largest. After this point, the upper and the lower pricing limit converge over time reducing the bidding advantage during the final stages of the expected project duration. In the illustrative case example, the bidding advantage of a highly diversified investor with sufficient financial resources is at peak level of the expected project duration approximately 50% above the level at the point T_{Amin}.[425]

[425] At this point it would be beneficial to investigate to which extent the model depends on the individual input parameters required. Since a detailed sensitivity analysis is conducted in chapter 9 after the model is expanded in a realistic market environment this question is not further investigated at this point.

8 Fund Raising Potential of R&D Option in a Realistic Environment

The discussion in the previous chapter is based on assumptions of an idealistic environment with known and constant market potential of a drug under development and the absence of market competition. These assumptions are relaxed in this chapter to create a more realistic view of the situation. Once the framework is changed from an idealistic to a realistic market view the impact of these changes on the previously derived R&D option financing range is investigated.

8.1 Description of Realistic Market Environment

To create a more realistic market view, the constant market potential is substituted by a variable following a stochastic process. Starting from an initial estimate of today's market potential MP(0), the future potential of a new drug is modeled as a stochastic process with five main factors influencing its development over time. These five factors are market trends, general uncertainty, potential project expansions, potential competition from other market participants and an uncertainty in the initial market estimate.

8.1.1 Market Trends

Up to this point the market potential of a new drug was treated as a constant parameter MP, which does not change between time t=0 as the point of patent application and time t=20 when the patent for this new drug expires and generic competition takes over the entire market. From now on the market potential is treated as a time dependent variable MP(t), which has a starting point MP(0) and is subject to changes between t=0 and t=20.

In reality there are trends that constantly influence the market potential of a new drug. These factors are continuous by nature and permanently cause the market potential to develop in a certain way. Real-life root causes that can be responsible for a trend in market potential for a specific drug can include:

- General demographic developments
- Increasing penetration of the population with a certain condition
- Diagnostic improvements increasing the number of patients diagnosed with a certain condition or disease
- Therapeutic drug replacements gradually making patients switch from one drug to a superior product over time
- Various other reasons

Irrespective of the cause of a trend it can be modeled using the following stochastic differential equation (8.1) with trend factor μ.

$$\frac{\partial MP(t)}{MP(t)} = \mu \partial t \qquad (8.1)$$

8.1.2 General Uncertainty

In addition to a predictable market trend there is uncertainty related to the extent to which this trend finally materializes. There are always small and unpredictable occurrences that have an impact on the future market potential of a drug under development. This can be considered the general uncertainty in trend forecasting. To include general uncertainty into the investigation the stochastic process U(t) with $0 \leq t \leq 20$ is defined as a standard Brownian motion with the following characteristics:

- U(0)=0
- The mapping $t \rightarrow U(t)$ is a continuous function on [0;20]
- The increments $[U(t_1)-U(t_0), U(t_2)-U(t_1), \ldots, U(t_k)-U(t_{k-1})]$ are independent for any k and any $0 \leq t_0 < t_1 < \ldots < t_k \leq 20$[426]
- U(t)-U(s) is normally distributed with N(0,t-s) for any $0 \leq s < t \leq 20$

As a consequence one can follow that $U(t) \sim N(0,t)$ for $0 < t \leq 20$.

With this process U(t) the future market potential MP of a drug can be modeled as a stochastic process following a geometric Brownian motion (GBM)[427]. With this definition, $MP \sim GBM(\mu,\sigma^2)$ fulfills the stochastic differential equation (SDE) (8.2).

$$\frac{\partial MP(t)}{MP(t)} = \mu \partial t + \sigma \partial U(t) \qquad (8.2)$$

If $MP \sim GBM(\mu,\sigma^2)$ it can be concluded that the ratio MP(t)/MP(0) is log-normally distributed with $(MP(t)/MP(0)) \sim LN([\mu - \tfrac{1}{2}\sigma^2]t, \sigma^2 t)$[428] and therefore

$$E[MP(t)] = e^{\mu t} MP(0) \text{ and } Var[MP(t)] = e^{2\mu t} MP^2(0)\left(e^{\sigma^2 t} - 1\right).$$

With the described Brownian motion of MP and an initial market potential MP(0), MP(t) can be written as (8.3)[429].

$$MP(t) = MP(0) e^{\left(\left[\mu - \frac{1}{2}\sigma^2\right]t + \sigma \partial U(t)\right)} \qquad (8.3)$$

---

[426] This is called the no-memory concept of a stochastic process and implies that historic events are irrelevant for the future development of the process. This is a concept often used in option theory but can also be criticized because many investors and businessmen object to the idea that history is irrelevant. For a discussion on this point see Boer (2002, p. 113).

[427] Because of its characteristics the geometric Brownian motion represents the most widely used model to approximate stock price movements Franke et al. (2004, p. 64).

[428] For details behind this conclusion see Glasserman (2004, p. 94) or Ikeda et al. (1996).

[429] Compare to Bingham and Kiesel (2004, p. 197)

Figure 8.1 displays three illustrative sample paths for the future market potential MP(t) of a new drug based on $MP(0)_1$, $MP(0)_2$ and $MP(0)_3$ with μ=0.015 and σ=0.05.

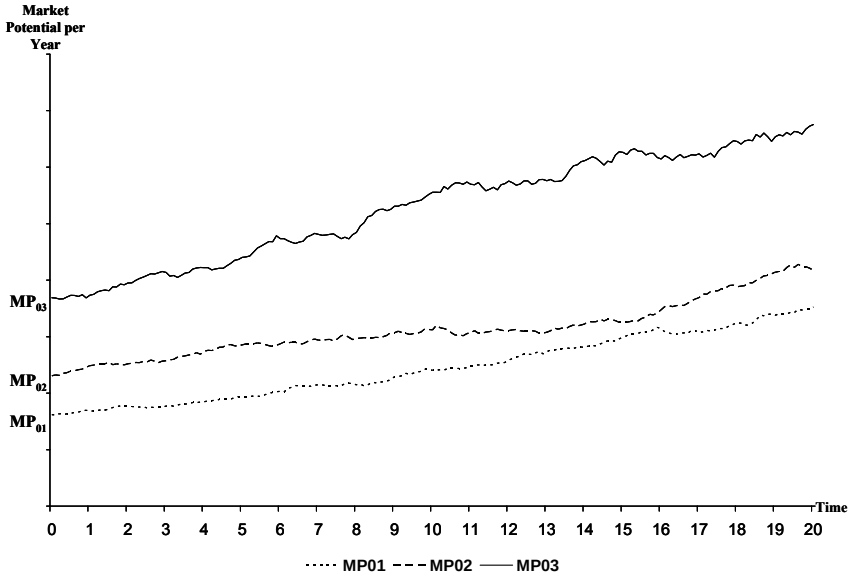

Figure 8.1: NCE market potential development – trend with diffusion

8.1.3 Potential Project Expansions

While the previous two sections describe the future market potential of a drug under development as a continuous trend diffusion process there are also randomly occurring events that have an impact on a project's market value. As Lampard (2001) states"… there are enormous opportunities to exploit the market, perhaps by product enhancements, new indications, new dosage forms or new drug delivery systems". These are all opportunities that have the potential to significantly increase the market potential of a new drug under development as they occur. As opposed to market potential developments described above, these potential project expansions do not take place on a continuous basis but rather on individual random occasions.[430]

As an example one can consider a project where a substance to cure high blood pressure is developed. With this indication the drug has a certain expected future market potential. Now the research team discovers that the same substance is also beneficial in the treatment of diabetes. This discovery immediately increases the total market potential of the drug and therefore the value of the development project. For the development of the future market potential this implies that there is not only a trend with diffusion but also the chance of positive jumps. To include this potential project expansion into the model of the future market potential an additional term is added to the stochastic differential equation (8.2) to form equation (8.4).

$$\frac{\partial MP(t)}{MP(t-)} = \mu \partial t + \sigma \partial U(t) + \partial J_P(t) \qquad (8.4)$$

With J_P being a piecewise constant sample path representing the jump process and MP(t-) being defined as the instance just before a positive jump formalized as (8.5)[431].

$$MP(t-) = \lim_{u \uparrow t} MP(u) \qquad (8.5)$$

The positive jump process $J_p(t)$ is given by the following equation (8.6) where the individual Y_j are random variables representing the size of a jump and N(t) is a simple counting process that counts the number of positive jumps in the time interval [0;t].

$$J_p(t) = \sum_{j=1}^{N(t)} (Y_j - 1) \qquad (8.6)$$

This implies that there is an undefined number of random arrival times $0<\tau_1<\tau_2<\ldots<t$. The placeholder $\partial J_p(t)$ used in equation (8.4) represents the jump in J_p occurring at time t. The respective size of this jump is given by (Y_j-1) at instances where $t=\tau_j$ and 0 in all cases where t does not coincide with any of the jump instances τ_j. The jump size can be derived using the market potential ratio just after and just before an occurring jump. This means that Y_j is defined as (8.7).

$$Y_j = \frac{MP(\tau_j)}{MP(\tau_j -)} \qquad (8.7)$$

Before this process can be modeled it is necessary to impose a distribution function to the occurrences and the potential sizes of these jumps. For the purpose of this study it is assumed that if a positive jump occurs, it increases the annual market potential of a new drug up to 40% without any value being more probable than others. This simply implies that Y_j is an evenly distributed variable over the interval [1; 1.4][432].

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[430] Another one-time occurrence that can be considered a positive jump in the value of a drug development project is a simple patent extension granted by regulatory authorities at some point during the project.

[431] This specific notification of MP(t-) is essential because the simple use of MP(t) would be ambiguous due to the potential jump occurring at t. If there is an opportunity for MP to jump at t it needs to be specified if MP(t) refers to the value of MP just before or just after the jump at t. In this study the convention also used by Glasserman (2004) is used assuming that stochastic processes are continuous from the right therefore MP(t) already includes the jump occurring at t while MP(t-) represents the value of the MP just before a potential jump occurs at time t.

[432] Jump sizes are very project-specific parameters. Selecting 40% as the maximum jump size can therefore not being considered a suggested factor to be generally used in real-life examples. This figure is simply selected for illustrative purposes. For every real case assessed, this parameter has to be investigated based on individual project characteristics.

To model the occurrences of the potential positive jumps the study builds on a simple Poisson process. This type of arrival process is in detail explained at Cinlar (1975, p. 78).[433] Under this assumption the time periods between two consecutive jump occurrences (τ_{j+1}-τ_j) are independent from each other and also independent from the counting process N(t). For the time from one jump occurrence to the next one noted as $P(\tau_{j+1}-\tau_j \leq t)$ the simple exponential distribution density function (8.8) can be used.

$$1 - e^{-\lambda_1 t}, t \geq 0 \qquad (8.8)$$

With exponentially distributed time periods between positive jumps of size [1; 1.4], MP(t) is represented by a jump-diffusion model using a compound Poisson process[434] to model positive jumps. Figure 8.2 shows three illustrative examples for MP(t) building on the initial starting expectations $MP(0)_1$, $MP(0)_2$ and $MP(0)_3$ for the expected annual market potential of a new drug under development.

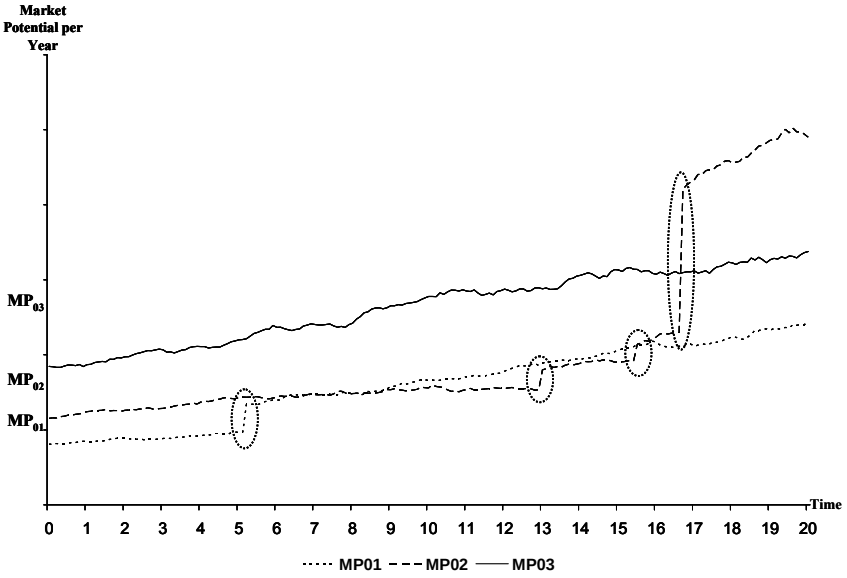

Figure 8.2: NCE market potential – single jump diffusion process

[433] This is in line with the work of Merton (1976) who considered jumps in stock prices when evaluating financial derivative securities and also used a Poisson process to model the occurrences in stock price jumps.

[434] For details on compound Poisson processes see Cinlar (1975, p. 90).

8.1.4 Competitive Market Environment

To complete the modeling of the market potential of a new drug it is considered that research activities are conducted in a competitive environment. While the R&D option represents an exclusive right on the outcome of a development project the underlying project itself does not represent an exclusive right. Others can seize some of the future cash flows by introducing alternative drugs on the market.[435]

The introduction of a competitive drug instantaneously reduces the market potential of a drug and therefore, competition can be interpreted as external negative shocks on the market potential. To include these shocks in the valuation model the jump diffusion process is expanded by another jump factor representing the risk of negative jumps. The resulting double-jump-diffusion process has to satisfy the stochastic differential equation (8.9), which represents the previous equation (8.4) expanded by the negative jump factor $\partial J_N(t)$.

$$\frac{\partial MP(t)}{MP(t-)} = \mu\partial t + \sigma\partial U(t) + \partial J_P(t) + \partial J_N(t) \qquad (8.9)$$

J_N in this context also represents a piecewise constant sample path to model the negative jump process. The negative jump process $J_N(t)$ is similar to the introduced positive jump process. It is defined by the following equation (8.10) where the individual V_v are random variables and M(t) is a simple counting process that counts the number of negative jumps in the time interval [0; t].

$$J_N(t) = \sum_{v=1}^{M(t)} (V_v - 1) \qquad (8.10)$$

This implies that there is an undefined number of random arrival times for negative jumps $0<\upsilon_1<\upsilon_2<\ldots<t$. The placeholder $\partial J_N(t)$ used in equation (8.9) represents the jump in J_N occurring at time t. The respective size of this jump is given by $(V_v\text{-}1)$ at instances where $t=\upsilon_v$ and 0 in all cases where t does not coincide with any of the negative jump instances υ_v. The only difference between the positive and the negative jump process lies in the size of the allowed jumps. While definition (8.11) of the negative jumps is similar to the positive ones, the allowed sizes are not.

$$V_v = \frac{MP(\upsilon_v)}{MP(\upsilon_v -)} \qquad (8.11)$$

Negative jumps can only reduce the value of MP(t) with a lower limit of zero because MP(t) can, under no circumstances, become a negative figure. This implies for the allowed jump size that $V_V \in [0;1[$.

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[435] This is discussed in detail in chapter 5.1.5. On the issue of non-exclusivity of real options see also Freihube (2001, p. 140) or Kilka (1995, p. 117).

For the distribution of negative jumps over time another compound Poisson process is used. This second compound Poisson process makes the time period between two consecutive negative jumps occurrences (υ_{v+1}-υ_v) independent from each other and from M(t). With this Poisson process the time between two negative jump occurrences is characterized by the following distribution density function (8.12).

$$1 - e^{-\lambda_2 t}, t \geq 0 \qquad (8.12)$$

Figure 8.3 shows the illustrative examples for MP(t) following the developed double-jump-diffusion-process with trend, building on the three initial expectations $MP(0)_1$, $MP(0)_2$ and $MP(0)_3$ for the market potential of a new drug under development.

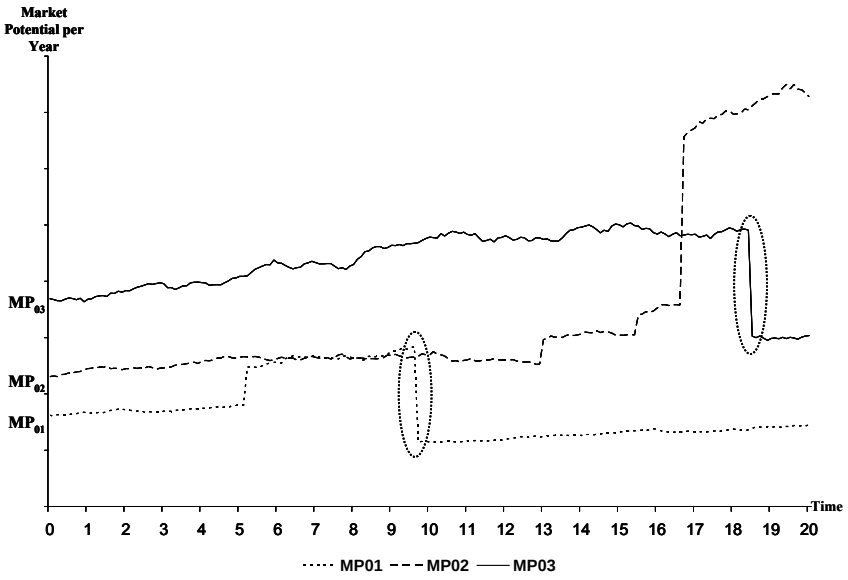

Figure 8.3: NCE market pot. – double jump diffusion process

8.1.5 Uncertainty in Initial Market Estimate

The last factor influencing the future market potential of a new drug is the uncertainty related to the starting point MP(0) of the described stochastic process. For the development of the upper and lower pricing limit in an idealistic market environment it is assumed that the market potential of a drug is known and constant over time. In the previous sections of this chapter the assumption of constant market potential over time is relaxed and the market potential development is described using a double-jump-diffusion process with trend with a known starting point MP(0).

In this section the assumption of a known starting point of the valuation process is relaxed and the known initial market potential MP(0) is substituted by a stochastic variable. The probability function of this initial market potential has to fulfill certain requirements:

- It can only allow positive values for MP(0). A negative market potential does not represent a realistic starting point.
- It should be a one peak function that assigns the highest probability to a market potential management considers most appropriate.

A probability function fulfilling these criteria is the lognormal distribution function, which is a one peak function that cannot take on negative values. From this point on, the lognormal distribution is used as a probability function for the initial market potential MP(0). This assumption appears appropriate considering that Copeland and Tufano (2004) already consider this kind of distribution function as "fairly standard"[436] for real-life issues.[437]

Instead of working with a single expected value for MP(0) at the beginning of the development project it is more appropriate to work with a range in which one expects the initial value of MP(0) to be. This expectation range is framed by a lower limit MP_l and an upper limit MP_u for the market potential MP(0) at the time of project valuation t=0.

Using this range as a probability interval and knowing that the natural log of the expected market potential is normally distributed allows the distribution parameters to be derived from the initial expectation range [MP_l; MP_u]. For a normally distributed stochastic variable it is known that 95% of all possible values can be observed within a range of two standard deviations around the expected mean value[438]. If the 95% interval is defined as [MP_l; MP_u] and MP(0) is log-normally distributed, the 95% interval for the natural log becomes:

$$\left[\ln(MP_l);\ln(MP_u)\right]=\left[\ln\left(\overline{MP_0}\right)-2\sigma_{\ln(MP_0)};\ln\left(\overline{MP_0}\right)+2\sigma_{\ln(MP_0)}\right] \qquad (8.13)$$

With the lognormal distribution assumption and the 95% boundary condition of (8.13) a probability distribution function of the natural logarithm of the future market potential can be established. To do so, the estimator for the volatility[439] $\sigma_{\ln(MP_0)}$ and the expected mean value of the initial market potential $\overline{MP(0)}$ can be derived from (8.13) using the following formulas (8.14) and (8.15).

$$\sigma_{\ln(MP(0))}=\frac{\ln(MP_u)-\ln(MP_l)}{4} \qquad (8.14)$$

$$\overline{MP(0)}=e^{\ln(MP_u)-2\sigma_{\ln(MP(0))}}=e^{\ln(MP_l)+2\sigma_{\ln(MP(0))}} \qquad (8.15)$$

By definition it is known that the natural logarithm of MP(0) follows a normal distribution $N(\ln\overline{(MP(0))};\sigma_{\ln(MP_0)})$ with the density function (8.16).

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[436] And use it to estimate the value of a plant to be built.

[437] It needs to be emphasized that the use of the log-normal distribution has to be evaluated for appropriateness before it is applied on a real project. Other distribution functions might prove more effective in specific cases.

[438] One can refer to Bol (1993, p. 83) or any other source on basic statistics for more details.

[439] On the importance of cash flow volatility in forecasting see Minton et al. (2002)

$$f(\ln(MP(0))) = \frac{1}{\sigma_{\ln(MP(0))}\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{\ln(MP(0))-\ln(\overline{MP(0)})}{\sigma_{\ln(MP(0))}}\right)} \qquad (8.16)$$

For the illustrative case example the 95% probability range is defined in Table 7.2 with $[MP_l;MP_u]=[80; 120]$ and therefore $[\ln(MP_l);\ln(MP_u)]=[4.38; 4.78]$. Figure 8.4 shows the probability density function of the natural logarithm of the initial market potential ln(MP(0)) in the illustrative case example.

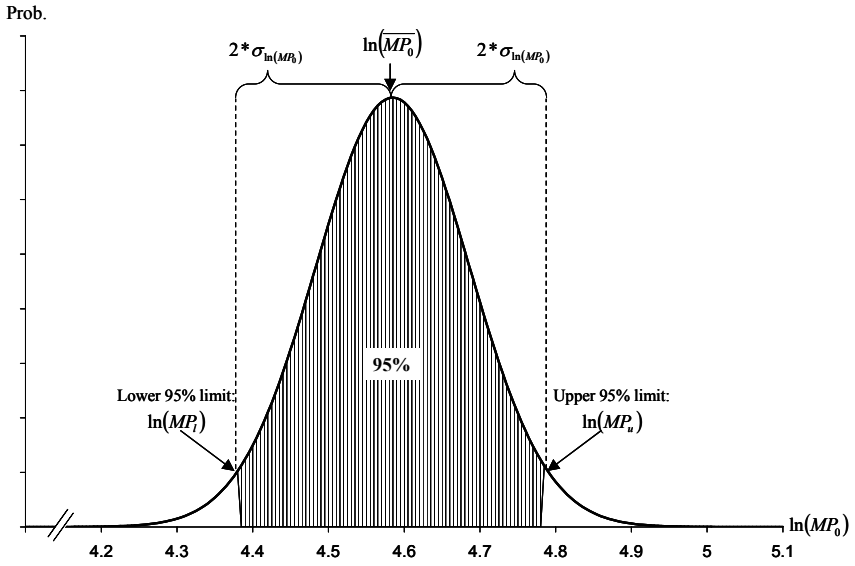

Figure 8.4: Illustrative distribution of natural logarithm of initial market potential

The lognormal distribution function of MP(0) corresponding to the normal distribution function displayed above is shown in the following Figure 8.5. The figure demonstrates the typical characteristics of the lognormal distribution function, which does not have any negative occurrences and is skewed towards the y-axis.

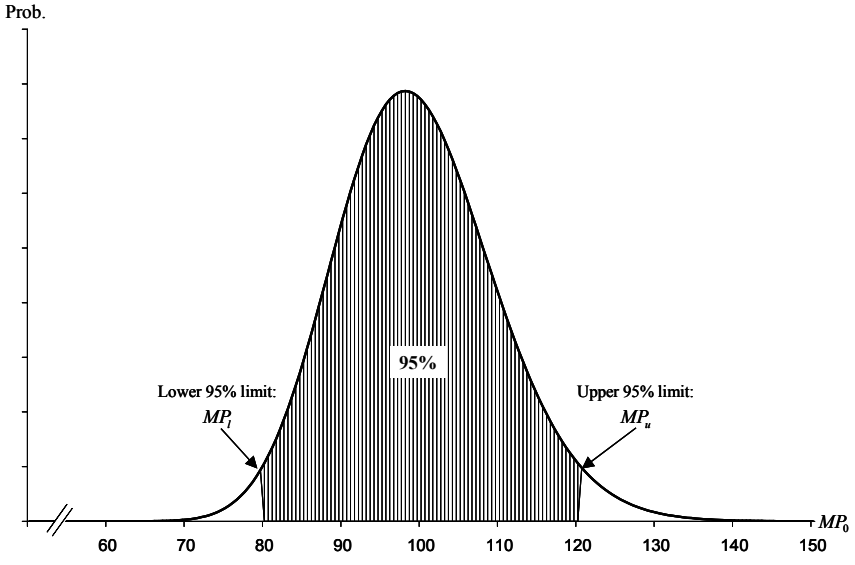

Figure 8.5: Illustrative lognormal distribution of initial market potential

The above discussion on the initial market potential is essential as a basis for the market potential simulations conducted in section 8.2.1.

8.2 R&D Option Financing Range in Realistic Environment

In the previous chapter the transformation from an idealistic to a more realistic market environment is described. In this chapter the focus is back on the financing potential of the R&D option and the impact the change in market environment has on its financing range.

Recalling the integration problem in the valuation of the financing range in an idealistic environment it becomes clear that substituting the constant parameter MP with a stochastic process adds complexity to the valuation problem. While the above model could be assessed using discrete summation, this approach is not sufficient for the valuation in the realistic environment. Another approximation technique is used to incorporate stochastic processes in the valuation. A method capable of assessing complex integrals in high dimensions and including stochastic process into the analysis is Monte Carlo Analysis (MCA).

MCA simulation is a powerful[440] tool well-suited when performing economic valuations for complex problems especially with a long time horizon.[441] An approach based on MCA is therefore the method of choice to approximate the financing potential of a R&D option in a realistic market environment. In chapter 6.4 it is shown how simulation or Monte Carlo analysis can be used to evaluate financial options. At this point, an adapted approach is used to derive the pricing limits of a R&D option.

Generally Monte Carlo simulation follows a six step process consisting of:

1. Identify uncertain input parameters
2. Determine probability distributions of uncertain input parameters
3. Model interrelations and dependencies between different input parameters
4. Model underlying stochastic processes influencing input parameters
5. Conduct simulation runs
6. Evaluate and interpret simulation results

In the previous sections of this study the first three steps are completed. While some input parameters and probability distributions are defined during the discussion of the fund raising potential in an idealistic market environment, the remaining parameters are identified and discussed in section 8.1.

---

[440] Longstaff and Schwartz (2001) consider Monte Carlo analysis such a powerful tool that they use it to investigate early exercise decisions of American options, which is, based on their comments, "one of the most challenging problems in derivative finance".

[441] An application in the pharmaceutical industry, for example, is the simulation of long-term cost effectiveness of new drugs as shown in Henriksson (2002) and Skaer et al. (2000) or clinical trial simulations at Hughes and Walley (2001).

The interrelations between the various parameters are also defined in the approximation formulas for the upper and the lower pricing limit in the idealistic market environment. The next step is to model the stochastic processes that substitute the market potential parameter MP(t) in the established valuation approach based on the discussion in chapter 8.1.

By knowing the underlying market potential of a new drug and therefore the value of the R&D project for one specific simulation run, one can derive the corresponding value of the R&D option for this specific case. Conducting the process of simulating a specific random sample path for the underlying asset and solving the valuation model for this specific case multiple times generates over time a close estimate of the final solution. This is the case because the law of large numbers eventually makes the average of all simulation runs converge to the solution of the underlying valuation problem.

8.2.1 Simulation of Future Market Potential

To describe the simulation process and to show indicative results for the valuation problem, this chapter is built around the introduced illustrative case example. In this simulation section the time continuous underlying stochastic process is approximated by a time discrete process with steps of size Δt. A total of n=1,000 simulation runs are conducted to allow the derivation of meaningful results.[442] At this point, the stochastic process (8.9) is recalled.

$$\frac{\partial MP(t)}{MP(t-)} = \mu \partial t + \sigma \partial U(t) + \partial J_P(t) + \partial J_N(t) \qquad (8.9)$$

This stochastic differential equation is transformed into the time discrete approximation (8.17) that allows the simulation of the process for MP(t) using standard spreadsheet calculation software.

$$\frac{MP(t+\Delta t) - MP(t)}{MP(t)} = \mu \Delta t + \sigma \Delta U(t) + \Delta J_P(t) + \Delta J_N(t) \qquad (8.17)$$

From this approximation the market potential at any time step $MP_i(t+\Delta t)$ during the individual simulation runs follows (8.18) with $i \in [1;1000]$.

$$MP_i(t+\Delta t) = MP_i(t) * [1 + \mu \Delta t + \sigma \Delta U_i(t) + \Delta J_{iP}(t) + \Delta J_{iN}(t)] \qquad (8.18)$$

While some of the components of equation (8.18)are independent from the conducted simulation run, others are not and are simulated individually to obtain the final n=1,000 simulations for $MP_i(t)$. Another presentation of (8.18) demonstrates this for the first time step starting at $MP_i(0)$ with step size Δt for all MP_i, $i \in [1;1000]$.

$$MP_i(\Delta t) = MP_i(0) * [1 + \mu \Delta t + \sigma \Delta U_i(\Delta t) + \Delta J_{iP}(\Delta t) + \Delta J_{iN}(\Delta t)] \qquad (8.19)$$

---

[442] Regarding methods on how to improve the efficiency of Monte Carlo Simulations refer to Glasserman (2004, p. 185)

Starting point of the simulation is the expected initial market potential $MP_i(0)$, with the distribution characteristics defined in section 8.1.5. The n=1,000 simulation runs for $MP_i(0)$ result in the distribution graph shown in Figure 8.6.

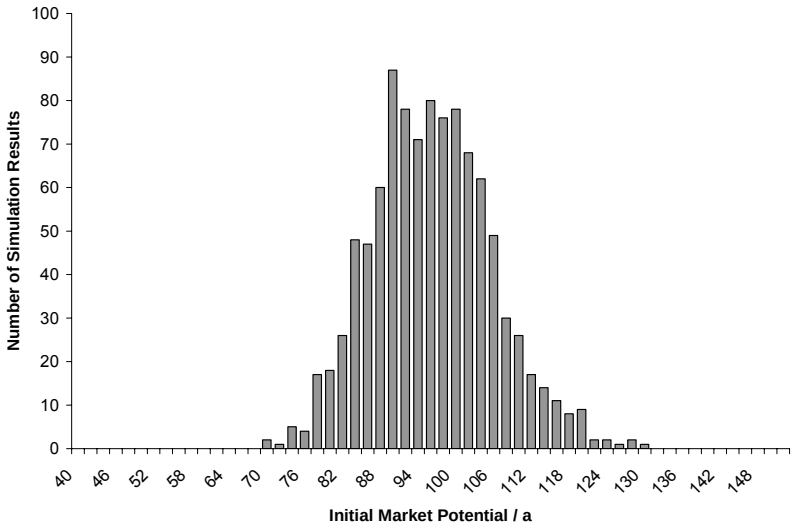

Figure 8.6: Simulation results for n=1,000 initial market potentials MP(0)

Starting from these $MP_i(0)$ the different components of (8.19) that depend on the individual simulation runs i are modeled. The first element that requires simulation is the term for general market uncertainty. To model a process with the characteristics described in chapter 8.1.2 the increments $\Delta U_i(t)$ can be easily calculated using (8.20)[443].

$$\Delta U_i(t) = U_i(t+\Delta t) - U_i(t) = \sqrt{\Delta t} * Z_i(t+\Delta t) \qquad (8.20)$$

With $Z_i(0)$, $Z_i(\Delta t)$, $Z_i(2\Delta t)$, …, being independent standard normally distributed random variables. To complete $i \in [1;1000]$ market potential simulations over the entire patent protection period for $t \in [0;20]$ it is necessary to generate the following set of random variables (8.21), which can be done easily using standard spreadsheet software.

$$Z = \begin{pmatrix} Z_1(\Delta t) & Z_1(2\Delta t) & \cdots & Z_1(20-\Delta t) & Z_1(20) \\ Z_2(\Delta t) & Z_2(2\Delta t) & \cdots & Z_2(20-\Delta t) & Z_2(20) \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ Z_{999}(\Delta t) & Z_{999}(2\Delta t) & \cdots & Z_{999}(20-\Delta t) & Z_{999}(20) \\ Z_{1000}(\Delta t) & Z_{1000}(2\Delta t) & \cdots & Z_{1000}(20-\Delta t) & Z_{1000}(20) \end{pmatrix} \qquad (8.21)$$

With the generated set of random variables and the knowledge that U(0)=0, the processes $U_i(t)$ can be described. For the initial time step Δt equation (8.19) can be rewritten as (8.22) for all $i \in [1;1000]$.

[443] As proposed for financial option valuation at Glasserman (2004, p. 81).

$$MP_i(\Delta t) = MP_i(0) * \left[1 + \mu\Delta t + \sigma\sqrt{\Delta t}Z_i(\Delta t) + \Delta J_{iP}(\Delta t) + \Delta J_{iN}(\Delta t)\right] \quad (8.22)$$

Figure 8.7 shows the distribution of n=1,000 random numbers for $Z_i(\Delta t)$ with the framework parameters Δt=0.1 and σ=5% used for the defined illustrative case example.

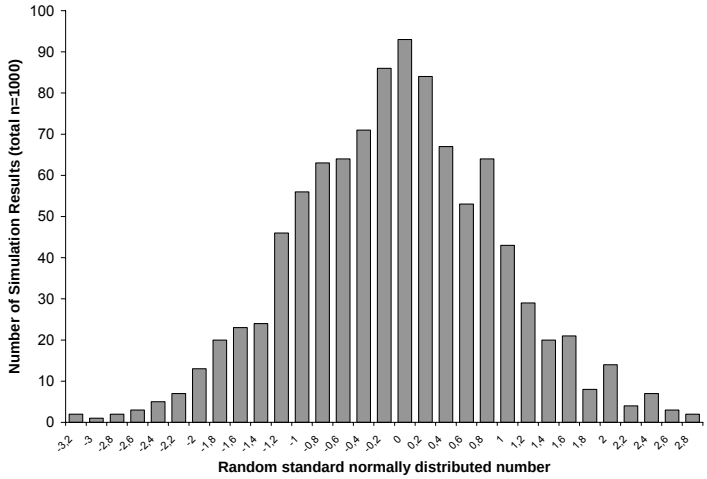

Figure 8.7: Result of n=1,000 random standard normally distributed parameters

Based on this set of random numbers the factor representing general uncertainty can be calculated. The distribution of the resulting factors for $\sigma\Delta U_i(\Delta t)$ is shown in Figure 8.8.

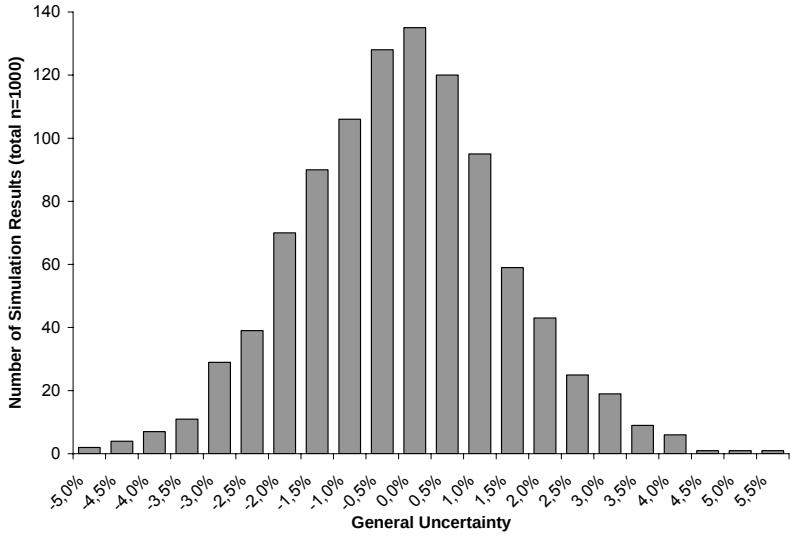

Figure 8.8: Distribution of n=1,000 general market uncertainty factors

After the initiation points $MP_i(0)$ are generated and the trend and market uncertainty factors are quantified, the remaining two jump factors for potential positive and negative jumps in market potential have to be simulated. The positive jump process $J_P(t)$ is defined as (8.6) and therefore the factor $\Delta J_{iP}(t)$ relevant for the simulation is only dependent on whether a jump occurs between t and $(t+\Delta t)$.

$$\Delta J_{iP}(t) = J_{iP}(t+\Delta t) - J_{iP}(t) = 0 \quad if \quad N(t+\Delta t) = N(t)$$
$$\Delta J_{iP}(t) = J_{iP}(t+\Delta t) - J_{iP}(t) > 0 \quad if \quad N(t+\Delta t) = N(t) + 1$$

If a jump occurs between t and (t+Δt) can be represented as a random variable and so can the size of this potential jump. The resulting positive jump factor $\Delta J_{iP}(t)$ can be interpreted as the product of a jump occurrence factor $P_i(t) \in [0;1]$ and a jump size factor $Y_i(t)$ for all $i \in [1;1000]$ as shown in (8.23).

$$\Delta J_{iP}(t) = P_i(t) * Y_i(t) \qquad (8.23)$$

Since it is assumed that the occurrence of positive jumps follows a Poisson process with parameter λ_1, one can define a random variable $R_i(t)$ that is evenly distributed in [0;1] so that each $P_i(t)$ takes on either 0 or 1 depending on the following relationship.

$$P_i(t) = 0 \qquad \text{if } R_i(t) > \left(1 - e^{-\lambda_1 \Delta t}\right)$$

$$P_i(t) = 1 \qquad \text{if } R_i(t) \leq \left(1 - e^{-\lambda_1 \Delta t}\right)$$

To assess the second factor $Y_i(t)$ a maximum size Y_{max} is defined setting an upper limit to the size of positive jumps. Parameter Y is defined in (8.7) as the ratio between the market potential after a jump and the market potential before a jump. In addition it is assumed for the illustrative example that a positive jump can, in a best case scenario, increase the market potential by 40% therefore it is known that $Y_i(t) \in [1;1.4]$. As a second restriction it is assumed that the size of the positive jumps is evenly distributed[444] within their occurrence range $[1;Y_{max}]$.

With the ability to generate $P_i(t)$ and $Y_i(t)$ over the entire observation period [0;20] using standard spreadsheet software, equation (8.22) for the market potential after the initial time step Δt with $i \in [1;1000]$ can be rewritten as (8.24).

$$MP_i(\Delta t) = MP_i(0) * \left[1 + \mu\sqrt{\Delta t} Z_i(\Delta t) + \left[P_i(\Delta t) * Y_i(\Delta t)\right] + \Delta J_{iN}(\Delta t)\right] \qquad (8.24)$$

The following Figure 8.9 visualizes how n=1,000 random variables for $Y_i(\Delta t)$ are combined with Poisson distributed random variables $P_i(\Delta t)$ for the occurrence of positive jumps at the first time step $t=\Delta t$. The figure is based on the jump range $Y_i \in [1;1.4]$ and on a Poisson process with $\lambda_1=0.02$, which can be interpreted as if a positive jump is on average expected to occur every $1/\lambda_1=50$ time periods Δt.

[444] The type of probability distribution used has to be decided on a case-by-case basis depending on the research project investigated.

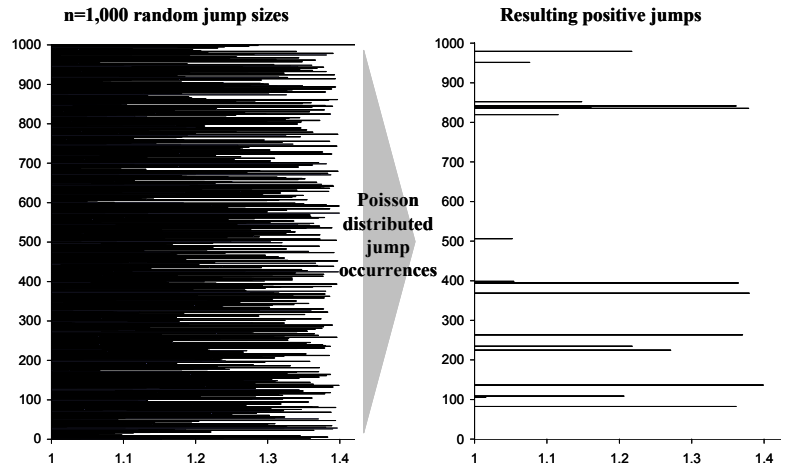

Figure 8.9: Simulation results for n=1,000 potential positive jumps

In order to simulate the second jump process representing potential negative jumps in market potential caused by market competition, a different approach is taken to consider the signaling effect of product entries into the market. To consider market competition in the simulation model three assumptions are made:

In light of the small number of industry players developing products in direct competition to each other, the number of market entrants is limited by definition. For the illustrative case the maximum number of competitors is set to one, which means that none or one other company is developing a substitute product and the counting process M(t) of equation (8.10) is limited to $M_{max}(t)=1$.

As long as no product is approved in a market, the probability that a negative shock occurs is larger compared to the time after a product is already on the market. Rational behind this assumption is that other companies are aiming more intensively to enter a new market than a market that is already occupied by competitors. This means that two different factors λ_{2E} and λ_{2L} are used to model the Poisson distributed occurrences of negative jumps with $\lambda_{2E} \geq \lambda_{2L}$. The first factor λ_{2E} applies to all $t<E(T_A)$ and λ_{2L} for all $t \geq E(T_A)$.

To reflect the first mover advantage of the company introducing a product into the market before all competitors do, the sizes of the potential negative jumps also differ before and after $E(T_A)$. To reduce complexity in the simulation model the negative jump sizes are fixed as opposed to stochastic variables as used for the positive jumps[445]. In case another company enters the market before the drug development process is expected to be completed at $E(T_A)$ a fixed market share of 50% is assumed to be lost and therefore $V_E=0.5$. In case the research conducting company captures the first mover advantage itself, the lost market share is assumed to be lower because it makes it more difficult for others to capture customers in the

[445] If more appropriate for an individual valuation case the constant factor can be replaced with a stocjastic parameter as done for the positive jump sizes above.

market[446]. In this case when a competitor enters the market after $E(T_A)$, the lost market share accounts for only 25% and therefore V_L=0.75.

To incorporate these assumptions in the negative jump factor $\Delta J_{iN}(t)$ of equation (8.18), the factor ΔJ_{iN} is modeled in a way similar to that of the positive jumps. The jump factor $\Delta J_{iN}(t)$ to be used is also a product of two factors following equation (8.25).

$$\Delta J_{iN}(t) = N_i(t) * [V_i(t) - 1] \qquad (8.25)$$

In this equation the first part $N_i(t)$ represents the negative jump occurrence whereas the second part $V_i(t)$ determines the size of the negative jump being the market share competitors take away if they enter the market at a certain time. Similar to the occurrence of positive jumps these negative jumps follow a Poisson distributed arrival process. To include the assumption that the chance of competitive market entry is higher before $t=E(T_A)$, the Poisson arrival process is broken down into two sub-processes with individual parameters λ_{2E} and λ_{2L} with $\lambda_{2E} \geq \lambda_{2L}$.

To simulate the occurrence of negative jumps, a random variable $R_i(t)$ is generated that is evenly distributed on [0;1] so that each $N_i(t)$ can be defined as either 0 or 1 depending on the following relationship.

$$N_i(t) = 0$$
$$\text{if} \left[R_i(t) > \left(1 - e^{-\lambda_{2E}\Delta t}\right) \wedge t < E(T_A)\right] \text{or} \left[R_i(t) > \left(1 - e^{-\lambda_{2L}\Delta t}\right) \wedge t \geq E(T_A)\right] \text{or} M(t) = 1$$

$$N_i(t) = 1$$
$$\text{if} \left[R_i(t) \leq \left(1 - e^{-\lambda_{2E}\Delta t}\right) \wedge t < E(T_A) \wedge M(t) = 0\right] \text{or} \left[R_i(t) \leq \left(1 - e^{-\lambda_{2L}\Delta t}\right) \wedge t \geq E(T_A) \wedge M(t) = 0\right]$$

With M(t) being a counting process of the following form

$$M(t) = \sum_{k=1}^{k=\frac{t}{\Delta t}-1} N_i(k * \Delta t) \qquad (8.26)$$

The above definitions change the general factor ΔJ_N from (8.25) to (8.27).

$$\begin{aligned} \Delta J_{iN}(t) &= N_i(t) * (1 - V_E) = N_i(t) * (-0.50) \quad if \quad t \leq E(T_A) \\ \Delta J_{iN}(t) &= N_i(t) * (1 - V_L) = N_i(t) * (-0.25) \quad if \quad t > E(T_A) \end{aligned} \qquad (8.27)$$

For the calculation example of the first time step of the market potential simulation, equation (8.24) can be refined to (8.28).

$$MP_i(\Delta t) = MP_i(0) * \left[1 + \mu\Delta t + \sigma\sqrt{\Delta t} Z_i(\Delta t) + \left[P_i(\Delta t) * Y_i(\Delta t)\right] + \left[N_i(\Delta t) * (-0.5)\right]\right] \qquad (8.28)$$

The spreadsheet simulation of the factor $N_i(\Delta t)$*[-0.5] returns the following parameters for $i \in [1;1000]$ simulation runs shown in Figure 8.10.

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[446] Compare to Hitt et al. (1999, p. 170)

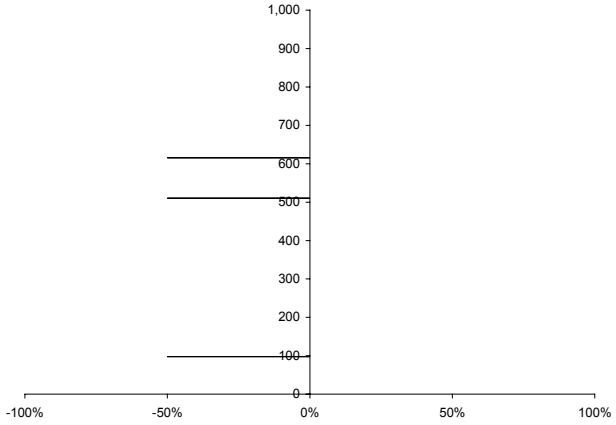

Figure 8.10: Simulation result for n=1,000 potential negative jumps

Up to this point it is demonstrated how the market potential simulation for the fist time step t=Δt can be completed. Based on this knowledge the simulation for the future market potential for the entire observation period [0; 20] can be completed. Building on the known relation (8.18), the future potential of a new drug can be calculated at every time step (k*Δt) using equation (8.29) for all $i \in [1,1000]$ and all $k \in [1;20/\Delta t]$.

$$MP_i(k\Delta t) = MP_i((k-1)\Delta t) * \left[1 + \mu\Delta t + \sigma\sqrt{\Delta t}Z_i(k\Delta t) + \left[P_i(k\Delta t) * Y_i(k\Delta t)\right] + \left[N_i(k\Delta t) * \left[V_i(k\Delta t) - 1\right]\right]\right] \quad (8.29)$$

With $V_i(k\Delta t)=0.5$ for all $k\Delta t<E(TA)$ and $V_i(k\Delta t)=0.75$ for all $k\Delta t \geq E(T_A)$.

Random examples of the n=1,000 simulations i of the market potential of the illustrative drug development project are displayed in Figure 8.11.

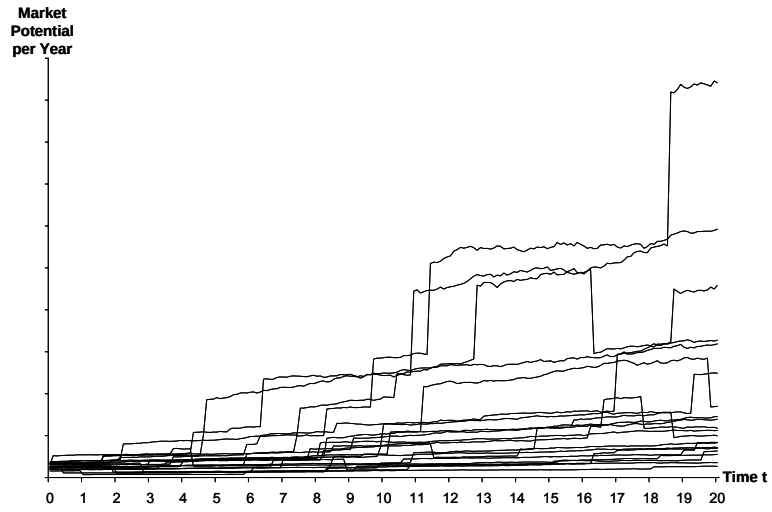

Figure 8.11: Selected MP(t) simulations following double jump diffusion process

It is important to recall that for the buyer of a R&D option it is irrelevant, which market potential a new drug has today. The relevant time period for the buyer of a R&D option and therefore also for the R&D option valuation is the period $t \in [T_A;20]$ after the drug is approved until the patent expires at t=20.

The approval date T_A and therefore the starting point for the relevant market potential is related to uncertainty. As for the approximation of the R&D option financing range in the idealistic market environment, this uncertainty has to be considered in the upcoming valuation section for the realistic market environment. Figure 8.12 visualizes the market potential distribution of the n=1,000 simulation runs at the best case project termination date $t=T_{Amin}=11$ and at the time of project expiration t=20.

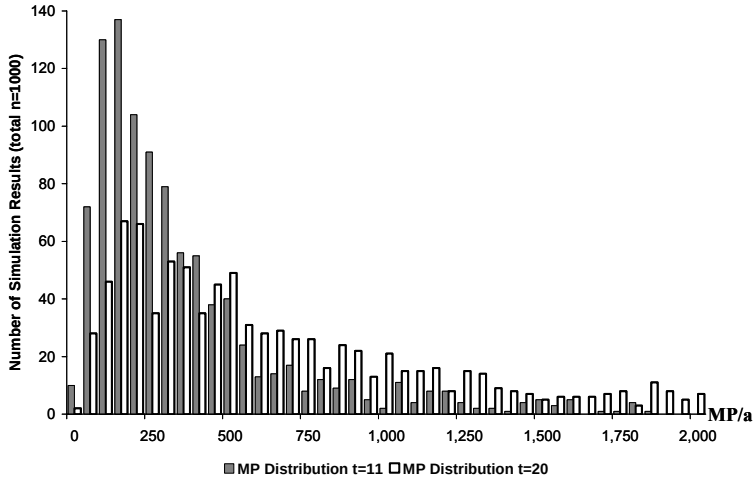

Figure 8.12: Distribution of simulation runs for MP(t) at t=11 and t=20

It can be seen that the density function of MP at $t=T_{Amin}=11$ has a high peak and few occurrences at very high MP levels. This is different for t=20 where the multiple factors impacting the development of MP cause the peak of the density function to be lower but at the same time allows more occurrences with very high and therefore valuable MP levels.

Figure 8.13 visualizes four random examples out of the n=1,000 simulation runs for the future market potential relevant for approximating of the value of the R&D project and therefore for the financing potential of the R&D option sale.

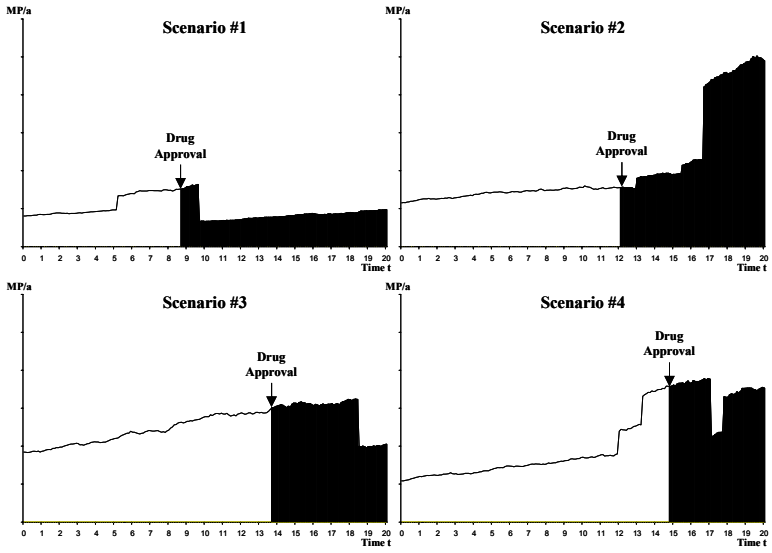

Figure 8.13: Valuation relevant future market potential (selected simulations)

Now, with the market potential of a new drug being simulated in a realistic market environment the next sections investigate how this change in market environment impacts the upper and the lower limit of the financing range of the R&D option.

8.2.2 Impact on Upper Pricing Limit

In this section it is discussed how the transformation from an idealistic to a realistic market environment affects the upper pricing limit of a R&D option. As a first step the significance of the time to final approval T_A is assessed. For any $T_A \in [0;20]$ the value of the project, represented by the shaded areas in Figure 8.13 for four examples, at the time of approval can be expressed as (8.30).

$$DAV_U(T_A) = \int_{T_A}^{20} MP(t) e^{-(r_{rf}+\alpha)(t-T_A)} \partial t \qquad (8.30)$$

DAV_U represents the value a fully diversified investor assigns at final drug approval to the market potential of a drug over the entire effective patent protection period. Since this type of investor only requires a risk premium for general market risk the relevant discount factor is set at $(r_{ft}+\alpha)$. With this drug approval value it is known that the R&D option represents a value of (8.31) at the time of drug approval for this type of investor.

$$C_U(T_A) = MAX\left[\int_{T_A}^{20} MP(t) e^{-(r_{rf}+\alpha)(t-T_A)} \partial t - X;0\right] \qquad (8.31)$$

For any time during the research process the value of the R&D option assuming the point of drug approval is reached can be written as (8.32).

$$C_U(t) = e^{-(r_{rf}+\alpha)(T_A-t)} MAX\left[\int_{T_A}^{20} MP(t) e^{-(r_{rf}+\alpha)(t-T_A)} \partial t - X;0\right] \qquad (8.32)$$

Incorporating the adjustment potential for technical project failure[447] changes (8.32) to (8.33).

$$C_U(t) = e^{-(r_{rf}+\alpha)(T_A-t)} * \left(1 - \left(\frac{\cos\left(\frac{11}{T_A}t + 3\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * MAX\left[\int_{T_A}^{20} MP(t) e^{-(r_{rf}+\alpha)(t-T_A)} \partial t - X;0\right] \qquad (8.33)$$

Taking a closer look at equation (8.33) shows that the value of the R&D option now depends to a large extent on the approval time T_A and on the future development of the market potential MP(t) of the new drug over time. In the previous section it was shown that the future market potential can develop in a wide variety of ways depending on a multitude of

[447] Potential technical project failure is discussed in detail in section 7.3.3 of this study.

different input factors therefore representing a complex part of the R&D option valuation problem. It is also shown in chapter 7.3.4.7 that the final approval date T_A of a drug development project is related to uncertainty and can change over time. To express this timing uncertainty in equation (8.33), the constant T_A is replaced by $T_A(t)$[448], which changes the model to (8.34).

$$C_U(t) = e^{-(r_{rf}+\alpha)(T_A(t)-t)} * \left(1 - \left(\frac{\cos\left(\frac{11}{T_A(t)}t + 3\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * MAX\left[\int_{T_A(t)}^{20} MP(t)e^{-(r_{rf}+\alpha)(t-T_A(t))}\partial t - X;0\right]$$

(8.34)

With the uncertainty in $T_A(t)$ and the stochastic processes behind MP(t) this complex valuation problem cannot be solved analytically. To approximate a solution, Monte Carlo Simulation is applied. With a given discount factor[449] and a given exercise price X, each simulation run $i \in [1;1000]$ is conducted with a different $T_{iA}(t)$ and a different future development path for $MP_i(t)$. These parameters $T_{iA}(t)$ and $MP_i(t)$ are generated for each simulation run i based on the described underlying stochastic processes. The valuation problem (8.34) is solved to derive a possible solution for each simulation $C_{Ui}(t)$ $i \in [1;1000]$.

$$C_{Ui}(t) = e^{-(r_{rf}+\alpha)(T_{iA}(t)-t)} * \left(1 - \left(\frac{\cos\left(\frac{11}{T_{iA}(t)}t + 3\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * MAX\left[\int_{T_{iA}(t)}^{20} MP_i(t)e^{-(r_{rf}+\alpha)(t-T_{iA}(t))}\partial t - X;0\right]$$

(8.35)

Every $C_{Ui}(t)$ represents a different scenario and not every $C_{Ui}(t)$ is necessarily close to the solution of the initial valuation problem (8.34). Since some outcomes overvalue and others undervalue the correct solution for $C_U(t)$, the average over all conducted simulation runs is calculated to approximate the value for $C_U(t)$.

$$C_U(t) = \frac{1}{n}\sum_{i=1}^{n} C_{Ui}(t) \qquad (8.36)$$

The law of large numbers ensures that the estimate (8.36) converges to the correct value of $C_U(t)$ as the number of simulation runs n increases. For the valuation problem discussed in

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[448] As opposed to $E(T_A)$.

[449] Which is assumed to be constant over time.

this study a sample of n=1,000 simulations is used and therefore the approximation for $C_U(t)$ can be written as (8.37).

$$C_U(t) = \frac{1}{1000}\sum_{i=1}^{1000} C_{Ui}(t) \qquad (8.37)$$

Before the individual simulations for $C_{Ui}(t)$ can be conducted it is necessary to model all interrelations and dependencies. While the previous section describes the modeling of the simulation run specific future market potential $MP_i(t)$ it is still necessary to model the development of $T_{iA}(t)$.

For the approval time T_A it is said that starting from an expected best case scenario with approval time T_{Amin} there is a risk of delay, which is exponentially distributed. Now it appears very interesting to estimate a value T_{Amax} to limit a 95% confidence interval, generate a single constant T_{iA} based on the resulting distribution function and use this value over the entire valuation period. By doing so, one excludes learning effects over the lifetime of a project and over all simulation runs timing uncertainty at $t=E(T_A)$ would still be the same as it is at t=0. As a result, an incorrect value is assigned to $C_U(t)$ as $E(T_A)$ is approached because the gained knowledge about project termination timing is neglected. To avoid this problem a random initial project duration $T_{iA}(0)$ is generated for every simulation run using (8.38) with Z_i being a random evenly distributed variable from the interval [0;1], which is then adapted over the expected course of the project.

$$T_{iA}(0) = T_{A\min} + \frac{\ln(1-Z_i)}{-\lambda_0} \qquad (8.38)$$

The distribution parameter λ_0 and the parameter $\lambda_{E(TA)}$, which is used below, are derived as described in chapter 7.3.4.7. In this section the learning effect over the lifetime of a project is discussed and a factor κ for learning speed is introduced. Building on this discussion, the termination date over the lifetime of a project follows (8.39) for $T_{iA}(t)$ with $t \in D_5$, $D_5=]0;E(T_A)[$ and $\kappa \in R_+^*$.

$$T_{iA}(t) = E(T_A) + \frac{\ln(1-Z_i)}{\left(\left(\frac{t}{E(T_A)}\right)^{\kappa} * \left(\lambda_0 - \lambda_{E(T_A)}\right)\right) - \lambda_0} \qquad (8.39)$$

Figure 8.14 visualizes the development of two random simulation runs for $T_{iA}(t)$ with $Z_1=0.840$ and $Z_2=0.220$ in relation to $[T_{Amin}(t); T_{Amax}(t)]$[450] and the constant $E(T_A)$.

[450] Representing the 95% confidence interval for project timing.

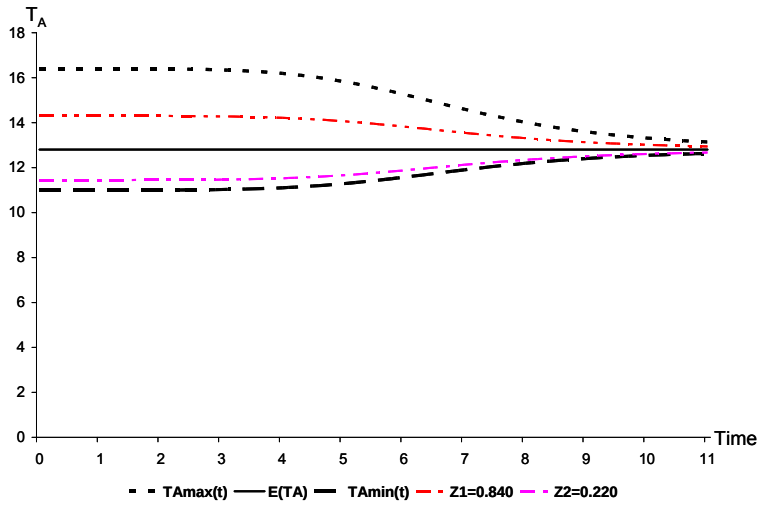

Figure 8.14: Simulation runs for expected project termination $T_A(t)$

With this model for $T_{iA}(t)$ the last component of equation (8.35) is defined and the actual simulation process can be initiated. Once the n=1,000 simulation runs are conducted the final solution for $C_U(t)$ is approximated using (8.37).

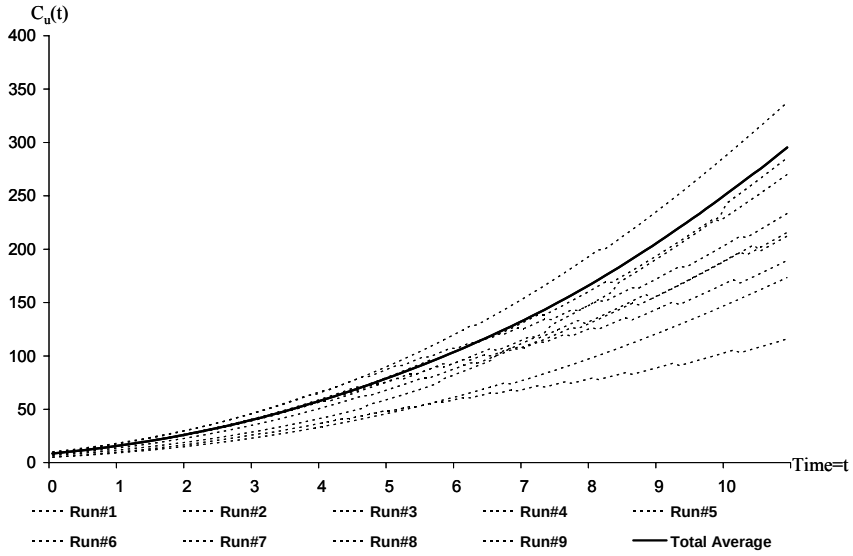

Figure 8.15: Selected simulations of upper pricing limit of R&D option

Figure 8.15 shows the results of nine individual simulations for $C_{Ui}(t)$ and the final estimate for $C_U(t)$ over the total of n=1,000 simulation runs[451].

8.2.3 Impact on Lower Pricing Limit

After showing how the upper pricing limit can be approximated in a realistic market environment, this section shows an approximation of the lower pricing limit to quantify the financing range of the R&D option. In chapter 7.4 the necessary adjustments to transform the

[451] The detailed results represent time discrete approximations of the continuous processes with time increments of $\Delta t=0.1$.

upper pricing limit to the lower limit are shown. Although the section refers to an idealistic market environment the adjustments to transform the upper to the lower pricing limit are analogous for the realistic market environment.

It also holds true in the realistic market environment that perfectly diversified investors do not require risk premiums for private risk factors while investors not able to diversify this risk do. This means that the two introduced risk premiums ε and ρ also have to be considered in the realistic environment when assessing the lower pricing limit.

A private risk factor, which is by definition excluded from the idealistic market environment, is the potential competition from alternative products. Consistent with the definition of private risk, highly diversified investors do not to require a return premium for taking on this type of risk. To consider that other investors who are not able to diversify their private risk exposure do require a return premium for this type of risk an additional risk premium β is introduced. Since competing products can enter the market at any time, the risk premium β has to be applied to the preceding research period as well as to the marketing period following T_A.

Considering this, equation (8.35) represents the valuation formula for the individual simulations to quantify the lower R&D option pricing limit in a realistic market environment.

$$C_{Li}(t) = e^{-(r_{rf}+\alpha+\beta+\varepsilon+\rho)(T_{iA}(t)-t)} * \left(1 - \left(\frac{\cos\left(\frac{11}{T_{iA}(t)}t + 3\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * MAX\left[\int_{T_{iA}(t)}^{20} MP_i(t)e^{-(r_{rf}+\alpha+\beta)(t-T_{iA}(t))}\partial t - X;0\right]$$

(8.35)

To demonstrate the valuation approach for the case example, the premium for potential risk of competing products β is set at an illustrative level of 5%. With this assumption and the developed valuation formula (8.35), a new set of n=1,000 simulations is conducted. Figure 8.16 shows the results of nine individual simulation runs for $C_{Li}(t)$ in addition to the final $C_L(t)$ to which the average of n=1,000 simulation runs converges.[452]

[452] As for the upper pricing limit above, the demonstrated results represent time discrete approximations of the continuous processes with time increments of $\Delta t=0.1$.

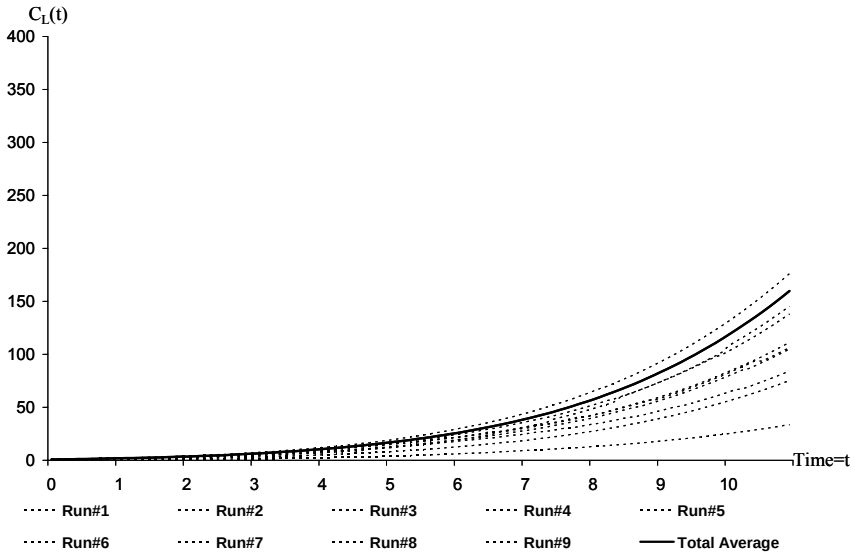

Figure 8.16: Selected simulations of lower pricing limit of R&D option

8.2.4 R&D Option Financing Range

During the previous sections it is demonstrated how much two extreme types of investors are theoretically willing to pay when acquiring a R&D option. Since market players do not represent these extreme types of investors, these expectations can be considered a theoretical upper and lower boundary of the financing range. As real-life investors generally have some opportunity to diversify risk and some level of financial resources available, their price expectations reside between the described extreme cases $C_U(t)$ and $C_L(t)$. Figure 8.17 visualizes this expected pricing range for the illustrative case example. It is limited on the upper end by the average of n=1,000 simulation runs for the upper pricing limit and limited on the lower end by the average of n=1,000 simulations for the lower limit.

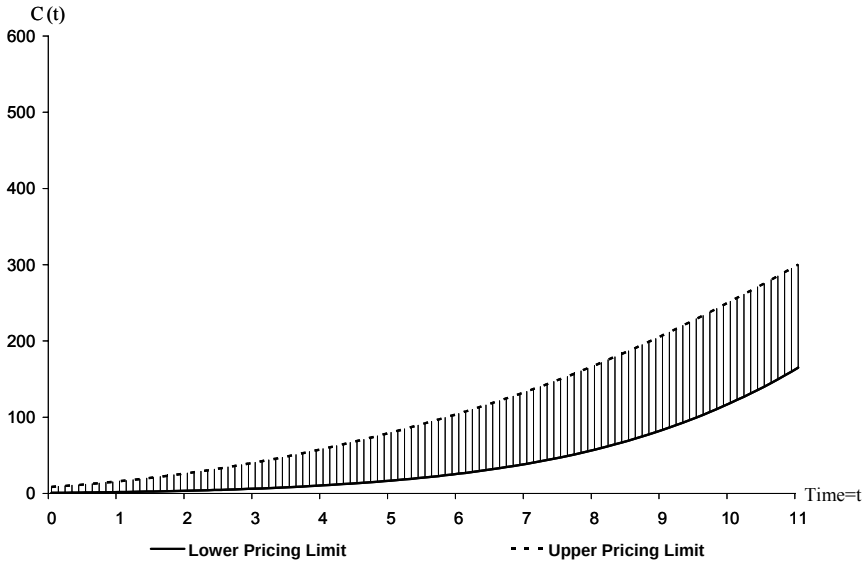

Figure 8.17: R&D option pricing range – realistic market environment

In considering the path of the financing range's boundaries a few points need to be mentioned. The first point is the fact that an undiversified investor is only willing to pay a

very low price to acquire a R&D option very early in the drug development process. Despite the early stage, the totally diversified investor is willing to pay a premium compared to the one-project investor at this time. In the illustrative case this premium amounts to approximately 7.5 million or over 900% at the time of patent application.[453]

Figure 8.18 shows the expected maximum premium a fully diversified investor is willing to pay for the acquisition of a R&D option in comparison to the lowest price in absolute and in terms relative to the lower pricing limit.

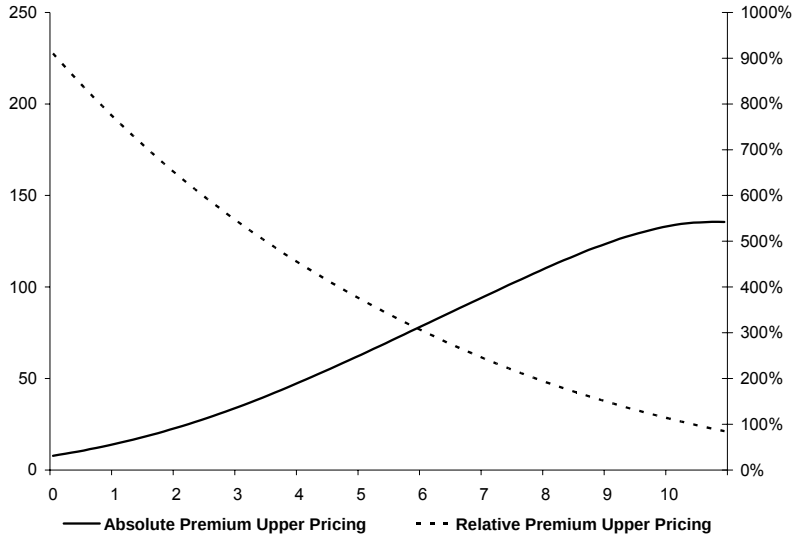

Figure 8.18: Width of R&D option pricing range – realistic market environment

From the very early stage of the R&D project the absolute difference between the pricing boundaries constantly increases towards the end of the minimum expected development period. At the end of this period it reaches an absolute premium of about 133 million in the illustrative case. Although the premium in absolute terms increases over the expected course of the project it does not in terms relative to the lower pricing limit. The relative premium is high early in the development process but decreases over time to a final premium of 88% for the illustrative case example at the end of the minimum project duration $t=T_{Amin}=11$.

8.2.5 Total Financing Potential of a R&D option

In a R&D option deal, the option premium is only one part of the total cash flows the research conducting company potentially receives. In addition to the sales price the research conducting company also receives the exercise price X in those cases where the project is completed successfully and the prospects are promising enough for the option buyer to exercise his option right. Some young drug developing companies are interested in the

[453] Being t=0.

exercising of the R&D option[454] and therefore the second potential payment at maturity is of strategic importance to these companies. For the option buyer, the second payment represents an insurance against the case that the option seller discontinues the development process while it serves as a final reward for the option seller for successful R&D efforts.

At this point it becomes necessary to include the exercising cash flow into the discussion. It becomes even more important if one considers the relationship between the exercise price and the achievable selling price of a R&D option. The lower the exercise price is set in a R&D option deal, the higher the expected selling price of the option and the higher the short term financing potential. While this increases the short-term cash flow it also gives the option owner the right to exercise his right with a smaller additional payment on the exercise date. The extreme case is represented by setting the exercise price to zero[455]. While this maximizes the short-term cash-flow achievable through the option sale it also eliminates any additional payment on the exercise date. This shows that it is necessary to investigate how short-term financing potential and exercise payment are interdependent. It should be discussed whether a strategy exists that can optimize the situation for the R&D option seller by ensuring a sufficient upfront payment to finance operations and also guaranteeing a significant exercise payment at the end of the research period.

With this in mind the questions arises as to whether an optimal exercise price can be found that maximizes the expected total cash flow from the R&D option deal. To investigate this question the term total financing potential is introduced. This total financing potential TF(t) is defined as the combination of the selling price C(t) of the R&D option plus the time adjusted expected final payment FP(t) at the end of the research and development activities.

$$TF(t)=C(t)+FP(t)$$

Since C(t) can only be represented as a range rather than one single value it is obvious that TF(t) is also represented by a range. After discussing the selling price of the R&D option in the previous chapters it is necessary to take a closer look at the time adjusted expected maximum final payment $FP_U(t)$, which can be defined as equation (8.40).

$$FP_U(t) = X * e^{-(r_{rf}+\alpha)(T_A-t)} * \omega_U(t) \qquad (8.40)$$

While the first two components of the formula discount the exercise price of the option back from the time of final drug approval T_A to the relevant valuation time t, the last term $\omega_U(t)$ determines if the payment takes place or if the option expires unexercised.

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[454] This can be the case if the young company does not want to or is not able to set up its own large-scale production, marketing and distribution organization.

[455] This is not a realistic setting because it would eliminate any incentive for the research conducting company to complete the research and development process. The example is only of illustrative value to demonstrate the theoretical impact of this scenario.

This decision factor ω(t) is set to zero if the option expires worthless and set to one if a rationale investor exercises the option at final drug approval, which is the case if the project value exceeds the exercise price. Equation (8.41) formalizes this relationship.

$$\omega_U(t) = \begin{cases} 0 \quad ; \quad MAX\left[\int_{T_A(t)}^{20} MP(t)e^{-(r_{rf}+\alpha)(t-T_A(t))}\partial t - X;0\right] = 0 \\ 1 \quad ; \quad MAX\left[\int_{T_A(t)}^{20} MP(t)e^{-(r_{rf}+\alpha)(t-T_A(t))}\partial t - X;0\right] \neq 0 \end{cases} \tag{8.41}$$

Similar to the valuation approach for the selling price of the R&D option, equation (8.41) depends on the uncertain market potential as well as on the uncertain time of final drug approval. Therefore it also depends on the previously conducted simulation runs for the market potential development. To demonstrate this dependency, equations (8.40) and (8.41) are adapted to become (8.42) and (8.43).

$$FP_{Ui}(t) = X * e^{-(r_{rf}+\alpha)(T_{iA}-t)} * \omega_{Ui}(t) \tag{8.42}$$

$$\omega_{Ui}(t) = \begin{cases} 0 \quad if \quad MAX\left[\int_{T_{iA}(t)}^{20} MP_i(t)e^{-(r_{rf}+\alpha)(t-T_{iA}(t))}\partial t - X;0\right] = 0 \\ 1 \quad if \quad MAX\left[\int_{T_{iA}(t)}^{20} MP_i(t)e^{-(r_{rf}+\alpha)(t-T_{iA}(t))}\partial t - X;0\right] \neq 0 \end{cases} \tag{8.43}$$

With these definitions and the simulation equations developed above, an upper limit for the total financing potential $TF_{Ui}(t)$ can be defined as (8.44).

$$TF_{Ui}(t) = e^{-(r_{rf}+\alpha)(T_{iA}(t)-t)} * \left(1 - \left(\frac{\cos\left(\frac{11}{T_{iA}(t)}t + 3\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * \left(X\omega_{Ui}(t) + MAX\left[\int_{T_{iA}(t)}^{20} MP_i(t)e^{-(r_{rf}+\alpha)(t-T_{iA}(t))}\partial t - X;0\right]\right) \tag{8.44}$$

By knowing the decision factor ωi(t), the two simulation formulas for the upper and the lower limit of the total financing potential $TF_{Ui}(t)$ and $TF_{Li}(t)$ can be written as (8.45) and (8.47).

$$TF_{Ui}(t) = e^{-(r_{rf}+\alpha)(T_{iA}(t)-t)} * \left(1 - \left(\frac{\cos\left(\frac{11}{T_{iA}(t)}t + 3\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * \omega_{Ui}(t) * \int_{T_{iA}(t)}^{20} MP_i(t)e^{-(r_{rf}+\alpha)(t-T_{iA}(t))}\partial t \tag{8.45}$$

With the relevant decision factor $\omega_{Ui}(t)$ being defined as (8.46).

$$\omega_{Ui}(t) = \begin{cases} 0 & if \quad \int_{T_{iA}(t)}^{20} MP_i(t) e^{-(r_{rf}+\alpha)(t-T_{iA}(t))} \partial t \le X \\ 1 & if \quad \int_{T_{iA}(t)}^{20} MP_i(t) e^{-(r_{rf}+\alpha)(t-T_{iA}(t))} \partial t > X \end{cases} \tag{8.46}$$

$$TF_{Li}(t) = e^{-(r_{rf}+\alpha+\beta+\varepsilon+\rho)(T_{iA}(t)-t)} * \left(1 - \left(\frac{\cos\left(\frac{11}{T_{iA}(t)} t + 3\right)\pi + 1}{2}\right)^{\frac{4}{5}}\right) * \omega_{Li}(t) * \int_{T_{iA}(t)}^{20} MP_i(t) e^{-(r_{rf}+\alpha+\beta)(t-T_{iA}(t))} \partial t \tag{8.47}$$

$\omega_{Li}(t)$ being defined as.

$$\omega_{Li}(t) = \begin{cases} 0 & if \quad \int_{T_{iA}(t)}^{20} MP_i(t) e^{-(r_{rf}+\alpha+\beta)(t-T_{iA}(t))} \partial t \le X \\ 1 & if \quad \int_{T_{iA}(t)}^{20} MP_i(t) e^{-(r_{rf}+\alpha+\beta)(t-T_{iA}(t))} \partial t > X \end{cases} \tag{8.48}$$

After setting up the simulation formulas for the total financing potential, a new set of n=1,000 simulation runs is conducted to investigate the expected development of the total financing potential over time. Doing so for the illustrative case example used throughout this study results in the total financing range, which is shown in Figure 8.19.

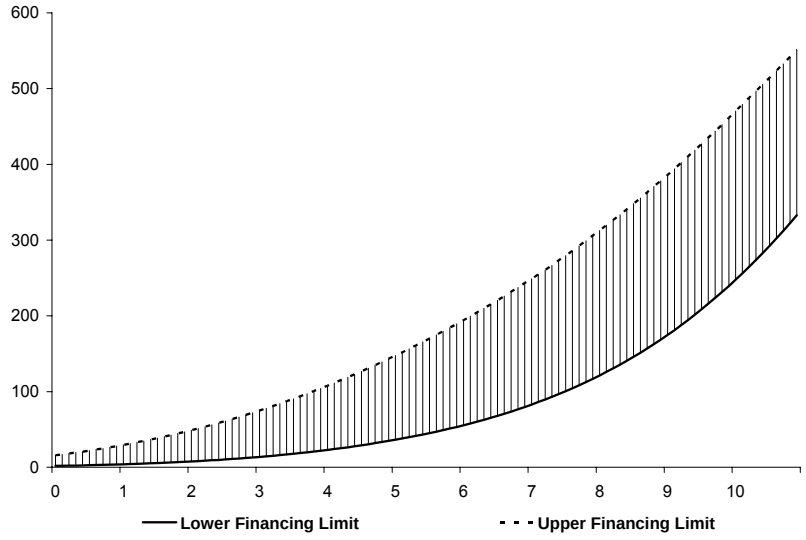

Figure 8.19: R&D option total financing range – realistic market environment

With regard to the pricing range of the R&D option discussed above, certain characteristics of this total financing range need to be highlighted. An analysis of the total financing potential instead of only the expected price of the R&D option favors closing the R&D option

deal with a highly diversified investor as expected. In the illustrative example it can be expected that closing the deal with this best case investor results in a 14 million advantage in total financing potential if the deal is closed right at the time a company applies for patent protection status. This advantage mainly results from the fact that at this research stage, the project is of only little value to the one-project investor.

Figure 8.20 shows the absolute and relative advantage of closing a R&D option deal with a highly diversified investor with ample financial resources as opposed to a one-project investor with limited resources based on the illustrative case example.

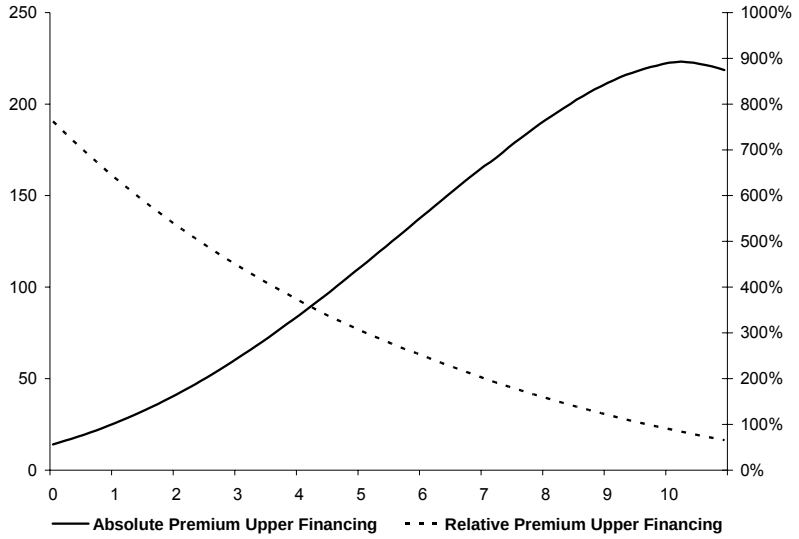

Figure 8.20: Width of option total financing range – realistic market environment

The behavior of the gap between the best and worst case investor for the total financing potential over time is similar to that of the R&D option price. Closing the R&D option deal with the best case investor results at any time in an advantage for the seller of the option. If measured in absolute terms, this advantage increases from about 14 million to a maximum of 225 million shortly before the end of the minimum expected drug development period in the illustrative case. After this peak is reached, the advantage measured in absolute terms starts to decrease as the expected end of the minimum drug development period is approached. If the R&D option deal is closed right before the minimum expected development period of a new drug, there is still an expected total benefit of 220 million in closing it with the best case investor. This is related to the fact that the final product itself represents a higher value to this investor than it does for the one-project investor and therefore the probability of receiving the final exercise payment is higher.

While the absolute advantage of closing the deal with the highly diversified investor shows a maximum, this is different if measured in relative terms. In relative terms a fully diversified investor loses his advantage over other investors over the course of the project. Early during the project there is a large relative benefit in closing the R&D option deal with the best case investor because the percentage premium amounts to over 750% at the start of the project for the illustrative case. This advantage decreases as the project progresses. Right before the

expected minimum project termination date the relative total advantage of closing the R&D option deal with the best case investor is expected to be reduced to about 66%.

With this in mind it can be said that the chances of a less diversified investors to enter a R&D option deal increase as the underlying project progresses because the relative premium a diversified investor is willing to pay decreases over time. Although the chances of the less diversified investor theoretically increase they are still limited because in absolute terms it is always more appealing for a research conducting company to close a R&D option deal with a highly diversified investor.

This conclusion is in line with the tendency in the biotechnology and pharmaceutical industry towards large research conducting entities with extensive research portfolios. If R&D options were a frequently applied financing tool in the market, these large entities would be most likely to win bidding contests for these options due to their indifference towards private risk. With the acquisition of each R&D option the risk diversification increases further [456] resulting in an even higher willingness to pay a premium compared to less diversified investors. This can serve as an argument for concentration processes in the drug developing industry.

In return it shows that small companies have difficulties in such an environment to acquire new projects by purchasing R&D options. This is because the funds they are willing to invest are always smaller compared to those of diversified companies and therefore the R&D seller is likely to exclude them from a R&D option bid.

Until this point the indications and conclusions from the analysis are drawn from one illustrative example. To avoid that this example represents a special, non-representative case, it is essential to investigate how sensitive the results are towards changes in the individual input parameters of the simulation model. In the following chapter, sensitivity analyses are conducted to investigate how variations in input factors change the results of the valuation approach.

[456] Assuming that risks of individual projects are not perfectly correlated.

9 Sensitivity Analysis of Valuation Approach

In the previous section, a model was developed to asses fund raising potential and total financing potential of a R&D option in a realistic market environment. The derived model does not represent a closed-form valuation formula but depends on input parameters that cannot objectively be derived from market sources and are therefore subject to managerial estimations. For such cases, Loch and Bode-Greuel (2001) recommend[457] investigating how changes in individual input parameters affect a model's valuation results. This type of investigation can be conducted from a strictly economical point of view as a comparative static[458] or from a more pragmatic standpoint as a one-dimensional sensitivity analysis.

In the first approach economists investigate how the output of a model changes if the valuation environment develops in a certain way. To perform this task it is necessary to model all interrelations and dependencies between input parameters. This is necessary because if one parameter of the valuation environment changes, others might depend on this parameter and react in a certain way. Especially for valuation models with multiple interdependent parameters, this type of sensitivity analysis can be highly complex as factor dependencies are often difficult to model.

The more pragmatic approach targets the question of how the result of a valuation model reacts if a single factor is over- or underestimated by the entity conducting the analysis. This type of analysis clearly indicates where closest focus should be placed when defining input parameters. To develop an answer to this question a one-dimensional sensitivity analysis is conducted that treats each input factor as an independent parameter. This approach has the advantage that only one input factor is changed at a time and the corresponding output changes are analyzed. As this entire study is written from a pragmatic and implementation focused standpoint, the second approach is selected for this section on model sensitivity.

Starting from the illustrative example, the parameters exercise price, development speed, probability and size of negative jumps, initial market uncertainty and the probability and size of positive jumps are adjusted to investigate the resulting change in the pricing and total financing potential of the R&D option.[459]

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[457] They explicitly stress the importance of sensitivity analysis in their study on evaluating growth options as sources of value for drug developing companies. "In addition, sensitivity analysis should be performed to see how much the risk profiles and expected profits change when key parameters are varied", Loch and Bode-Greuel (2001, p. 242).

[458] Compare to Hoy et al. (2001) or Chiang and Wainwright (2005).

[459] At this point it is important to state that a sensitivity analyses based on the illustrative case example does not allow the derivation of generally valid conclusions. It does give indications about the general behaviour of the model but especially the magnitude of the observed effects strongly depends on the individual project case, which serves as a starting point for the sensitivity analysis. For this reason, it is emphasized that for every real-life valuation problem with different baseline parameters an individual sensitivity analysis should be conducted.

9.1 Exercise Price

One of the most important parameters when discussing the pricing of an option is its exercise price. In section 3.1.3 it is shown that for the case of a European call option an increasing exercise price reduces the option's value. This relationship also holds true for a R&D option on a drug development project. Figure 9.1 simulates in the top two charts how changes in the parameter X impact the pricing limits of the R&D option for the illustrative case example. Two conclusions can be drawn from these simulations. Firstly, the negative impact of exercise price increases on the option price can be confirmed and secondly, that the later the option is sold during the R&D process the larger the absolute impact of this exercise price change.

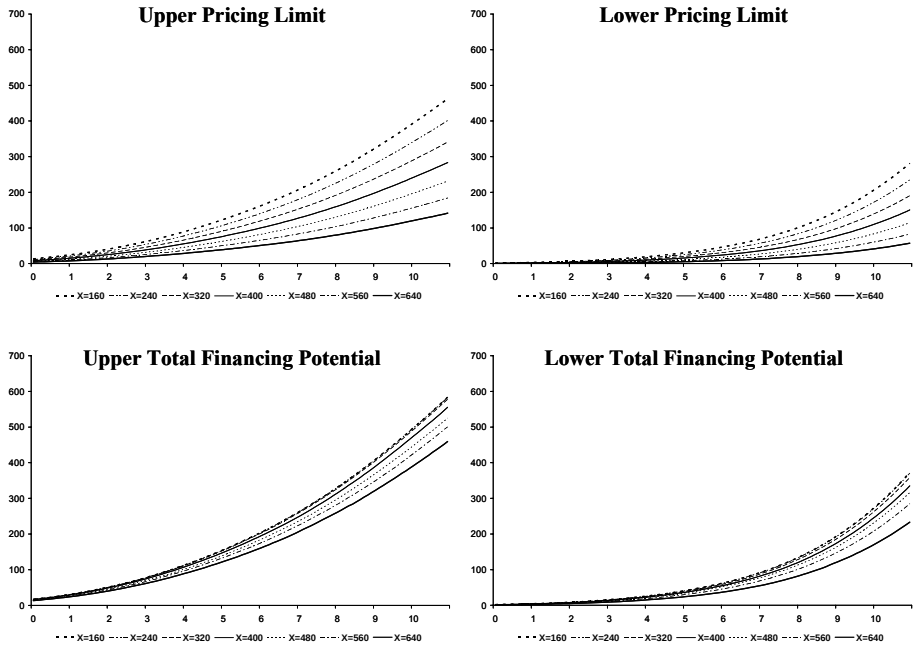

Figure 9.1: Sensitivity of valuation model to changes in exercise price

With this relationship it can be said that the largest cash generation potential of a R&D option exists if the exercise price is set to X=0. Although this is theoretically sound, it is not a realistic setting due to multiple reasons. Setting X=0 cannot be considered an option deal because it does not involve any exercise payment and is therefore from a cash flow perspective equal to selling the entire project. Without an exercise payment to be earned at the end of the research period there is no incentive for the research conducting company to continue its research activities and therefore no option buyer is willing to accept such a very low exercise price. The opportunity to earn a significant exercise payment can be considered "an insurance" for the buyer that the underlying project is pursued by the option seller.

This emphasizes the importance of taking a closer look at the behavior of the total financing potential if a different exercise price is selected. The two lower charts in Figure 9.1 illustrate the impact of a changed exercise price on the total financing potential for selected cases. It can be noted that a reduction of the exercise price causes a smaller percentage change than it does for the option price. As long as the exercise price is not increased to a very large figure,

changes in the total financing potential are relatively small. This results from the relation that if the exercise price is reduced, the probability that the research conducting company receives the exercise price increases even though the amount to be expected is smaller. The opposite development takes place for small increases of X. Such increases reduce the probability that the company receives the agreed exercise payment. The final payment itself increases compensating the company to a certain degree for the reduced probability. In total the resulting reduction is relatively small for the simulation where X is increased by +20% to X=480. This increase only reduces the upper and the lower total financing potential by about 6% at the beginning of the research period.

The situation changes if the exercise price is raised to a very large figure. This results in a reduced total financing potential. The following two figures, Figure 9.2 and Figure 9.3, illustrate this behavior for the total financing limits based on the four examples X=240, X=400, X=480 and X=1,000 with all other parameters remaining unchanged. The two figures demonstrate that the total financing potential is similar for the cases X=240, X=400 and X=480 but the ratio between option price and expected exercise value changes. The total potential is reduced significantly at the case where X is set to X=1,000. In this case especially the lower total financing limit is reduced by over 90%.

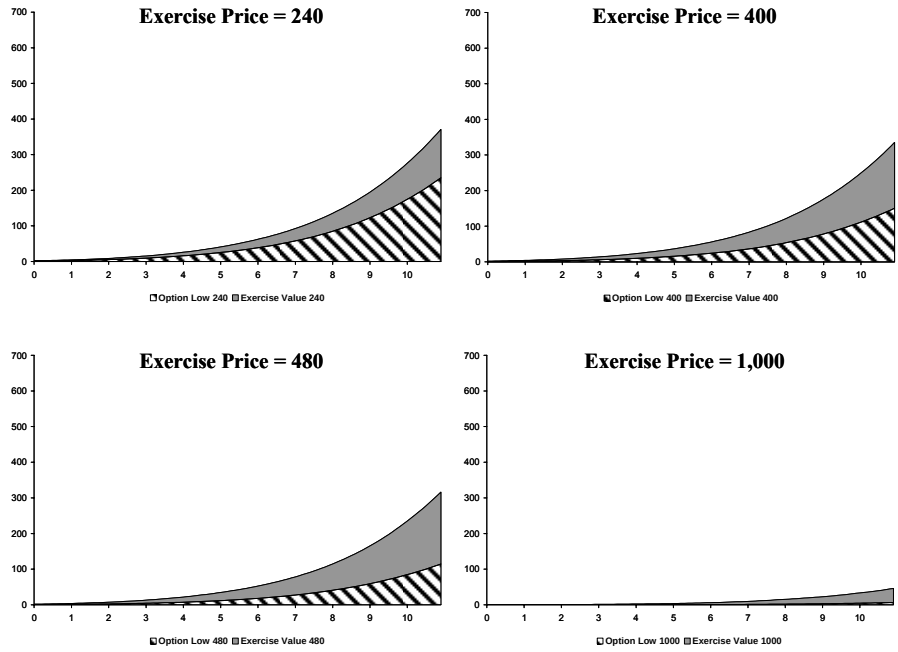

Figure 9.2: Impact of exercise price changes on lower total financing limit

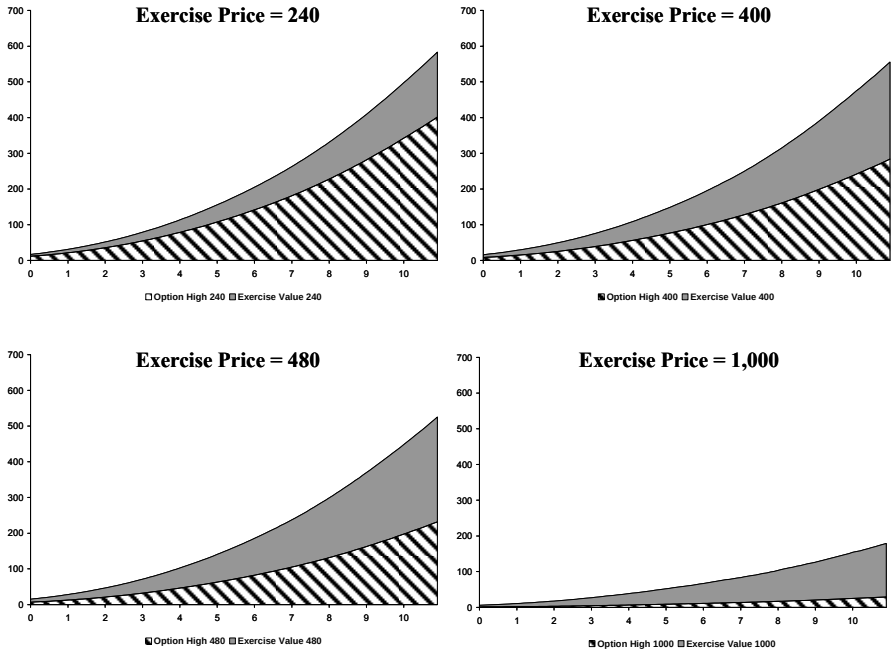

Figure 9.3: Impact of exercise price changes on upper total financing limit

Table 9.1 shows the impact of changes in the exercise price X for seven different cases compared to the illustrative example with all other factors remaining unchanged.

New Exercise Price	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
160	- 60%	High Pricing	+61.7%	+61.7	+63.1
		Low Pricing	+96.3%	+93.7	+86.9
		High Total Fin.	+4.8%	+4.9	+3.3
		Low Total Fin.	+12.7%	+12.5	+11.2
240	- 40%	High Pricing	+40.6%	+40.6%	+41.6%
		Low Pricing	+61.9%	+60.3%	+56.3%
		High Total Fin.	+4.6%	+4.8%	+3.9%
		Low Total Fin.	+11.9%	+11.7%	+10.7%
320	- 20%	High Pricing	+19.8%	+19.8%	+20.3%
		Low Pricing	+29.1%	+28.4%	+26.6%
		High Total Fin.	+3.5%	+3.8%	+3.6%
		Low Total Fin.	+7.0%	+7.1%	+7.0%
480	+ 20%	High Pricing	-17.9%	-17.9%	-18.3%
		Low Pricing	-26.1%	-25.5%	-23.9%
		High Total Fin.	-6.1%	-5.3%	-5.0%
		Low Total Fin.	-6.2%	-6.0%	-5.5%
560	+ 40%	High Pricing	-34.0%	-34.2%	-35.1%
		Low Pricing	-48.5%	-47.6%	-44.9%
		High Total Fin.	-10.8%	-9.9%	-8.9%
		Low Total Fin.	-18.1%	-17.3%	-15.0%
640	+ 60%	High Pricing	-48.6%	-48.9%	-50.1%
		Low Pricing	-66.0%	-65.1%	-62.1%
		High Total Fin.	-17.9%	-17.3%	-16.2%
		Low Total Fin.	-34.7%	-33.7%	-30.4%
1,000	+ 150%	High Pricing	-88.5%	-88.9%	-89.8%
		Low Pricing	-97.3%	-97.0%	-95.7%
		High Total Fin.	-65.1%	-65.4%	-67.1%
		Low Total Fin.	-90.4%	-89.6%	-86.3%

Table 9.1: Model sensitivity to changes in exercise price

Apart from the direct impact on price and total financing potential of the R&D option, a change in exercise price also has an impact on the magnitude of the investigated ranges as illustrated in Figure 9.4. The charts demonstrate that the absolute range between upper and lower pricing limit of the R&D option increases during the first part of the project to reach a peak just before the minimum expected project duration. At this peak the advantage of selling the R&D option to a fully diversified investor is maximized. The smaller the selected exercise price, the larger the absolute magnitude of this financing range and therefore the greater the advantage of selling the option to a fully diversified investor. This relationship is illustrated in the two charts on the left-hand side of Figure 9.4.

Because of the relation between option price and expected exercise payment, the situation is more complex for the gap between upper and lower total financing limit, which is displayed on the two right hand graphs of Figure 9.4. Here it does not automatically hold true that the lower the exercise price the larger the gap between the upper and the lower total financing limit of the R&D option deal. It can be seen that the difference in premiums to be generated by closing the option deal with different exercise prices is relatively small throughout the entire expected project duration.

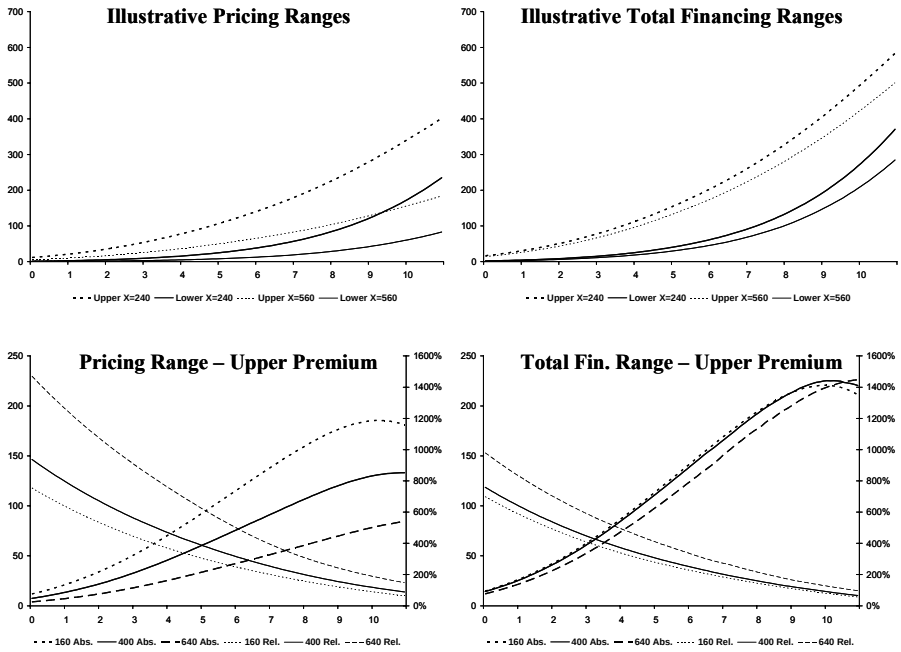

Figure 9.4: Range sensitivity to changes in exercise price

Table 9.2 shows in more detail how a change in exercise price impacts the width of the pricing and financing range for six examples compared to the standard case example.

New Exercise Price	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
160	- 60%	Pricing Premium	+58.0%	+52.5%	+35.2%
		Tot. Fin. Premium	+3.7%	+2.1%	-8.2%
240	- 40%	Pricing Premium	+38.3%	+35.0%	+24.4%
		Tot. Fin. Premium	+3.6%	+2.2%	-6.1%
320	- 20%	Pricing Premium	+18.8%	+17.3%	+12.8%
		Tot. Fin. Premium	+3.0%	+2.6%	-1.4%
480	+ 20%	Pricing Premium	-17.0%	-15.8%	-11.8%
		Tot. Fin. Premium	-6.1%	-5.0%	-4.2%
560	+ 40%	Pricing Premium	-32.5%	-30.3%	-23.6%
		Tot. Fin. Premium	-9.8%	-7.3%	+0.1%
640	+ 60%	Pricing Premium	-46.7%	-44.2%	-36.1%
		Tot. Fin. Premium	-15.7%	-11.4%	+4.5%

Table 9.2: Range sensitivity to changes in exercise price

9.2 Development Speed

The second key parameter driving the value of options is time to maturity. For a European call option on a non-dividend paying stock it is known that increasing time to maturity increases the value of the option. By definition[460], the R&D option does not have a fixed time to maturity but expires when the underlying development project reaches final drug approval. Since this time period is not fixed but depends on the development speed of the project, this parameter is investigated as a time to maturity equivalent.

For the project used for illustrative purposes throughout this study the expected minimum time to final regulatory approval is expected to be eleven years and therefore T_{Amin}=11. For the purpose of the sensitivity analysis in this section it is investigated, which impact a change in development speed to T_{Amin}=4.4, T_{Amin}=6.6, T_{Amin}=8.8, T_{Amin}=13.2, T_{Amin}=15.4 and T_{Amin}=17.6 has on the pricing range and the total financing potential with all other input parameters remaining unchanged. For each of these scenarios a new set of n=1,000 simulation runs is conducted for the time period $t \in [0; T_{A\min}]$. Figure 9.5 shows the impact a change in development speed has on the expected pricing range of the R&D option in addition to the impact on the expected total financing potential.

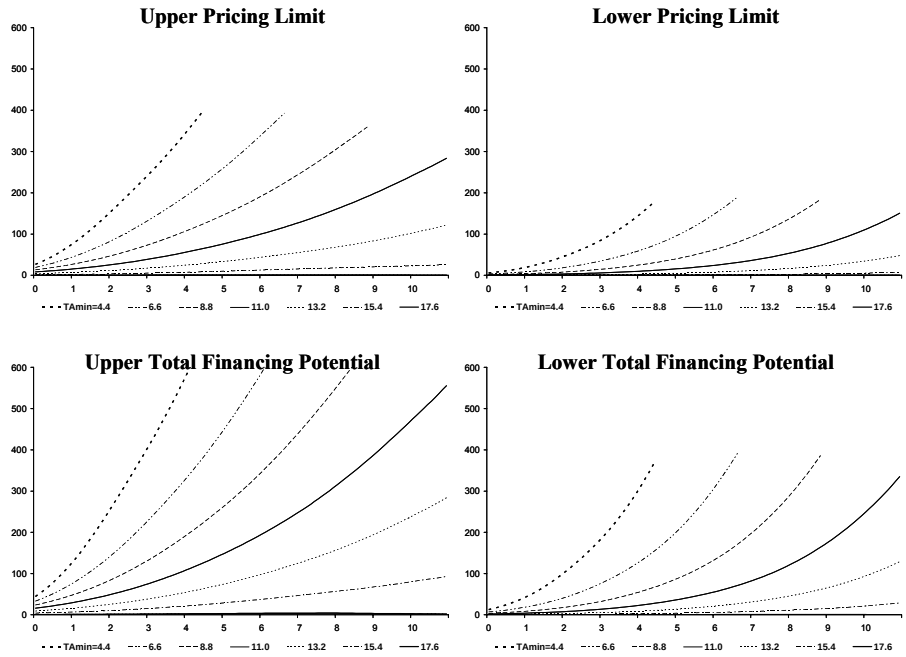

Figure 9.5: Sensitivity of valuation model to changes in project duration

The results are contrary to what one would expect from financial option theory on the behavior of European call options. The figure above shows a negative relationship between R&D option price and time to maturity represented by the expected drug development speed. The longer the time to maturity, the lower the pricing limits of the R&D option. Although

[460] Compare chapter 5.3.2.

this behavior is not what one would expect, there is a rational explanation for it. The described R&D option sensitivity is different from the behavior of traditional stock options because of a structural difference of these two types of options. While the underlying asset of a stock option has a theoretically unlimited lifetime, the underlying of the R&D option does not. The lifetime of the R&D project, which represents the underlying of the R&D option, is limited by the lifetime of the related patents[461]. Since patents are granted for a total period of twenty years, a longer time to maturity decreases the value of the R&D option because it reduces the effective patent protection period[462] between the time of final drug approval and the expiration of the granted patent rights. Since the effective patent protection period is one of the main drivers of the total value of the underlying R&D project the decreasing option value can be explained by the reduction of this period. Each year time to maturity is decreased the underlying project gains an additional year of patent protection with high margin revenues that add value to the project. One source in scientific literature that gives first indications about a negative relationship between time to maturity and the value of a drug development project can be found at Banerjee (2003).[463]

Investigating the detailed data for the figures above confirms that time to maturity is a significant driver of the R&D option's expected pricing range. Details on differences between the standard project example and the six additional scenarios investigated for this sensitivity analysis can be derived from the following Table 9.3.

Apart from the absolute level of the R&D option pricing and total financing limits, changes to the time to maturity also affect the difference between the upper and lower limit of these ranges. Figure 9.6 shows the expected pricing and total financing range of the alternative case scenarios T_{Amin}=6.6 and T_{Amin}=15.4. Besides the expected fact that the graphs are compressed or stretched over time depending on T_{Amin}, it can also be observed that the width of the initial difference between upper and lower limits increase as the maturity of the R&D option decreases.

[461] Assuming generic competition takes over the entire market after patent expiration.

[462] For a more detailed discussion on the effective patent protection period one can refer to chapter 5.1.3 and chapter 5.3.2.

[463] Other studies (e.g. Mitchell and Hamilton (1988, p. 18)) conclude that a longer time to maturity increases the value of a R&D option but do not consider the decreasing effective patent protection period in their study.

New Timing	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
T_{Amin}=4.4	- 60%	High Pricing	+219.3%	--	--
		Low Pricing	+619.5%	--	--
		High Total Fin.	+175.5%	--	--
		Low Total Fin.	+579.5%	--	--
T_{Amin}=6.6	- 40%	High Pricing	+131.8%	+240.2%	--
		Low Pricing	+299.0%	+514.5%	--
		High Total Fin.	+105.6%	+201.7%	--
		Low Total Fin.	+274.2%	+453.9%	--
T_{Amin}=8.8	- 20%	High Pricing	+60.8%	+91.3%	--
		Low Pricing	+111.3%	+156.1%	--
		High Total Fin.	+48.5%	+77.2%	--
		Low Total Fin.	+100.5%	+139.5%	--
T_{Amin}=13.2	+ 20%	High Pricing	-48.9%	-56.1%	-57.0%
		Low Pricing	-61.9%	-67.5%	-68.2%
		High Total Fin.	-41.8%	-49.8%	-44.8%
		Low Total Fin.	-55.9%	-61.9%	-61.6%
T_{Amin}=15.4	+ 40%	High Pricing	-82.8%	-87.1%	-90.9%
		Low Pricing	-91.0%	-93.4%	-95.3%
		High Total Fin.	-74.4%	-80.6%	-79.8%
		Low Total Fin.	-86.0%	-89.4%	-91.4%
T_{Amin}=17.6	+ 60%	High Pricing	-98.9%	-99.3%	-100%
		Low Pricing	-99.7%	-99.8%	-100%
		High Total Fin.	-97.1%	-98.2%	-99.7%
		Low Total Fin.	-99.1%	-99.4%	-100%

Table 9.3: Model sensitivity to changes in project duration

The lower section of the figure shows the development of the absolute and relative premium an investor willing to pay the highest price for the R&D option can be expected to invest in the R&D option in comparison to the investor willing to pay the lowest price. It not only visualizes the stated point that a reduction in time to maturity increases the initial premium, it also shows that the maximum level of this pricing premium throughout the project is higher for those cases where time to maturity is short.

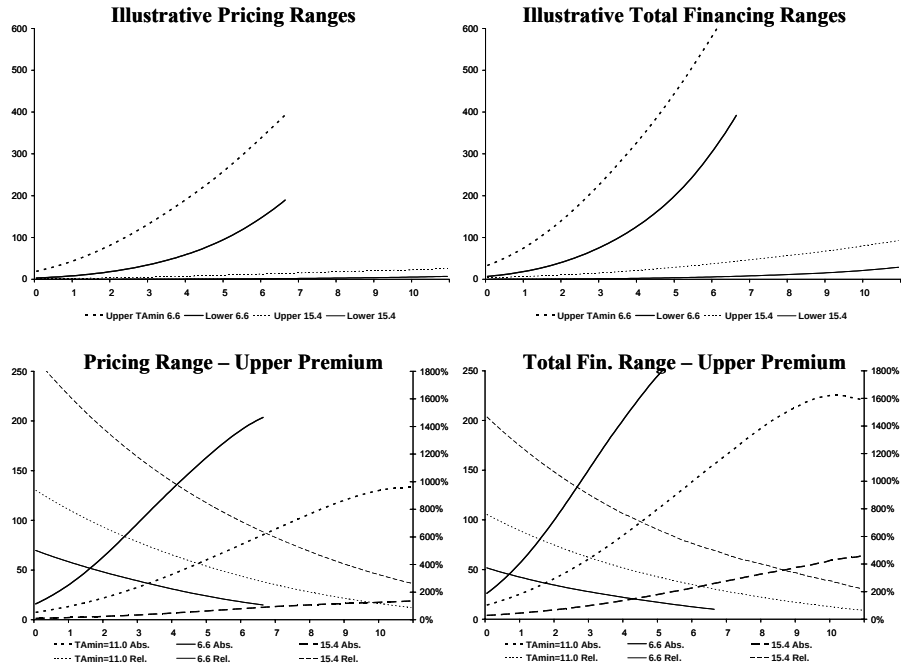

Figure 9.6: Range sensitivity to changes in project duration

For the alternative case with T_{Amin}=6.6, the pricing premium of the R&D option can be expected to grow by 114% compared to the standard case with T_{Amin}=11 whereas the total financing premium grows by 83%. The other comparisons later during the expected drug development period are not as meaningful because alternative project scenarios are at different stages of the pharmaceutical value chain at one specific point in time, which makes those comparisons misleading and less meaningful. Table 9.4 summarizes the magnitude of these changes for the alternative scenarios in comparison to the case example with T_{Amin}=11.

New Timing	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at t=1/2*T_{Amin}	Output change vs. SCE at t=T_{Amin}
T_{Amin}=4.4	- 60%	Pricing Premium	+176.6%	--	--
		Tot. Fin. Premium	+122.3%	--	--
T_{Amin}=6.6	- 40%	Pricing Premium	+113.9%	+161.4%	--
		Tot. Fin. Premium	+83.4%	+110.5%	--
T_{Amin}=8.8	- 20%	Pricing Premium	+55.4%	+72.7%	--
		Tot. Fin. Premium	+41.7%	+54.7%	--
T_{Amin}=13.2	+ 20%	Pricing Premium	-47.7%	-52.8%	-43.9%
		Tot. Fin. Premium	-40.0%	-45.4%	-20.3%
T_{Amin}=15.4	+ 40%	Pricing Premium	-81.9%	-85.3%	-85.7%
		Tot. Fin. Premium	-72.9%	-77.4%	-62.9%
T_{Amin}=17.6	+ 60%	Pricing Premium	-98.8%	-99.2%	-99.9%
		Tot. Fin. Premium	-96.9%	-97.7%	-99.2%

Table 9.4: Range sensitivity to changes in project duration

9.3 Threat of Substitute Products and Competition

The third input factor of the valuation model to be potentially under- or overestimated is the factor of negative jumps in market potential. This factor for potential negative jumps representing the threat of substitute products and competition can change in two different ways. On the one hand, the factor can be misinterpreted that quantifies the probability of negative jumps and on the other hand, the expected change in market potential can be misjudged that occurs if a negative jump actually take place. Both of these cases are investigated in comparison to the illustrative case example[464].

As a first step the impact of a change in the lambda factor is investigated. The results are straightforward and are displayed in Figure 9.7. The higher the probability of negative jumps in market potential the lower the value of the R&D option and vice versa. The same holds true for the total financing potential of a R&D option deal.

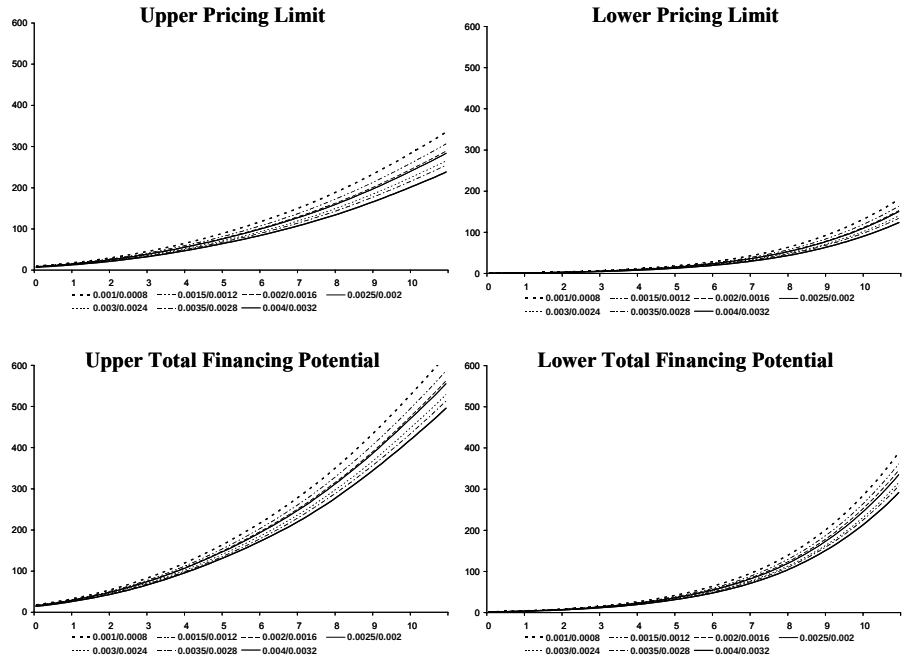

Figure 9.7: Sensitivity of valuation model to changes in negative jump probability

Table 9.5 summarizes the magnitude of the resulting changes on the pricing limits and on the total financing limits for six jump scenarios compared to the standard case.

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[464] For the standard case it is assumed that the occurrence of negative jumps follows a Poisson process with factor λ. This factor is set at λ=0.0025 for the time before and at λ=0.002 for the time after the expected project termination to account for potential first mover advantages. For the size of negative jumps it is assumed that if a competitor enters the market as a first mover it takes away 50% market share while a market entrant after expected drug approval is only able to capture 25% market share. To account for the oliopolistic market structure in most biotechnology and pharmaceutical market segments the number of direct competitors is artificially limited to one for the standard project. This means that a maximum of one negative jump in market potential is allowed to occur.

New Lambda	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
0.001/ 0.0008	- 60%	High Pricing	+17.6%	+17.7%	+18.2%
		Low Pricing	+19.5%	+19.5%	+19.8%
		High Total Fin.	+11.7%	+12.1%	+12.3%
		Low Total Fin.	+16.5%	+16.7%	+16.1%
0.0015/ 0.0012	- 40%	High Pricing	+7.7%	+7.7%	+8.1%
		Low Pricing	+8.0%	+8.0%	+8.7%
		High Total Fin.	+4.8%	+5.1%	+5.6%
		Low Total Fin.	+7.5%	+7.7%	+7.9%
0.002/ 0.0016	- 20%	High Pricing	+1.8%	+1.8%	+1.9%
		Low Pricing	+1.2%	+1.3%	+1.7%
		High Total Fin.	+1.2%	+1.4%	+1.3%
		Low Total Fin.	+2.5%	+2.8%	+3.2%
0.003/ 0.0024	+ 20%	High Pricing	-6.0%	-6.1%	-6.5%
		Low Pricing	-7.5%	-7.4%	-7.1%
		High Total Fin.	-4.6%	-4.1%	-4.6%
		Low Total Fin.	-5.2%	-5.0%	-5.7%
0.0035/ 0.0028	+ 40%	High Pricing	-10.0%	-10.1%	-10.2%
		Low Pricing	-11.5%	-11.4%	-10.9%
		High Total Fin.	-7.8%	-7.8%	-7.5%
		Low Total Fin.	-8.8%	-8.7%	-8.2%
0.004/ 0.0032	+ 60%	High Pricing	-15.0%	-15.2%	-16.1%
		Low Pricing	-17.4%	-17.4%	-17.7%
		High Total Fin.	-10.7%	-10.7%	-10.5%
		Low Total Fin.	-13.0%	-12.5%	-13.0%

Table 9.5: Model sensitivity to changes in probability of negative jumps

In addition it is worthwhile to investigate how factor adjustments change the magnitude of the resulting pricing and financing ranges. The graphs in Figure 9.8 illustrate the pricing and financing ranges of the two cases where lambda is increased and decreased by 40%. It can be seen that early during the drug development process the impact of a factor change on the two ranges is relatively small but increases as the project progresses. The lower graphs confirm this point and also show that the relative size of the premium to be expected from a fully diversified investor is only affected to a small degree by a change in this input parameter.

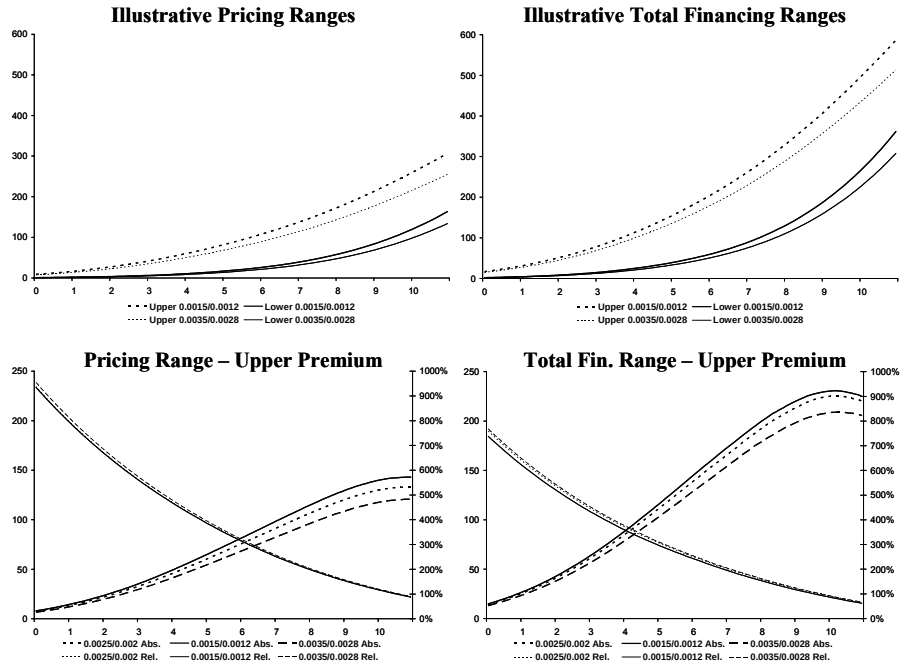

Figure 9.8: Range sensitivity to changes in negative jump probability

Table 9.6 shows the quantitative results of these factor changes in comparison to the standard case example.

New Lambda	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
0.001/ 0.0008	- 60%	Pricing Premium	+17.4%	+17.2%	+16.3%
		Tot. Fin. Premium	+11.1%	+10.5%	+6.7%
0.0015/ 0.0012	- 40%	Pricing Premium	+7.7%	+7.6%	+7.4%
		Tot. Fin. Premium	+4.5%	+4.2%	+2.2%
0.002/ 0.0016	- 20%	Pricing Premium	+1.9%	+2.0%	+2.1%
		Tot. Fin. Premium	+1.0%	+0.9%	-1.6%
0.003/ 0.0024	+ 20%	Pricing Premium	-5.9%	-5.7%	-5.8%
		Tot. Fin. Premium	-4.5%	-3.8%	-3.2%
0.0035/ 0.0028	+ 40%	Pricing Premium	-9.9%	-9.7%	-9.3%
		Tot. Fin. Premium	-7.7%	-7.5%	-6.4%
0.004/ 0.0032	+ 60%	Pricing Premium	-14.7%	-14.6%	-14.1%
		Tot. Fin. Premium	-10.4%	-10.0%	-6.9%

Table 9.6: Range sensitivity to changes in negative jump probability

After investigating the impact of changes to the probability of negative jumps the sensitivity of the model towards changes in negative jump size is investigated. As for the probability, the impact of changes in the size of negative jumps behave as one would expect. The pricing as well as the total financing limits of a R&D option deal are negatively impacted by an increase in the size of potential negative jumps. Figure 9.9 shows how the pricing and total financing limits react to changes in the size of negative jumps in market potential with all other parameters remaining unchanged.

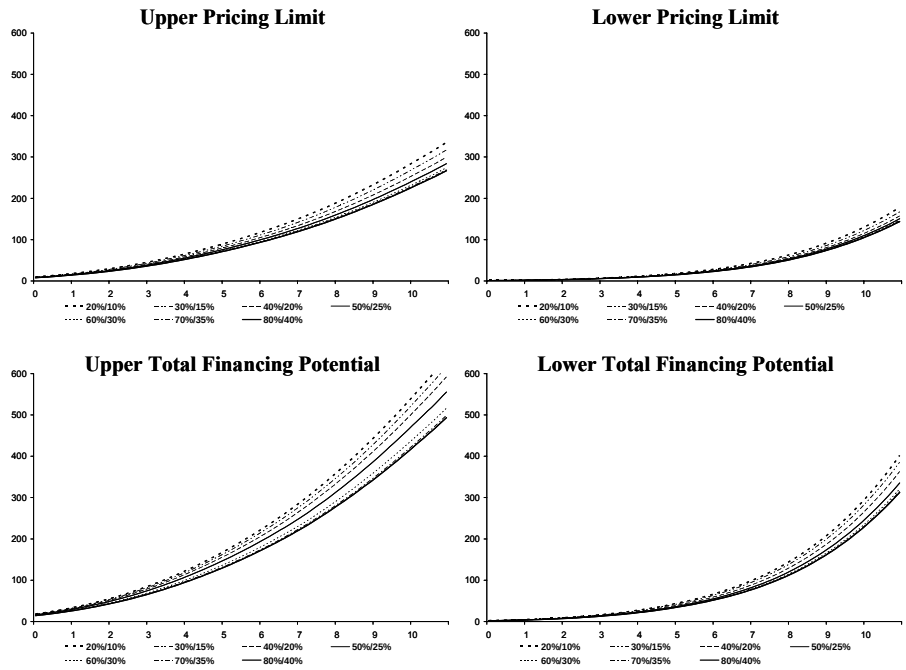

Figure 9.9: Sensitivity of valuation model to changes in size of negative jumps

The resulting relative changes of the pricing and financing limits are only affected to a small degree over the course of the project. Table 9.7 shows the details of the sensitivity analysis for the six investigated adjustments in negative jump size.

New Jump Size	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
20 / 10	- 60%	High Pricing	+17.7%	+17.8%	+18.1%
		Low Pricing	+17.8%	+17.9%	+18.4%
		High Total Fin.	+13.8%	+14.4%	+14.8%
		Low Total Fin.	+20.5%	+20.7%	+19.9%
30 / 15	- 40%	High Pricing	+11.4%	+11.5%	+11.7%
		Low Pricing	+10.3%	+10.5%	+11.1%
		High Total Fin.	+10.3%	+10.7%	+11.0%
		Low Total Fin.	+15.4%	+15.8%	+15.1%
40 / 20	- 20%	High Pricing	+5.4%	+5.4%	+5.5%
		Low Pricing	+4.1%	+4.2%	+4.6%
		High Total Fin.	+5.9%	+6.2%	+6.7%
		Low Total Fin.	+7.5%	+7.5%	+8.3%
60 / 30	+ 20%	High Pricing	-3.6%	-3.6%	-3.5%
		Low Pricing	-2.2%	-2.2%	-2.4%
		High Total Fin.	-7.3%	-7.1%	-7.2%
		Low Total Fin.	-3.7%	-3.5%	-4.3%
70 / 35	+ 40%	High Pricing	-5.4%	-5.3%	-5.2%
		Low Pricing	-3.2%	-3.3%	-3.6%
		High Total Fin.	-10.5%	-10.3%	-10.3%
		Low Total Fin.	-5.3%	-5.2%	-6.1%
80 / 40	+ 60%	High Pricing	-6.2%	-6.1%	-6.0%
		Low Pricing	-4.0%	-4.1%	-4.5%
		High Total Fin.	-11.9%	-11.5%	-11.3%
		Low Total Fin.	-5.8%	-6.7%	-7.9%

Table 9.7: Model sensitivity to changes in size of negative jumps

Analyzing the impact of a change in the size of a potential negative jump results in a similar picture as described for a change in the probability of negative jumps. Figure 9.10 visualizes two illustrative pricing and total financing ranges and shows how the size of these ranges compares to the standard case example. It reduces the size of these ranges if the potential size of negative jumps increases. This holds true for the size of the pricing range as well as for the total financing range.

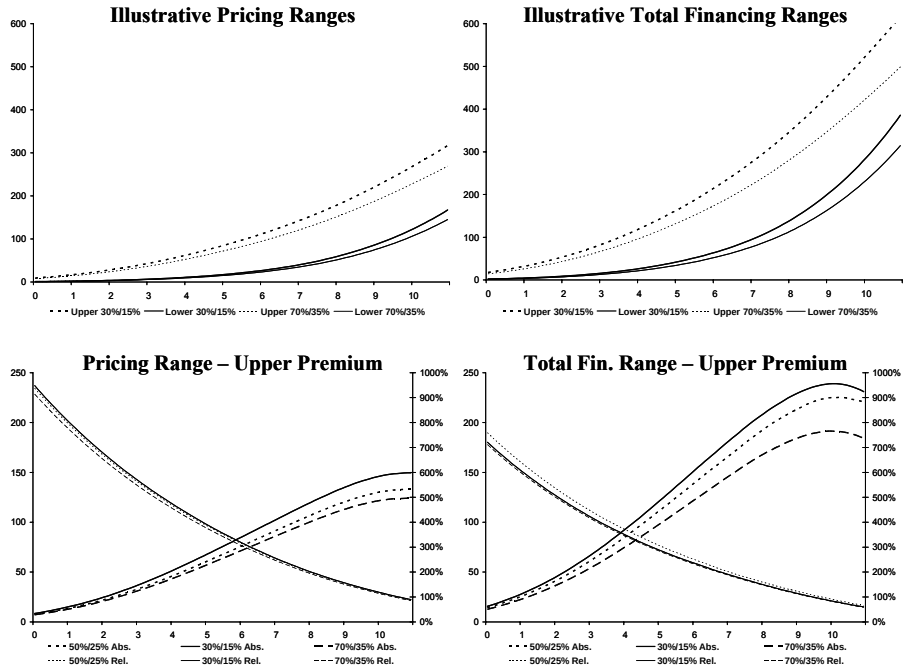

Figure 9.10: Range sensitivity to changes in negative jump size

The magnitude of these size changes is shown in Table 9.8 for the six investigated cases in comparison to the standard case example.

New Jump Size	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
20% / 10%	- 60%	Pricing Premium	+17.7%	+17.8%	+17.8%
		Tot. Fin. Premium	+12.9%	+12.0%	+7.2%
30% / 15%	- 40%	Pricing Premium	+11.6%	+11.8%	+12.4%
		Tot. Fin. Premium	+9.6%	+8.9%	+5.2%
40% / 20%	- 20%	Pricing Premium	+5.5%	+5.7%	+6.5%
		Tot. Fin. Premium	+5.6%	+5.8%	+4.2%
60% / 30%	+ 20%	Pricing Premium	-3.8%	-4.0%	-4.9%
		Tot. Fin. Premium	-7.7%	-8.4%	-11.3%
70% / 35%	+ 40%	Pricing Premium	-5.6%	-5.9%	-7.0%
		Tot. Fin. Premium	-11.2%	-12.2%	-16.5%
80% / 40%	+ 60%	Pricing Premium	-6.5%	-6.7%	-7.9%
		Tot. Fin. Premium	-12.7%	-13.6%	-18.0%

Table 9.8: Range sensitivity to changes in negative jump size

9.4 Initial Market Uncertainty

In chapter 8.1.5 the assumption of a known initial market potential is relaxed and the initial market potential is introduced as a stochastic variable following a lognormal distribution function. When evaluating the pricing and total financing limits of a R&D option the characteristics of the distribution of the initial market potential are of high relevance because they represent the starting point for the double-jump-diffusion process the market potential is expected to follow. Setting up the initial market potential distribution is related to managerial subjectivity and therefore it is investigated how changing uncertainty in the initial market potential affects the pricing and total financing limits of the R&D option.

As a starting point for the sensitivity analysis the illustrative case of this study is used[465]. To investigate how the pricing and total financing limits react to changes in uncertainty in the initial market potential three different cases are investigated. For the first case the changing uncertainty is expressed by modifying the volatility factor $\sigma_{\ln(MP_0)}$ to become $a * \sigma_{\ln(MP_0)}$. The second case investigates the more intuitive case where management adjusts the initial 95% interval symmetrically in absolute terms. This means that the initial range [MP_l; MP_u]=[80; 120] is adjusted by a factor b. The modified initial range therefore becomes [MP_l+b; MP_u-b]. These two cases are investigated separately because case one does not affect $\overline{\ln(MP_0)}$ while the second case does. The third case does not investigate a change in uncertainty itself but a misinterpretation of the entire market potential level. To model this case the initial range [MP_l; MP_u] is shifted by a factor c to become [c*MP_l; c*MP_u].

Case 1:

For this case the uncertainty related to the initial estimate expressed by the standard deviation $\sigma_{\ln(MP0)}$ of the distribution function is adjusted. This is done through an adjustment factor that modifies the standard deviation to become $a*\sigma_{\ln(MP0)}$. Six alternative cases are investigated with factors increasing or decreasing the standard deviation by 20%, 40% or 60%. The mean of the underlying lognormal distribution function $\overline{\ln(MP_0)}$ is not affected by this type of adjustment.

Figure 9.11 shows the impact of the adjustments in standard deviation on the pricing and total financing limits of the R&D option. The graph indicates that even significant changes in the standard deviation only have a minor impact on the pricing and total financing limits of the R&D option.

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[465] For this case management of the research conducting company expects the current market potential of a new drug with 95% certainty to be between a lower market limit MPl and an upper market limit MPu with [MPl; MPu]=[80; 120]. With the assumed lognormal distribution it is known that the natural logarithm of this market potential follows a normal distribution with $N\left(\overline{\ln(MP_0)}; \sigma_{\ln(MP_0)}\right)$ in this case N(4.59; 0.10).

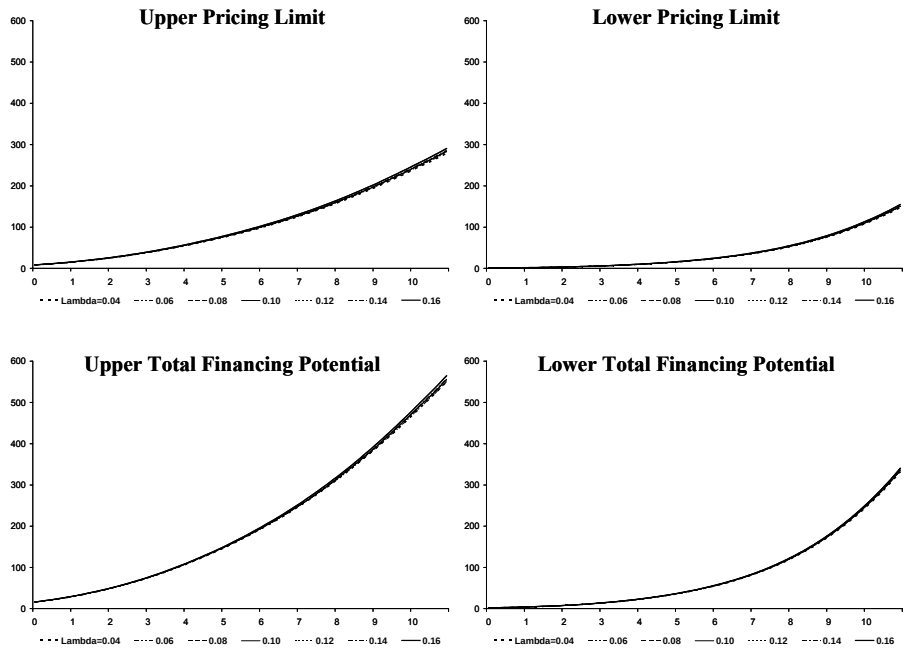

Figure 9.11: Sensitivity of valuation model to changes in initial market volatility

Summarizing the data displayed reveals that even if standard deviation is increase by 60%, the changes to the pricing limits do not exceed 3%. The corresponding changes to the total financing potential are even smaller with all other factors remaining unchanged.

The observable changes for the opposite case where standard deviation is decreased differ in terms of direction and magnitude. Decreasing the standard deviation also decreases the financing limits as well as the total financing potential but to an extent below the case of the respective standard deviation increase.

New Initial Uncert.	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
0.041	- 60%	High Pricing	-1.5%	-1.5%	-1.6%
		Low Pricing	-2.0%	-2.0%	-1.9%
		High Total Fin.	-1.1%	-0.9%	-0.9%
		Low Total Fin.	-1.0%	-0.8%	-1.0%
0.061	- 40%	High Pricing	-0.9%	-0.9%	-1.0%
		Low Pricing	-1.2%	-1.1%	-1.1%
		High Total Fin.	-0.8%	-0.7%	-0.8%
		Low Total Fin.	-0.2%	+0.1%	-0.3%
0.081	- 20%	High Pricing	+0.1%	+0.1%	+0.2%
		Low Pricing	-0.1%	-0.1%	+0.2%
		High Total Fin.	-0.1%	-0.1%	+0.2%
		Low Total Fin.	+0.1%	+0.6%	+1.1%
0.122	+ 20%	High Pricing	+0.1%	+0.1%	+0.2%
		Low Pricing	-0.1%	-0.1%	+0.2%
		High Total Fin.	-0.1%	-0.1%	+0.2%
		Low Total Fin.	+0.1%	+0.6%	+1.1%
0.142	+ 40%	High Pricing	+0.9%	+0.9%	+0.9%
		Low Pricing	+0.9%	+0.9%	+1.0%
		High Total Fin.	+0.1%	+0.7%	+0.4%
		Low Total Fin.	+0.8%	+1.5%	+1.6%
0.162	+ 60%	High Pricing	+2.4%	+2.4%	+2.5%
		Low Pricing	+3.0%	+3.0%	+2.9%
		High Total Fin.	+1.0%	+1.2%	+1.7%
		Low Total Fin.	+1.4%	+1.5%	+1.6%

Table 9.9: Model sensitivity to changes in initial market volatility

These findings are in line with financial option theory where an increase in volatility increases the value of a call option. As for the other sensitivity analyses conducted, the impact of the parameter change is also investigated. Since observed changes on the pricing and financing limits above are minor it is expected that the changes on the observable range sizes are minor as well. The following Figure 9.12 and Table 9.10 confirm this expectation.

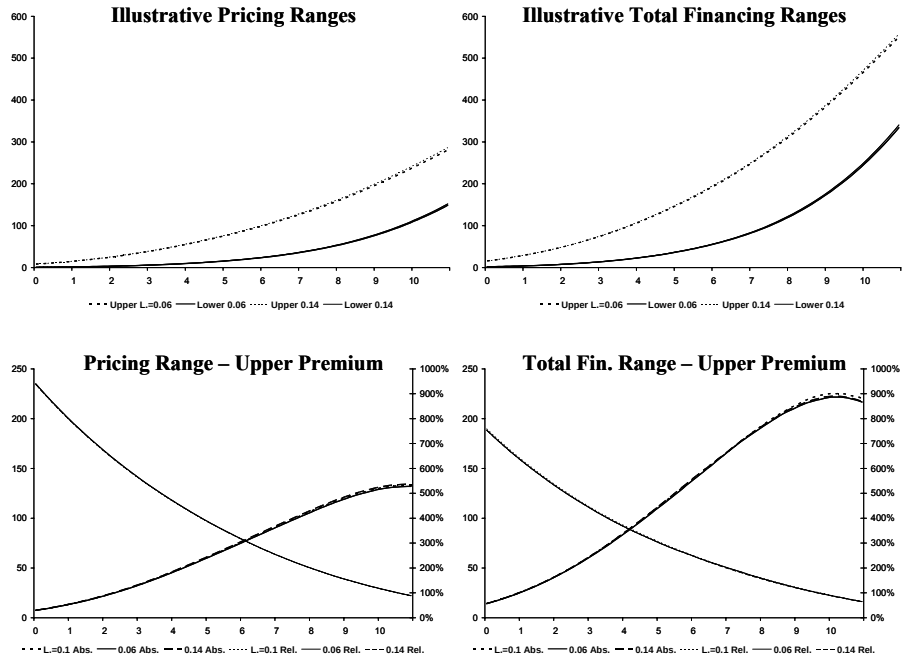

Figure 9.12: Range sensitivity to changes in initial market volatility

New Initial Uncert.	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
0.041	- 60%	Pricing Premium	-1.5%	-1.4%	-1.3%
		Tot. Fin. Premium	-1.1%	-0.9%	-0.7%
0.061	- 40%	Pricing Premium	-0.8%	-0.8%	-0.9%
		Tot. Fin. Premium	-0.9%	-1.0%	-1.6%
0.081	- 20%	Pricing Premium	+0.1%	+0.1%	+0.2%
		Tot. Fin. Premium	+0.1%	+0.3%	-1.1%
0.122	+ 20%	Pricing Premium	+0.1%	+0.1%	+0.2%
		Tot. Fin. Premium	-0.1%	-0.3%	-1.1%
0.142	+ 40%	Pricing Premium	+0.9%	+0.9%	+0.8%
		Tot. Fin. Premium	-0.1%	+0.4%	-1.4%
0.162	+ 60%	Pricing Premium	+2.3%	+2.3%	+2.0%
		Tot. Fin. Premium	+0.9%	+1.1%	+1.9%

Table 9.10: Range sensitivity to changes in initial market volatility

Case 2:

The second case of sensitivity analysis on the initial market estimate investigates uncertainty in a way that is more intuitive to the practitioner when estimating initial market ranges. Instead of modifying the standard deviation of the lognormal distribution function, which is more of an abstract figure for the practitioner, this case considers the impact of changing the initial range of the relevant market potential. To achieve this, the width of the initial range $[MP_l; MP_u]=[80; 120]$ is adjusted, modifying the range to become $[MP_l+b; MP_u-b]$. The factor b therefore narrows or widens the initial range symmetrically. As opposed to the previous case, this adjustment affects both, the mean of the log-normal distribution function as well as the relevant standard deviation.

For the purpose of this analysis the impact of the six different factors for $b \in [-12;-8;-4.4;8;12]$ are investigated. These factors lead to an increase or a decrease of the initial range of 20%, 40% or 60%. The impact of these different adjustment factors are displayed in Figure 9.13. The figure shows that the smaller the uncertainty expressed by the size of the initial range, the higher the pricing limits as well as the total financing limits. Although this effect becomes visible in the graph it is not of large magnitude.

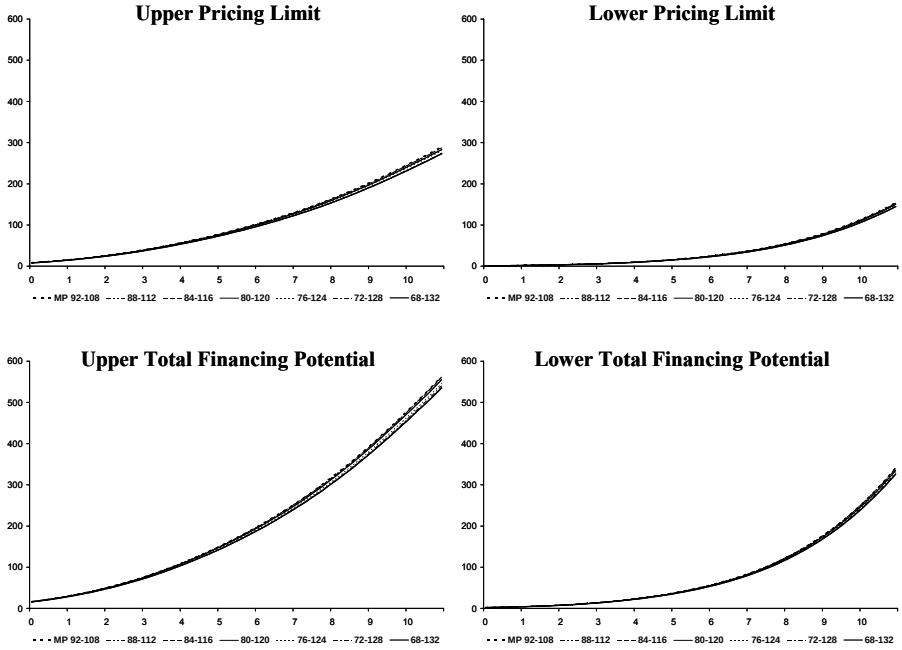

Figure 9.13: Sensitivity of valuation model to changes in initial market range

This could lead to the conclusion that in this case the value of the R&D option behaves differently from what can be expected from financial option theory. If uncertainty is measured by the width of the initial range for the market potential it appears as if the larger the uncertainty, the lower the value of the option, which would not comply with financial option theory and the previously considered case 1. The detailed results from the various simulation scenarios shown in Table 9.11 appear to support this conclusion.

New Initial Range	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
92-108	- 60%	High Pricing	+2.2%	+2.2%	+2.2%
		Low Pricing	+2.7%	+2.6%	+2.6%
		High Total Fin.	+1.3%	+1.5%	+1.5%
		Low Total Fin.	+1.7%	+1.9%	+1.8%
88-112	- 40%	High Pricing	+1.6%	+1.5%	+1.3%
		Low Pricing	+1.9%	+1.9%	+1.6%
		High Total Fin.	+0.9%	+1.1%	+1.3%
		Low Total Fin.	+1.2%	+1.3%	+1.2%
84-116	- 20%	High Pricing	+1.7%	+1.7%	+1.5%
		Low Pricing	+2.0%	+2.0%	+1.7%
		High Total Fin.	+0.9%	+1.0%	+1.0%
		Low Total Fin.	+1.7%	+1.6%	+1.9%
76-124	+ 20%	High Pricing	-0.9%	-1.0%	-1.1%
		Low Pricing	-0.8%	-0.8%	-1.0%
		High Total Fin.	-1.8%	-1.7%	-1.7%
		Low Total Fin.	-0.5%	-0.1%	-0.3%
72-128	+ 40%	High Pricing	-3.6%	-3.6%	-3.1%
		Low Pricing	-4.5%	-4.4%	-3.6%
		High Total Fin.	-3.4%	-3.2%	-2.6%
		Low Total Fin.	-3.4%	-2.8%	-1.7%
68-132	+ 60%	High Pricing	-3.7%	-3.6%	-3.6%
		Low Pricing	-4.1%	-4.0%	-3.7%
		High Total Fin.	-3.7%	-3.4%	-3.5%
		Low Total Fin.	-3.3%	-3.1%	-2.7%

Table 9.11: Model sensitivity to changes in initial market range

This is misleading because it is not the width of the initial market range that drives the limits of the option pricing range and the ranges for the total financing potential down but the mean of the log-normal distribution function. It is important to consider how the underlying distribution function changes if the scenario is changed by adapting the initial market potential range using $[MP_l+b;\ MP_u-b]$. If b takes on a negative value it appears as if uncertainty increases because the 95% range is widened. Although this is true a second effect caused by the assumption of a lognormal distribution of the market potential has a larger impact on the option's value.

Because of the assumption of a lognormal distribution, which is not a symmetric distribution function, a change in b also changes the mean of the market potential distribution and this effect is more relevant than the width of the range for the initial market potential. The case where b takes on a negative value also decreases $\overline{\ln(MP_0)}$, which is the more important driver

of the option value. Figure 9.14 visualizes how widening the initial 95% range from a width of 20 (b=10) to a width of 80 (b=-20) decreases $\overline{\ln(MP_0)}$.

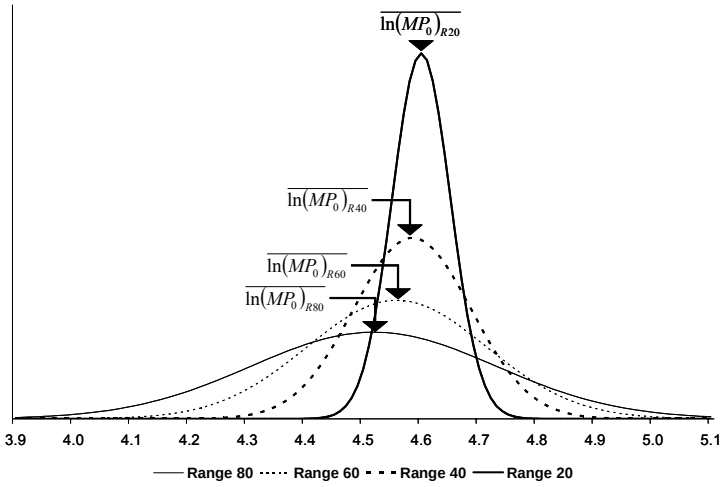

Figure 9.14: Impact of initial market range on expected level of ln(MP)

As shown in the preceding paragraphs, this intuitive way of increasing uncertainty related to the initial market potential represents in reality a combination of two different parameter changes. In addition to a change in the standard deviation of the normal distribution function of the natural logarithm of the initial market potential it also changes the mean of this function. The change in the mean of the function can be considered a change in the level of the market potential and therefore this case is not suited for a one-dimensional sensitivity analysis of the individual factor market uncertainty. Although not suited for the sensitivity analysis the described case gives practitioners a valuable indication on things to consider when setting up and changing initial market potential estimates.

Case 3:

The last case investigated in relation to the initial market potential is the one where the magnitude of the initial market potential is under or overestimated. To investigate the impact such an under or overestimation has on the pricing and total financing ranges, multiple scenarios are evaluated where the initial market range [MP_l; MP_u] of the illustrative project example is shifted by a factor c to become [c*MP_l; c*MP_u]. In particular the six cases $c \in$ [0-4;0.6;0.8;1.2;1.4;1.6] are investigated with all other input factors remaining unchanged. Figure 9.15 illustrates the pricing and total financing limits of these cases in comparison to the illustrative project example.

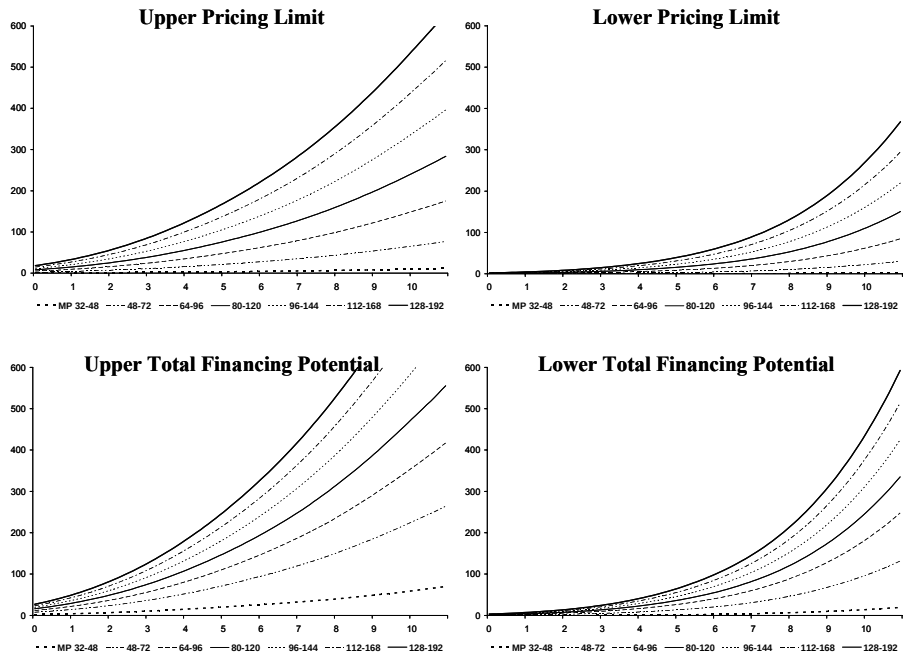

Figure 9.15: Model sensitivity to changes in level of initial market potential

The above figure shows the intuitive positive relation between market range shifts and the pricing and total financing limits. Increasing the initial expectations increases the pricing level of the R&D option as well as the total financing potential while decreasing expectations reduces them. This result is in line with financial option theory where an increase in the observable stock price, as the equivalent to the magnitude of the initial market potential, increases the value of a call option on a non-dividend paying stock. How large this impact of market level shifts becomes for the various scenarios investigated can be derived from Table 9.12.

New MP Level	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
32-48	- 60%	High Pricing	-95.4%	-95.5%	-96.0%
		Low Pricing	-98.8%	-98.7%	-98.2%
		High Total Fin.	-86.4%	-86.4%	-87.2%
		Low Total Fin.	-95.9%	-95.6%	-94.2%
48-72	- 40%	High Pricing	-71.7%	-72.0%	-72.8%
		Low Pricing	-82.1%	-81.5%	-79.9%
		High Total Fin.	-51.9%	-51.6%	-51.8%
		Low Total Fin.	-63.9%	-62.8%	-60.8%
64-96	- 20%	High Pricing	-37.5%	-37.6%	-38.2%
		Low Pricing	-45.5%	-45.0%	-43.8%
		High Total Fin.	-25.4%	-24.8%	-24.4%
		Low Total Fin.	-27.6%	-26.9%	-26.1%
96-144	+ 20%	High Pricing	+39.1%	+39.1%	+39.8%
		Low Pricing	+48.1%	+47.5%	+46.1%
		High Total Fin.	+23.0%	+23.5%	+23.6%
		Low Total Fin.	+26.8%	+27.2%	+26.6%
112-168	+ 40%	High Pricing	+80.9%	+80.9%	+82.0%
		Low Pricing	+100.9%	+99.4%	+95.8%
		High Total Fin.	+45.8%	+46.3%	+45.8%
		Low Total Fin.	+53.9%	+53.9%	+53.3%
128-192	+ 60%	High Pricing	+121.6%	+121.6%	+122.6%
		Low Pricing	+153.5%	+151.1%	+144.5%
		High Total Fin.	+67.5%	+68.0%	+66.5%
		Low Total Fin.	+78.8%	+78.7%	+76.9%

Table 9.12: Model sensitivity to changes in level of initial market potential

In addition to the direct impact a misinterpretation of the initial market potential level has on pricing and total financing limit it is also investigated how the size of these range behaves. The following Figure 9.16 shows the pricing and total financing range for the two cases c=0.6 and c=1.4. In addition, the two lower graphs of the figure show how the sizes of these ranges behave over the expected course of the project in comparison to the illustrative project example.

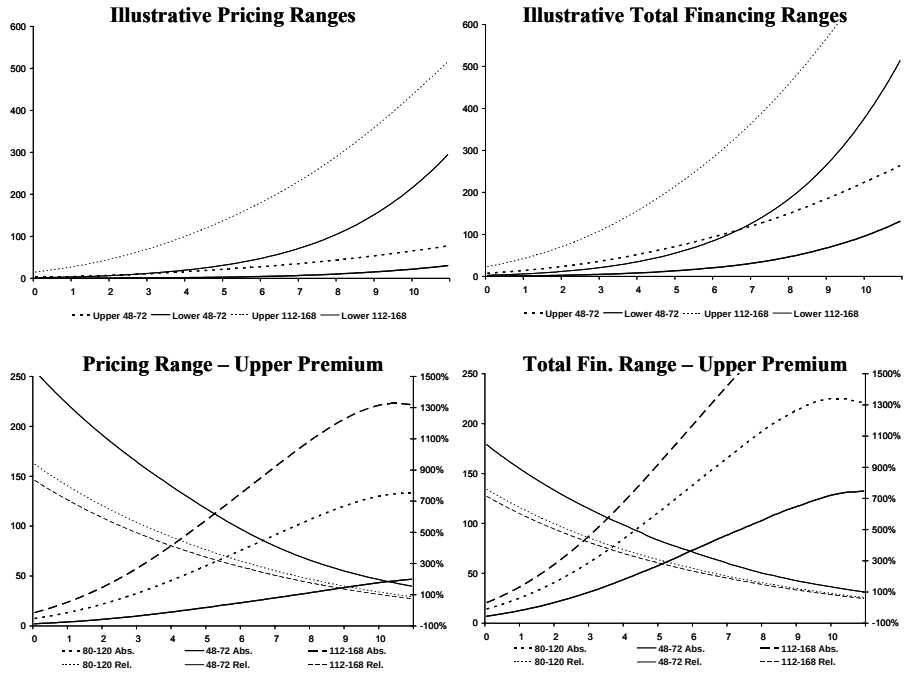

Figure 9.16: Range sensitivity to changes in level of initial market potential

The graphs show that both the absolute and the relative premium of the upper limits are significant. They show that an increase in market potential level of 20% increases the size of the gap between upper and lower pricing limits by 38%. A 20% decrease in market potential level on the other hand decreases the gap size of the pricing range by 37%. These figures are lower for the total financing premium where the impact is 23% for the 20% increase and -25% for the respective decrease. Additional results for the six investigated cases can be derived from Table 9.13.

New MP Level	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
32-48	- 60%	Pricing Premium	-95.1%	-94.6%	-93.4%
		Tot. Fin. Premium	-85.1%	-83.1%	-77.0%
48-72	- 40%	Pricing Premium	-70.6%	-69.2%	-64.5%
		Tot. Fin. Premium	-50.3%	-47.5%	-38.7%
64-96	- 20%	Pricing Premium	-36.6%	-35.4%	-31.7%
		Tot. Fin. Premium	-25.1%	-24.0%	-22.1%
96-144	+ 20%	Pricing Premium	+38.2%	+36.7%	+32.5%
		Tot. Fin. Premium	+22.5%	+22.1%	+19.2%
112-168	+ 40%	Pricing Premium	+78.7%	+75.6%	+65.8%
		Tot. Fin. Premium	+44.7%	+43.6%	+34.8%
128-192	+ 60%	Pricing Premium	+118.2%	+113.2%	+97.0%
		Tot. Fin. Premium	+66.1%	+64.2%	+51.4%

Table 9.13: Range sensitivity to changes in level of initial market potential

Apart from the positive relationship between initial market potential and R&D option price as well as total financing potential, the table shows that the level of initial market potential is a key input factor for the valuation model. When evaluating a R&D option, special attention

should therefore be paid to this input factor because a misinterpretation has a major impact on the results of the analysis.

9.5 Ability to Broaden Product Market

The last factor influencing the valuation model is the probability that a product market can potentially be expanded. This potential occurrence of positive jumps is introduced and discussed in chapter 8.1.3. It is shown that two input factors need to be considered that can potentially be misinterpreted. On one hand there is the probability that positive jumps occur and on the other hand the size of these potential jumps.

During a first step the sensitivity to changes in positive jump probability is investigated while a second step covers the sensitivity to expected positive jump sizes. Similar to the previous sections all changes are reported in comparison to the illustrative project example[466]. For the sensitivity of the model to changes in the positive jump probability six scenarios are investigate with lambda factors $\lambda \in [0.0012;0.0018;0.0024;0.0036;0.0042;0.0048]$. As one would expect there is a positive relationship between the probability of positive jumps and the pricing and total financing limits of the R&D option. Figure 9.17 visualizes the results of the alternative case simulations in comparison to the standard project.

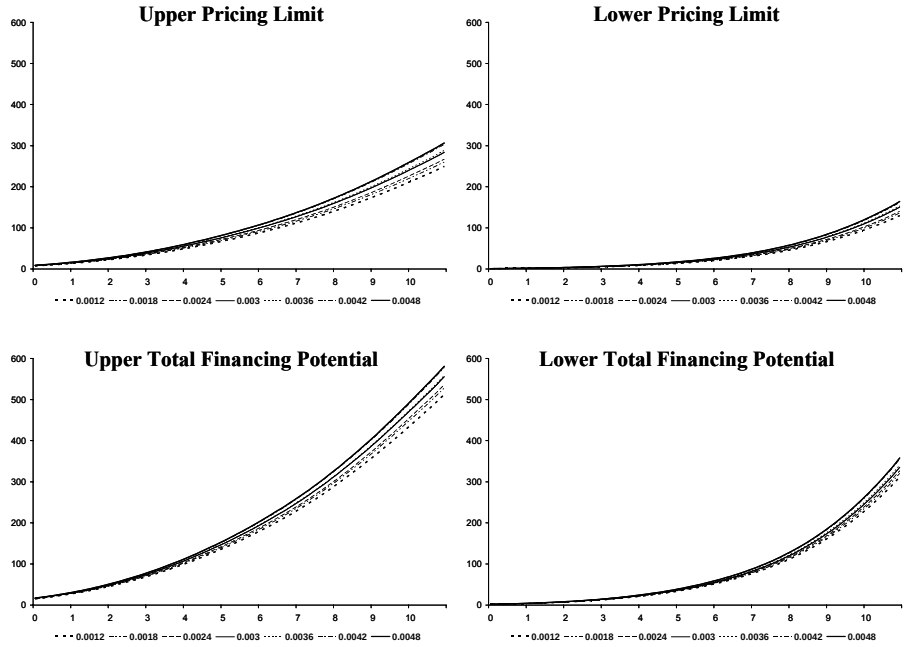

Figure 9.17: Model sensitivity to changes in probability of positive jumps

[466] For this project example the arrival time between positive jumps is assumed to follow a Poisson distribution with a Lambda factor λ=0.003 and the size of the jumps is assumed to be within the interval [+/-0%; +40%].

In terms of magnitude this factor is not one of the key value drivers of the R&D option price and the total financing potential. Table 9.14 shows the detailed results of the six alternative scenarios in comparison to the standard case example.

New Lambda	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
0.0012	- 60%	High Pricing	-11.8%	-11.9%	-12.1%
		Low Pricing	-14.6%	-14.5%	-13.8%
		High Total Fin.	-7.4%	-7.5%	-7.6%
		Low Total Fin.	-7.2%	-7.0%	-7.1%
0.0018	- 40%	High Pricing	-8.1%	-8.2%	-8.3%
		Low Pricing	-10.0%	-9.9%	-9.6%
		High Total Fin.	-8.1%	-8.2%	-8.3%
		Low Total Fin.	-4.4%	-4.2%	-4.5%
0.0024	- 20%	High Pricing	-5.3%	-5.4%	-5.9%
		Low Pricing	-6.4%	-6.4%	-6.9%
		High Total Fin.	-3.4%	-3.3%	-3.4%
		Low Total Fin.	-2.5%	-2.5%	-2.6%
0.0036	+ 20%	High Pricing	+1.3%	+1.3%	+1.6%
		Low Pricing	+1.5%	+1.5%	+1.8%
		High Total Fin.	+0.1%	+0.3%	+0.6%
		Low Total Fin.	+1.6%	+1.8%	+1.7%
0.0042	+ 40%	High Pricing	+6.8%	+6.7%	+6.8%
		Low Pricing	+7.6%	+7.5%	+7.6%
		High Total Fin.	+3.4%	+3.8%	+4.0%
		Low Total Fin.	+5.4%	+5.6%	+6.0%
0.0048	+ 60%	High Pricing	+7.6%	+7.6%	+8.0%
		Low Pricing	+8.7%	+8.7%	+9.1%
		High Total Fin.	+4.4%	+4.4%	+4.6%
		Low Total Fin.	+6.2%	+6.8%	+6.7%

Table 9.14: Model sensitivity to changes in probability of positive jumps

As for the other sections on model sensitivity, the impact of changes in the probability of positive jumps on the size of the pricing and total financing range is investigated. Similar to results for the ranges themselves, there is also a positive relationship between the size of the ranges and the probability that positive jumps in market potential are expected to occur. Figure 9.18 shows the ranges of two alternative case examples and the absolute and relative premium of the upper pricing and total financing limit in comparison to the illustrative case example. The positive relation between the probability of positive jumps and the width of the pricing and financing range can be observed in the lower two graphs. In these graphs the absolute difference between the upper and the lower limit of both ranges increases as the lambda factor as a measure for the probability of positive jumps increases.

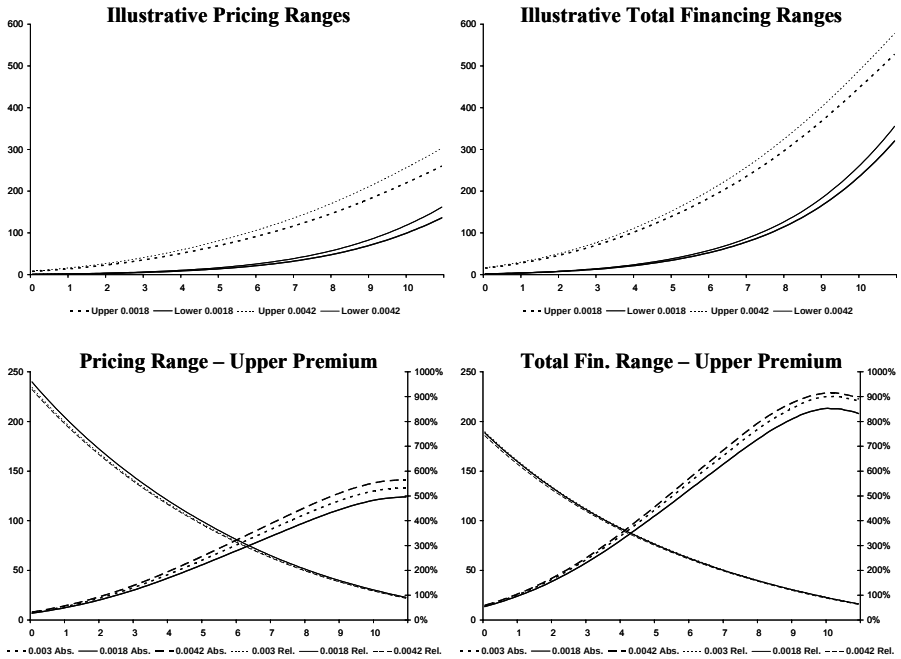

Figure 9.18: Range sensitivity to changes in probability of positive jumps

The following Table 9.15 shows the magnitude of these changes for the alternative lambda factors in comparison to the standard case example.

New Lambda	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
0.0012	- 60%	Pricing Premium	-11.5%	-11.2%	-10.1%
		Tot. Fin. Premium	-7.4%	-7.8%	-8.4%
0.0018	- 40%	Pricing Premium	-7.9%	-7.7%	-6.8%
		Tot. Fin. Premium	-5.1%	-5.4%	-5.1%
0.0024	- 20%	Pricing Premium	-5.2%	-5.1%	-4.7%
		Tot. Fin. Premium	-3.6%	-3.7%	-4.5%
0.0036	+ 20%	Pricing Premium	+1.2%	+1.2%	+1.3%
		Tot. Fin. Premium	-0.1%	-0.3%	-1.1%
0.0042	+ 40%	Pricing Premium	+6.7%	+6.4%	+6.0%
		Tot. Fin. Premium	+3.2%	+3.1%	+1.1%
0.0048	+ 60%	Pricing Premium	+7.5%	+7.2%	+6.8%
		Tot. Fin. Premium	+4.1%	+3.5%	+1.4%

Table 9.15: Range sensitivity to changes in probability of positive jumps

The second aspect to be investigated when discussing the impact of positive jumps is the potential size of these jumps if they occur. To demonstrate the impact of input factor changes on the valuation model for this parameter, the maximum limit is changed in six scenarios with the maximum jump sizes being set to 16%, 24%, 32%, 48%, 56% and 64%.[467]

[467] For the illustrative project example the market potential of a new drug can be expanded through a positive jump by about [+/-0%; +40%].

Figure 9.19 visualizes the effect these modifications of the maximum size of a potential positive jump have on the pricing limits of the R&D option on the one hand and on the expected total financing range on the other. Allowing a larger maximum jump size drives upper as well as lower pricing limit up while a reduction decreases these limits.

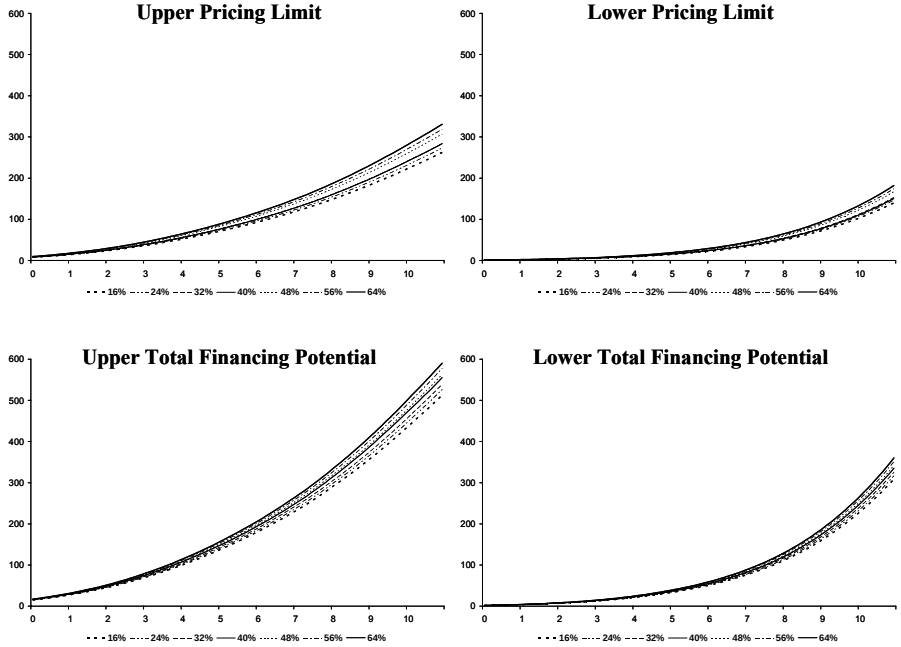

Figure 9.19: Model sensitivity to changes in size of positive jumps

To validate this observation and to demonstrate the magnitude of the changes in pricing and total financing limits, the following Table 9.16 shows the changes that can be observed between the illustrative project example and the different alternative scenarios investigated.

New Jump Size	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
16%	- 60%	High Pricing	-6.8%	-6.9%	-7.5%
		Low Pricing	-6.4%	-6.5%	-7.1%
		High Total Fin.	-7.5%	-7.2%	-7.7%
		Low Total Fin.	-8.7%	-8.1%	-7.9%
24%	- 40%	High Pricing	-3.2%	-3.3%	-3.8%
		Low Pricing	-2.0%	-2.2%	-2.9%
		High Total Fin.	-5.2%	-5.1%	-5.2%
		Low Total Fin.	-6.3%	-5.5%	-5.4%
32%	- 20%	High Pricing	0.5%	+0.4%	+0.1%
		Low Pricing	2.4%	+2.2%	+1.6%
		High Total Fin.	-3.2%	-2.9%	-3.0%
		Low Total Fin.	-3.8%	-2.8%	-2.9%
48%	+ 20%	High Pricing	8.2%	+8.2%	+8.2%
		Low Pricing	11.8%	+11.6%	+10.8%
		High Total Fin.	1.3%	+1.7%	+1.2%
		Low Total Fin.	0.8%	+1.9%	+2.0%
56%	+ 40%	High Pricing	12.2%	+12.2%	+12.4%
		Low Pricing	16.7%	+16.4%	+15.7%
		High Total Fin.	3.5%	+3.9%	+3.8%
		Low Total Fin.	3.8%	+4.9%	+4.8%
64%	+ 60%	High Pricing	16.3%	+16.3%	+16.7%
		Low Pricing	21.8%	+21.5%	+20.7%
		High Total Fin.	5.8%	+6.2%	+6.1%
		Low Total Fin.	6.6%	+7.3%	+7.5%

Table 9.16: Sensitivity of valuation model to changes in size of positive jumps

The demonstrated positive relation between maximum positive jump size and pricing and total financing range also holds true for the width of the observed ranges. Figure 9.20 shows these ranges for two of the alternative case scenarios and the development of the premium of the upper limit in comparison to the lower limit. It shows that increasing the maximum jump size widens the absolute gap between upper and lower pricing limit as well as the range of the total financing potential although to a smaller extent. It is also interesting to note that the peak just before the expected minimum project duration is less distinct in cases where the maximum allowed jump size is lower.

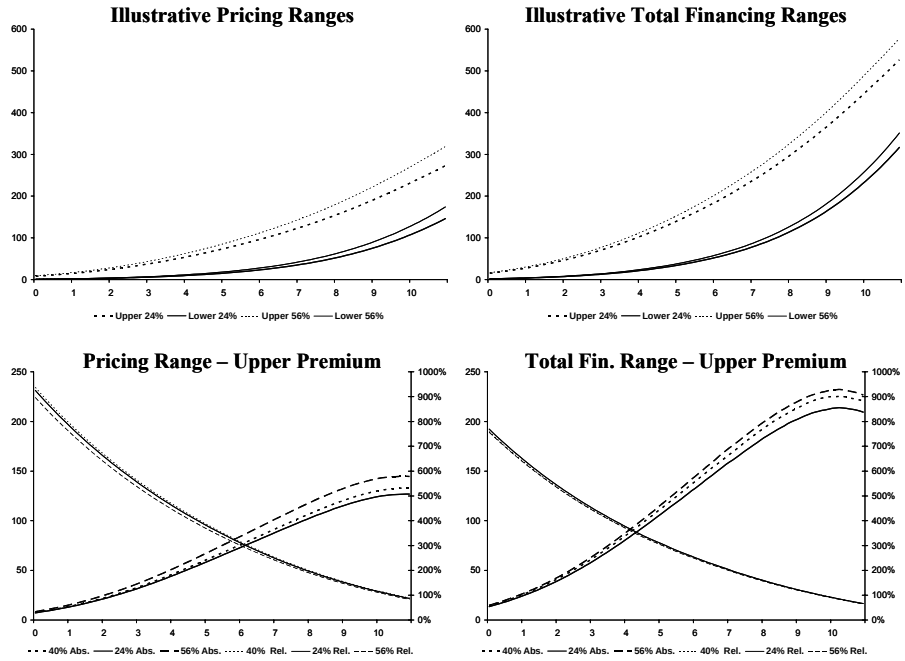

Figure 9.20: Range sensitivity to changes in size of positive jumps

The magnitude of the changes in width of the pricing and financing ranges are displayed in detail for the investigated cases in the following Table 9.17.

New Jump Size	Parameter change vs. standardized case example (SCE)	Output	Output change vs. SCE at t=0	Output change vs. SCE at $t=1/2*T_{Amin}$	Output change vs. SCE at $t=T_{Amin}$
16%	- 60%	Pricing Premium	-6.8%	-7.0%	-7.9%
		Tot. Fin. Premium	-7.4%	-6.9%	-7.3%
24%	- 40%	Pricing Premium	-3.3%	-3.6%	-4.8%
		Tot. Fin. Premium	-5.1%	-4.9%	-5.0%
32%	- 20%	Pricing Premium	+0.3%	-0.1%	-1.6%
		Tot. Fin. Premium	-3.2%	-2.9%	-3.1%
48%	+ 20%	Pricing Premium	+7.8%	+7.2%	+5.1%
		Tot. Fin. Premium	+1.4%	+1.6%	+0.1%
56%	+ 40%	Pricing Premium	+11.7%	+11.0%	+8.5%
		Tot. Fin. Premium	+3.5%	+3.5%	+2.4%
64%	+ 60%	Pricing Premium	+15.7%	+14.8%	+11.9%
		Tot. Fin. Premium	+5.7%	+5.7%	+4.1%

Table 9.17: Range sensitivity to changes in size of positive jumps

9.6 Sensitivity Space of Valuation Approach

Based on the sensitivity analysis above the resulting sensitivity space of the developed valuation model can be constructed. A sensitivity space allows the direct visual comparison of the impact input parameter changes have on the output of a model. This enables the identification of the most critical input parameters users should investigate carefully when applying a valuation model. Figure 9.21 shows the sensitivity space of the developed pricing model at the time of patent application for the illustrative case example.

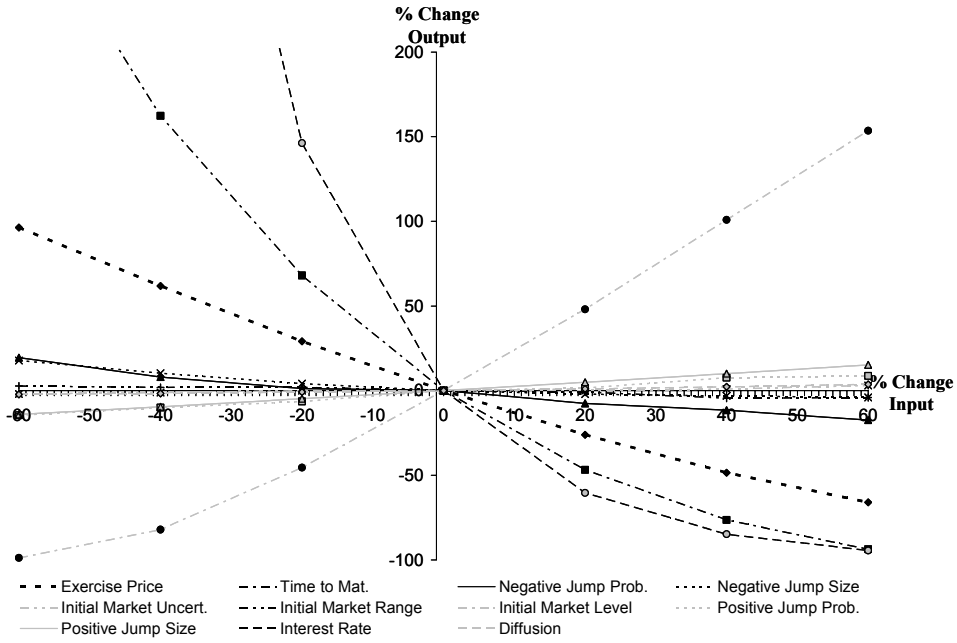

Figure 9.21: Sensitivity space lower R&D option price at t=0

The sensitivity diagram shows that input parameters can be separated into two classes. One class consists of parameters that have a major impact on the outcome of the model while those of the other class that only have a minor impact. The class of input parameters with a predominant impact have to be determined carefully when the model is applied. Over- or underestimating them can cause a significant over- or undervaluation of the R&D option.

Parameters having a predominant effect are the expected duration of the R&D project being equivalent to the option's time to maturity, the applied discount rate, the expected initial market potential of the drug under development and the exercise price. As opposed to the other major parameters the exercise price cannot be over- or underestimated because it is fixed in the option contract. However, selecting an appropriate exercise price has an important impact on the expected price of the R&D option.

The second class of parameters are factors of minor relevance. Over- or underestimating them causes the expected price to change to a significantly smaller relative extent than the input parameter change. Parameters falling into this category in the illustrative case are the size and probability of negative as well as of positive jumps and the uncertainty related to the initial market potential.

Conducting the same analysis for the total financing potential of the R&D option at the time of patent application generates a similar result with the main difference being the effect of the exercise price applied. Figure 9.22 visualizes the sensitivity space for the total financing potential of the R&D option in the illustrative case example. While the significance of most input parameters remains similar as determined for the option price above, the role of the exercise price becomes less significant for the total financing potential. This is related to the two contrary effects exercise price changes have on the total financing potential, which were explained in detail in chapter 9.1.

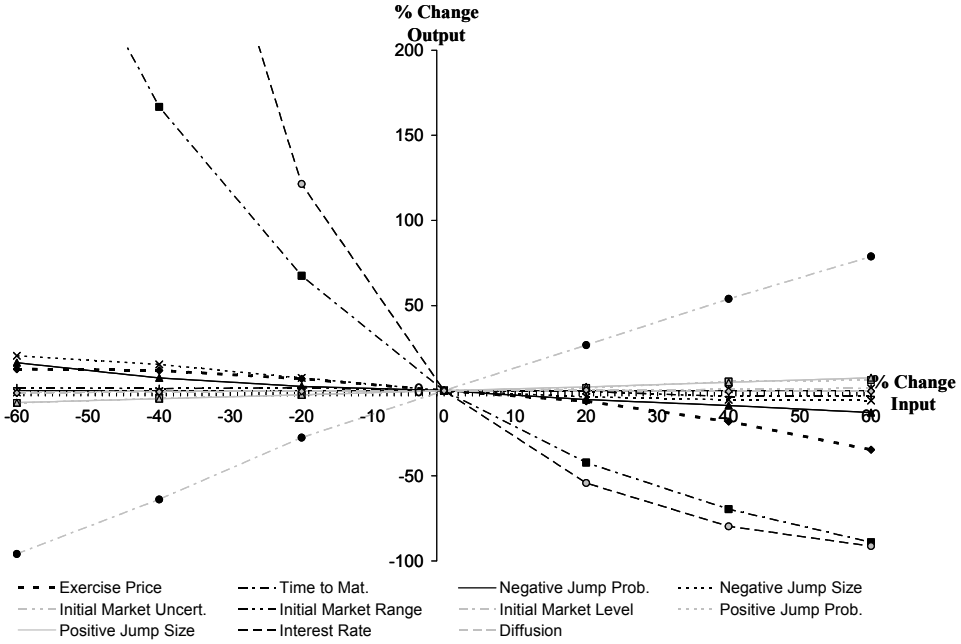

Figure 9.22: Sensitivity space lower R&D option financing limit at t=0

10 Concluding Remarks

Chapter 10 completes the main body of this study with two concluding sections. The first one summarizes the main findings from this work and emphasizes its primary contributions. The second section highlights selected issues that are not covered in this study but represent valuable topics for additional future research.

10.1 Summary and Main Findings

The objective of this study is to investigate the idea of selling option rights on ongoing drug development projects as a potential tool for young biotechnology companies to raise funds to finance ongoing operations. Three aspects represent the main focus areas of this study:

1. An investigation of the practical demand for an innovative financing tool like a R&D option within the biotechnology industry.
2. A description of the characteristics of a potential R&D option deal and how the underlying drug development project compares to financial and to other types of real options.
3. The development of a subjective valuation model to "ex ante" estimate the financing potential of a R&D option deal over the expected duration of a drug development project and to identify the key parameters that represent the main value drivers of the option.

The following approach is taken to cover these main areas of interest. In an introductory chapter the situation of the pharmaceutical and biotechnological industry is described to create an understanding of the environment that builds the framework for this study. It is demonstrated that the main problem of major players in the pharmaceutical industry is product innovation to ensure future growth and profitability. The key issues for the younger biotechnology industry are shown to be different by nature and mainly center around the problem of insufficient corporate funding and the necessity to raise additional funds to finance ongoing and future research and development activities.

As important background information for the remainder of this study, the second chapter describes in detail how the standard research and development process for an innovative new drug is structured. The cost structure related to this average R&D process is described and the resulting financing requirements for the research conducting company are derived. It is shown that drug development is a lengthy and costly process, which involves significant technical failure risk. The average drug development project takes 14 years from project initiation until final drug approval and requires financial resources on a pre-tax level of about US$800 million including the cost of failed projects. Only one out of several thousand tested

compounds finally reaches the point of final drug approval and only three out of ten[468] having reached that point finally recover their own research and development cost.

The third chapter introduces some key concepts of financial option theory and their practical applications to build the theoretical foundation for the main part of this study. In addition, the main factors influencing the value of a basic financial option are discussed. The remainder of this chapter deals with real options and how they are generally classified in scientific literature. In addition, a more practical approach to classify real options is introduced. This approach classifies the different types of real options based on how close their characteristics are compared to basic financial options. The concluding remarks in this chapter show that a drug development project represents a real option of the most complex type. The characteristics of this type of real option differ significantly from the more widely known and scientifically more extensively investigated financial options. The most critical differences often neglected in studies on this topic are the lacking exclusivity, the fact that they are not traded on complete markets and the problem that they generally do not have fixed maturity dates. These differences have a significant impact on the valuation of this type of real option and make the use of established risk-neutral valuation methods inappropriate. Instead, they require the development of a subjective model for their valuation.

Chapter four discusses the availability of different sources of financing to young biotechnology companies in the current market environment. It is explained that internal financing is not an option for these companies and also external financing is often difficult and only available during later stages of the R&D process when final drug approval is foreseeable. However, availability and conditions of external financing are dependent on the existing market environment and sometimes the financing window is closed for multiple year periods. It is also shown that external non-debt financing is not necessarily the fund raising method of choice for young companies because it can lead to an unwanted loss of ownership and control. Public grants represent an exception but their decreasing availability and a focus on late stage financing makes them less available for the majority of young biotech companies. As a conclusion of this chapter it is found that there is a need among young biotechnology companies for innovative fund raising methods, especially during early stages of clinical trials when cash requirements increase significantly.

The subsequent chapter five describes the general concept of how selling option rights on ongoing research projects can theoretically be used for financing purposes. It is demonstrated that from a theoretical standpoint such a concept has multiple advantages for the research conducting company as the option writer as well as for large pharmaceutical companies, which are most likely to act as the buying side of a R&D option deal. The main advantage for the writer is the fact that such a deal does not involve any transfer of ownership in the company and therefore ensures independence from third parties. A second key advantage is the reduced risk related to future cash flows because the expected exercise price and therefore

[468] See Figure 1.5.

the final payoff of the project in case of option execution is already known at the point an option deal is closed. For large pharmaceutical companies the main advantage is the ability to secure access rights on future product innovations with a reduced upfront investment compared to internal R&D. This allows the creation of option portfolios indirectly expanding the buyers' product pipelines, diversifying their development risk and increasing the probability of finding a future blockbuster product.

In addition, the chapter discusses the key risk factors of drug development being technological risk, uncertain market entry timing, unknown product lifetime, general market uncertainty and competition. These risk factors are also investigated in terms of their relevance for the parties involved in a R&D option deal. It is argued that technological risk, the risk of competitive products entering the market and uncertain project timing represent private risk factors that can be diversified by entities owning large research portfolios.

Although selling options on ongoing drug development projects appears to be an attractive financing method from a theoretical standpoint the key question remains as to how much money can be raised through such a financing concept along the various stages of the drug development process. To answer this question, chapter six presents selected option valuation models and their use in the financial assessment of drug development projects representing the underlying asset of the R&D option. The objective of this section is to investigate whether these models can be used to determine the correct price of a R&D option. The four main methods used in financial option theory often transferred into drug development valuation are tree based valuation methods, risk-neutral option valuation following Black-Scholes, compound option techniques and simulation approaches. The investigations in this chapter show that existing option valuation models with the exception of simulation techniques cannot appropriately be applied one to one to the valuation of a R&D option deal. The necessity to establish a subjective valuation approach to approximate the financing potential of a R&D option is shown. Establishing a subjective approach becomes necessary because there is no existing liquid market for R&D options. The price settlement is always the result of individual negotiations between the buying and the selling side of the option agreement and therefore private, non-diversifiable risk factors have to be considered. The application of risk neutral valuation methods is inappropriate because the involved risk factors are not market traded and duplication strategies cannot be applied.

Chapter seven, which represents with chapter eight the largest part of this study, deals with the fundamental question how much money one can expect to raise if a R&D option is sold. It is shown that the final price settlement driven by the willingness of the buying side to invest in the R&D option depends on its ability to diversify private risk factors and the availability of free financial resources. Since the ability to diversify risk and the availability of funds to invest vary between potential buyers it is not possible to determine the one and only correct price of a R&D option. To consider differences between potential buyers the expected price of the option and the related total financing potential is quantified as a range, which is limited by extreme types of investors. The upper limit of the financing range is determined by fully diversified large investors without financial resource constraints for new

investments. On the lower end of the range the limit is set by a one-project investor without any opportunity to diversify private risk and very limited funds to be invested.

In chapter seven the limits of the financing range are quantified step-by-step for a simplified, idealistic environment, which is characterized by a known and constant market potential of a new drug under development and by an absence of competitive forces. The key innovation of this approach is the modeling of the technical risk component of a drug development project by using a continuous failure risk function. Another innovation is the modeling of the expected project duration as a stochastic process instead of using fixed values. An exponentially distributed project delay function is selected after a log-normally distributed project duration approach is discussed and abandoned for modeling project durations.

Eventually a model to estimate the upper pricing limit of a R&D option is built, which cannot be solved numerically. In this model it is assumed that private risk factors are diversified away by a potential buyer and therefore no risk premium is expected as a compensation for this type of risk. In this chapter, a solution to this problem is derived using discrete approximation methods. Based on these results, a second adapted model is built, which quantifies the lower pricing limit of a R&D option in an idealistic market environment. The valuation approach developed in this chapter is demonstrated step-by-step based on an illustrative example of a drug development project.

In chapter eight the valuation approach is expanded into a more realistic view by considering price relevant input factors, which are neglected in the idealistic market view of chapter seven. Additional factors in the realistic model of the upper pricing limit are potential general market trends, unexpected variations in market trends, potential market expansions, influences from competitive forces and a general uncertainty in the initial market estimate for a new drug under development. The resulting valuation model is complex and its solution is approximated by applying Monte Carlo Simulation techniques. Similar to the approach of the previous chapter, a second model is built that includes private risk premiums that cannot be diversified by certain investors to determine a lower pricing limit of the R&D option.

To demonstrate the approach, the case example is adapted to illustrate steps of the valuation approach in the realistic environment. The resulting option value for the illustrative case is higher than the one derived in chapter seven. One of the reasons for this increasing value is the opportunity of a positive market development and a potential underestimation of the initial market potential at the point of project valuation. Since option owners can fully participate in potential upsides but do not have to participate in downside developments, these upside opportunities drive the value of the R&D option.

In concluding, it can be said that in a realistic market environment with a wide range of potential price influencing factors, selling a R&D option can be a tool to raise financial resources. To reach option prices that ensure interesting pricing levels for the R&D option writer, it is preferred to close a R&D option deal with partners able to diversify private risk factor involved in the R&D process to a significant extent. This is especially true during early phases of the R&D process while being less significant in relative terms towards the end of the expected project duration. With the expected R&D option pricing range increasing

significantly during the research process and the maximum benefit of selling to a diversified investor being far into the drug development process, the innovative financing approach cannot be expected to solve young biotech companies' financing problems. It can be considered an alternative financing tool during later stages of the research process because there are indications that selling a R&D option is more attractive during advanced development stages such as phase II clinical trials or later. The innovative idea becomes attractive at later project stages when alternative financing methods such as venture capital, licensing deal or public offerings also become available. With this in mind the practical implementation of selling R&D options on ongoing drug development projects for financing purposes depends more on the different characteristics compared to other financing sources than on its attractiveness at times when other tools are not available.

As a by-product of the conducted study the arguments and conclusions can also serve as an argumentation base for the consolidation within the pharmaceutical industry. Large players with large research portfolios enabling them to significantly diversify private risk will most likely be willing to place the highest bid for a R&D option on an attractive research project[469]. This on the other hand enables them to build even larger research portfolios of attractive and promising projects making them even larger market players with better diversification opportunities in the future. Smaller players on the other hand have difficulties in winning bidding contests against these large players and therefore have to strengthen their research pipeline with fewer and more resource intensive internal projects.

In the concluding chapter nine additional investigations are conducted to analyze the sensitivity of the developed valuation model in a realistic market environment to changes in its input parameters. Four main findings are derived from this section:

1. The positive relation between option value and exercise price of a financial call option also holds true for the R&D option. Despite this straightforward conclusion, setting the exercise price of the R&D option is a sensitive issue because there is a tradeoff between an immediate payment resulting from the option premium to be paid and a future payment that can be expected in case the option is exercised. Additional research on setting the best exercise price is recommended because the future payment at expiration represents the main incentive for the option writer to continue its research activities.
2. As opposed to European financial call options on a non-dividend paying stock, the value of the R&D option does not increase with increasing time to maturity. The opposite is true and the option value decreases as the time to maturity represented by the expected project duration increases. This is caused by the fact that increasing time to maturity decreases the effective patent protection period of a new drug. There are three main reasons behind this difference to financial options:

- The time value of money decreases the present value of future cash flows, the more they are estimated to occur in the future.
- The longer the time to maturity the shorter the time a product can be sold in the market under patent protection and therefore the smaller the total market potential.
- The non-exclusivity of real options allows competitors during the time to maturity to enter the market with a substitute product, reducing the remaining market share for the product under investigation.

3. While increases in uncertainty expressed by the volatility of the underlying stock increase the value of financial options this is not necessarily true for the value of the R&D option. Here it depends which uncertainty parameter is adjusted. While increasing risk of competitive market entry reduces its value, additional uncertainty in the initial market potential or potential project expansions increase the pricing range of the R&D option.
4. Changes in interest rates have a different impact on the pricing range of the R&D option than they have on a simple call option. Hull (2006, p. 362) shows that as interest rates increase so does the value of the call option. With interest rate increases reducing the present value of future cash flows and growth rates for drug development projects not necessarily developing as described at Hull (2006), the R&D option value decreases as interest rates increase.

Table 10.1 summarizes the findings from the sensitivity analysis in comparison to the behavior of a standard European financial call option.

Influencing Factor Call Option	**Increasing factor value causes price of option to …**	**Influencing Factor R&D Option**	**Increasing factor value causes price of option to …**
Exercise Price	Decrease	Exercise Price	Decrease
Uncertainty / Volatility	Increase	Uncertainty in Initial Market Estimate	Increase
		Potential Risk of Competition	Decrease
		Potential Ability to Expand Market	Increase
Time to Maturity	Increase	Time to Maturity	Decrease
Price of Underlying	Increase	Expected Level of Initial Market Potential	Increase
Risk-free Interest	Increase	Discount Rate	Decrease

Table 10.1: R&D option price influencing factors in a realistic environment

[469] They would also be willing to place the highest bid if the project were directly for sale without an option agreement. The direct project sale is equivalent to an option deal with exercise price X=0.

The primary contributions of this study are manifold. First of all an innovative idea is introduced on how young biotechnology companies can theoretically use the sale of option rights on ongoing drug development projects for corporate financing purposes. At the same time the idea represents a way how small companies can, over the sales price of the R&D option, benefit from risk diversification opportunities of large pharmaceutical companies.

The study discusses how misleading a simple one to one application of existing financial option valuation models can be if applied to complex real option situations as the specific case of the R&D option or to the valuation of drug development projects as real options in general. In a real-life environment the value of these options sometimes behaves significantly different than standard financial options. The most obvious example demonstrated in this study is that an increasing time to maturity decreases the value of the R&D option instead of increasing it as one would expect from financial option theory. This is an important finding not extensively discussed in scientific literature. In addition, the finding should be mentioned that not every type of uncertainty increases the value of a R&D option. Certain one-sided risk factors such as technical failure risk or competitive forces can also significantly decrease its value. This is a factor sometimes neglected in studies on real options because real options are often treated as exclusive options, which some of them are not. Including competitive forces as a stochastic process in the option valuation model is a new approach[470] that allows the subjective consideration of a competitive threat on an individual project.

The study also represents the first approach where the technical risk involved in the biotechnological and pharmaceutical drug development process is modeled using a continuous time function for potential project failure. Most other studies on the valuation of pharmaceutical research as real options are based on the idea of discrete risk jumps at predefined decision points. An additional significant contribution of this study relates to the uncertain time to maturity of the discussed R&D option. No other sources are known to the author[471] that include a stochastic model for the uncertain project lifetime into the valuation model of a drug development project as done in the valuation model of this study.

Finally the study represents a valuation approach with a large number of input parameters to assess the value of a real option. Despite the fact that most of these parameters are subjective by nature and bear the risk of over- or underestimation, it is the first model that allows the explicit consideration of all key value drivers of a drug development project. Although the model is quite complex, does not generate the one correct expected sales price for a R&D option and is not necessarily superior to other valuation models with fewer input factors, it forces the evaluating entities to investigate and think about all required input parameters.

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[470] Competition in general and also in relation to real options has been discussed extensively. Examples include Grossman and Shapiro (1987) and Weeds (2002).

[471] In an older study by Fischer, Kay M. (1996, .p 247), the problem of uncertain time to maturity of most real options is still considered an unsolved problem.

These parameters can easily be neglected when simply and incorrectly applying a closed-form valuation equation with few parameters from financial option theory. It is therefore not only the result of the valuation model that generates valuable information for the evaluating entity, but also the way until the model is set up and all input parameters are defined and agreed upon. The process of gathering the required input data itself creates a very comprehensive picture of the existing business situation and the value of a drug candidate under development and the option to be written on it. This knowledge is highly valuable to the practitioner when physically negotiating a R&D option deal.

10.2 Outlook and Future Research

With a study like this, it is unfortunately impossible to cover all relevant aspects of a complex topic like the potential sale of R&D options as an innovative financing instrument. While the focus of this study lies on the introduction of the concept, the verification of the practical need and the development of a subjective valuation model, there are other important issues that require further investigation. There are three areas of future research that can be considered mandatory to reach a final comprehensive assessment of the applicability of the introduced financing approach.

The first area is related to the existing asymmetric information distribution between the writer and the potential buyer of a R&D option. Potential investors in the R&D option face the problem that the research conducting company willing to sell the option possesses information about the underlying project that are not accessible to them. With this information advantage the research conducting company could potentially try to sell options on projects that appear attractive to outsiders but are bound to fail based on internal information[472]. The funds raised could then be used for other projects that are under full control of the research conducting company while the project underlying the option is abandoned and the option expires worthless. This phenomenon is often referred to as adverse selection and was first studied by Akerlof (1970). Spremann (1970) showed for extreme cases that asymmetric information and the related adverse selection problems can eventually lead to an entire market breakdown. Within the market stock IPO, asymmetrical information between investors on one hand and issuers and underwriters on the other hand lead to the so-called underpricing, which is required by investors to compensate them for a potential information asymmetry.[473]

The existence of this phenomenon might have a significant impact on the potential implementation of the R&D option concept. In this context of asymmetric information it also needs to be investigated to which extent the prospect of receiving an exercise payment is a sufficient incentive for the research conducting company to pursue and complete the work on the ongoing project the option is sold on. How the exercise price should be selected to satisfy the interests of both parties involved in a R&D option deal appears to be the central question. On the one hand, the selling party can raise more funds short-term by setting a very low exercise price for the negotiating counterpart interested in a higher exercise payment to give the research conducting company the necessary incentive to continue and complete the R&D process and reduce the upfront investment. Setting the exercise price too high might cause another problem depending on the seller's corporate maturity. Assuming a project is completed and final drug approval is granted but the exercise price is set unrealistically high,

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[472] This phenomenon is covered in a general investment environment by Myers and Majluf (1984) or Wohlschieß (1996, p. 10).

[473] Discussions on underpricing and adverse selection in IPOs can be found at Ritter (1984), Ritter (1991) or Michaely and Shaw (1994).

the option owner is not going to exercise his right and the option expires unexercised. In this situation the seller still owns all rights on the product but might not have the capability to market the product and manufacture it to an extent necessary to serve the market. Especially for very young companies with limited capabilities in later stages of the pharmaceutical value chain it appears desirable to set the exercise price in a way that execution of the option right can be expected if the research and development process is successfully completed. These issues around asymmetric information and setting an optimal exercise price should be discussed in an additional study.

The second area of future research with an influence on the attractiveness of a R&D option deal as a financing instrument is more accounting related. It should be investigated how a R&D option deal affects a company's reporting instruments. The manner in which financing deals affect balance sheet and profit and loss statements is a point that deserves additional considerations since these are important tools for companies to communicate with their environment as well as with existing and potential investors. The signaling effect from balance sheet and profit and loss statement changes can be expected to be more significant for the smaller company selling the option than for a larger one expected to act as the buyer for this type of option.

The third and last major area that deserves attention is less economic but more legal by nature. Here it should be investigated how the physical R&D option contract should be structured to give all parties involved in a deal the maximum amount of security. As an example of an issue that should definitely be discussed in this context, one could state the potential abandoning of project activities. It should be defined when and under which circumstances the research conducting company has the right to declare a project as having failed and when it has the right to abandon it before the point of final drug approval and therefore before the maturity date of the option is reached. Another important legal issue is the question if and under which circumstances the option is tradable for the option buyer. There might be a situation where the buyer wants the option right to be tradable and therefore transferable to other market players whereas this might not be in the interest of the research conducting company. Issues like these could be covered in a comprehensive legal discussion on R&D options.

In addition to these necessary areas of future research another study could be initiated in direct succession to the presented study. For the purpose of this study an illustrative case example is defined to demonstrate the developed valuation approach. An additional study could expand this view and try to implement the approach on real-life cases. Here it would be beneficial to determine whether the absence of objectively measurable input parameters represents a critical problem for the implementation of the model. This would then be similar to the critique Copeland and Tufano (2004, p. 92) express for the application of financial option models on real-life problems.

PART IV: Appendices

11 App. A: Deriving a Risk Function from Standardized Failure Risk

In chapter 7.3.3 the risk of failure during a standard drug development project was defined to follow the function (7.9) with t_S being the time after a project was initiated and T_{AS} being the total development time from project initiation until final drug approval.

$$FR(t_S) = \left(\frac{\cos \frac{t_S}{T_{AS}} \pi + 1}{2} \right)^{\frac{4}{5}} \tag{7.9}$$

For the purpose of this study the main reference point in time is not the time a development project is initiated but rather the time a company files for patent protection for a new drug. This point in time is defined as the first time it is possible to sell an option on the R&D option because at that time an intangible asset is created. For standardization purposes it is also defined in chapter 5.3.2 that the time patent protection is granted is equivalent to the point where laboratory research ends and the stage of pre-clinical trials is entered.

Instead of using the failure risk function (7.9), the equation is adapted to a new reference point t representing the time of patent application. In this scenario T_S represents the time between the start of the project and patent application and T_A represents the time between patent application and drug approval. This implies that the duration T_{AS} of a development project can be broken down into the two time periods T_S and T_A expressed by (11.1).

$$T_{AS} = T_S + T_A \tag{11.1}$$

Referencing time to t instead of t_S implies that t is simply a shift by the duration T_S of the first project phase as expressed by (11.2).

$$t_S = t + T_S \tag{11.2}$$

With the new reference point, (7.9) can be transformed into a new function (11.3) representing the technical risk after patent application denoted as TR(t).

$$TR(t) = \left(\frac{\cos \left(\frac{t + T_S}{T_A + T_S} \right) \pi + 1}{2} \right)^{\frac{4}{5}} \tag{11.3}$$

With the known figures for the standard pharmaceutical development process from Table 2.1, the risk of technical failure of the average project at time t after patent application can be rewritten as (11.4).

$$TR(t) = \left(\frac{\cos\left(\frac{t + T_S}{T_A + T_S} \right)\pi + 1}{2} \right)^{\frac{4}{5}} = \left(\frac{\cos\left(\frac{t+3}{14} \right)\pi + 1}{2} \right)^{\frac{4}{5}} \quad (11.4)$$

Equation (11.4) only holds true for the average drug development project but does not yet fulfill the requirement from chapter 7.3.3.1 that the standardized technical risk function has to be dependent an expected time of final drug approval $E(T_A)$, which can vary depending on the type of project investigated. When tailoring the standard risk function to any project with an expected time of approval $E(T_A)$ it is known that the new standardized technical risk function TR(t) has to fulfill the following two conditions introduced in chapter 7.3.3.1.

Condition 1:

$$TR(0) = FR(3) = \left(\frac{\cos\left(\frac{3}{14} \right)\pi + 1}{2} \right)^{\frac{4}{5}} = 91.2\% \quad (11.5)$$

Condition 2:

$$TR\left(E\left(T_A\right)\right) = 0 \quad (11.6)$$

It is assumed above that the risk pattern of any new project investigated is independent from its actual time to patent application. $E(T_S)$ is introduced as the calculatory time between the real start of the project and the time of patent application. Keeping the two conditions described above in mind, $E(T_S)$ needs to be defined as (11.7) for the new function to follow the standard risk pattern.

$$E\left(T_S\right) = \frac{T_S * E(T_A)}{T_A} \quad (11.7)$$

Equation (11.4) can now be rewritten to fit any development project. This adapted technical risk function is expressed by (11.8).

$$TR(t) = \left(\frac{\cos\left(\frac{t + E\left(T_S\right)}{E(T_A) + E(T_S)} \right)\pi + 1}{2} \right)^{\frac{4}{5}} \quad (11.8)$$

Substituting $E(T_S)$ with (11.7) finally leads to equation (11.9) representing the technical failure risk function used throughout this study.

$$TR(t) = \left(\frac{\cos\left(\frac{t + \left(\frac{T_S * E(T_A)}{T_A} \right)}{E(T_A) + \left(\frac{T_S * E(T_A)}{T_A} \right)} \right) \pi + 1}{2} \right)^{\frac{4}{5}} = \left(\frac{\cos\left(\frac{\frac{T_A}{E(T_A)} t + T_S}{T_A + T_S} \right) \pi + 1}{2} \right)^{\frac{4}{5}} = \left(\frac{\cos\left(\frac{\frac{11}{E(T_A)} t + 3}{14} \right) \pi + 1}{2} \right)^{\frac{4}{5}}$$

(11.9)

12 App. B: Comparison of One- and Two-Exponent Failure Risk

In chapter 7.3.3 a one exponent formula is used to describe standard failure risk for a drug development project. The equation is of form (7.6) with $t_S \in D_{tS}$, $D_{tS}=[0;T_{AS}]$ and $\gamma \in R_+^*$.

$$FR(t_S) = \left(\frac{\cos \frac{t_S}{T_{AS}} \pi + 1}{2} \right)^{\gamma} \tag{7.6}$$

In this equation the single exponent $\gamma \in R_+^*$ alters the function as visualized in Figure 12.1 for multiple different exponent values.

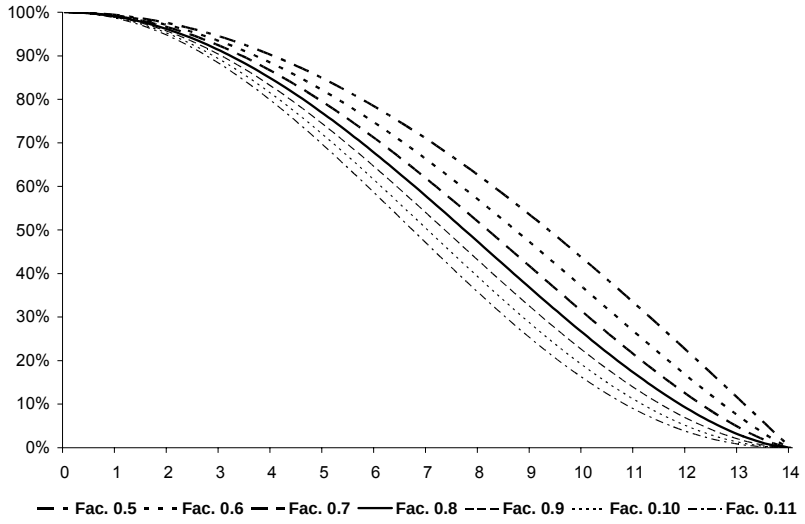

Figure 12.1: Visualization of various one exponent failure risk functions

Alternatively to the single exponent failure risk function it is tested if an alternative two exponent function of the form (12.1) can more accurately model the expected development of failure risk during a project. Equation (12.1) with $t_S \in D_{tS}$, $D_{tS}=[0;T_{AS}]$, $\lambda \in R_+^*$ and $\gamma \in R_+^*$ includes a second exponent to increase modeling flexibility by altering the argument of the cosine function.

$$FR^*(t_S) = \left(\frac{\cos \left(\frac{t_S}{T_{AS}} \right)^{\lambda} \pi + 1}{2} \right)^{\gamma} \tag{12.1}$$

To visualize the impact of the second exponent λ, Figure 12.2 shows various two exponent failure risk functions of form (12.1), keeping the first exponent γ constant at a value of 0.8.

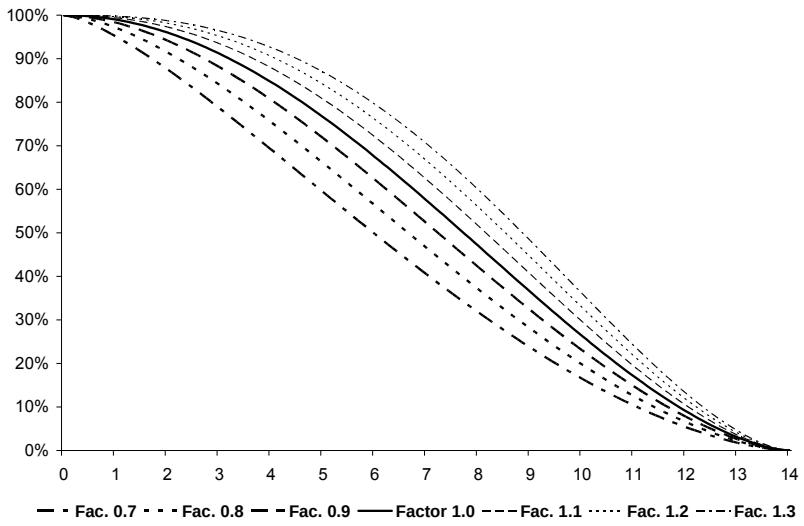

Figure 12.2: Visualization of various two exponent failure risk functions

To check the modeling capabilities of the two component failure risk function (12.1) a relative least squared error check is performed. At this check the two parameters λ and γ are selected in a way that minimizes the following relative error function $Q^*(\lambda;\gamma)$. Similar to (7.8), $\overline{FR}(t_{Si})$ represent the actual failure rates listed in Table 5.1 and displayed in Figure 7.6.

$$Q^*(\lambda;\gamma) = \sum_{i=1}^{15}\left(\frac{\overline{FR}(t_{Si}) - FR^*(t_{Si})}{\overline{FR}(t_{Si})}\right)^2 = \sum_{i=1}^{15}\left(\frac{\overline{FR}(t_{Si}) - \left(\frac{\cos\left(\frac{t_{Si}}{14}\right)^{\lambda}\pi + 1}{2}\right)^{\gamma}}{\overline{FR}(t_{Si})}\right)^2 \qquad (12.2)$$

The relationship between λ, γ and $Q^*(\lambda;\gamma)$ is displayed in Figure 12.3 with $\lambda \in [0.98;1.17]$ and $\gamma \in [0.70;0.90]$. The plot shows a local minimum at Q*(1.12; 0.87).

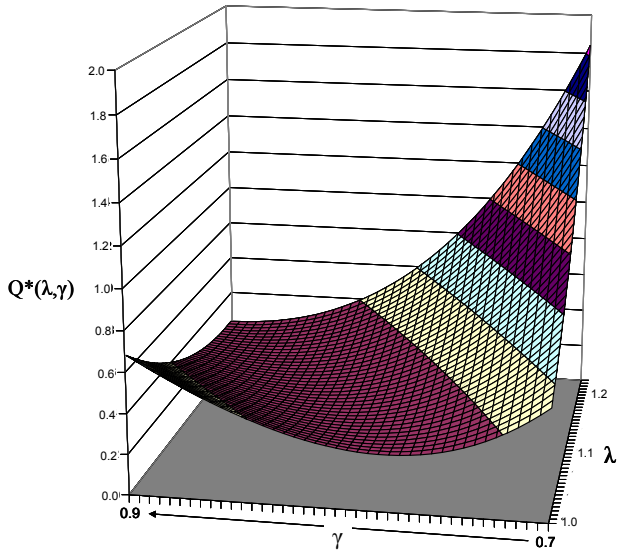

Figure 12.3: Relative error function for two exponent failure risk approximation

A direct comparison of MIN[Q*(λ;γ)] with MIN[Q(γ)] reveals a slight advantage of the two exponent failure risk approximation function over the one exponent failure risk approximation function with Q*(1.12;0.87)=0.23<Q(0.79)=0.26.

Figure 12.4 shows the direct comparison of the path of the one exponent failure risk approximation function and the two component failure risk approximation function.

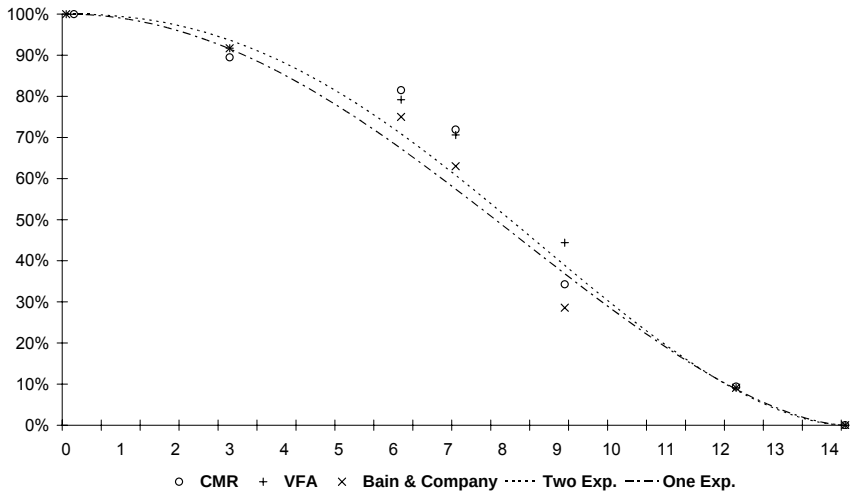

Figure 12.4: Comparison of optimized one and two exponent failure risk function

Because of the relatively small advantage of the two exponent failure risk approximation function and to reduce modeling complexity throughout this study, the one exponent approximation function is used.

13 App. C: Readjustment of Time Dependant Technical Risk

In chapter 7.3.3.1, a formula is derived expressing the probability that a project cannot successfully be completed at a certain point in time t. This technical risk function is denoted as TR(t) with t representing the time after the end of the base development phase of a project.

As time progresses, a real-life project might not exactly follow the standardized path pre-defined by TR(t) and it might become necessary to adjust the technical risk to reflect the individual characteristics of the progress of a specific project. There are three effects that can take place during the course of a project that might require different adjustments to the technical risk formula:

Only the expected time of project completion $E(T_A)$ changes but otherwise the project progress behaves as it does in a "normal" project. The project progress shows irregularities because a project phase can either be completed faster than expected or it is delayed compared to the standard timing defined in Table 2.1 but the research conducting company still considers the end of the project as realistic.

A combination of case 1 and 2 where irregularities in project progress also require the expected completion date $E(T_A)$ of a project to be changed.

All three cases require adjustments to the technical risk formula (7.10) but they are different in terms of adjustment complexity.

$$TR(t) = \left(\frac{\cos\left(\frac{\frac{11}{E(T_A)}t + 3}{14} \right)\pi + 1}{2} \right)^{\frac{4}{5}} \qquad (7.10)$$

Adjustments to this formula can become necessary for different reasons and with different expectations about the future progress of the drug development project. During this section the three different cases introduced above are described, each with a different correlation to the initial project expectations.

Case 1:

If, at some stage during the course of a "normal" project, it becomes clear that the initial assumption $E(T_A)$ for the completion of the project cannot be held, a simple adjustment to the formula has to be carried out. If the project is still expected to be completed in a normal way and with normal progress, the shape of the curve for TR(t) is not changed but rather stretched or compressed over time depending on the new time horizon.

Such a new situation only requires the applied parameter $E(T_A)$ to be adjusted without any other changes to the formula for TR(t). Figure 13.1 shows an illustrative example of an adjustment of $E(T_A)$ during the course of a project. In this example the initial expectation $E_1(T_A)=11$ is adapted at t=3 and remains either unchanged or follows one of the four displayed alternative paths with $E_2(T_A)=9$, $E_3(T_A)=10$, $E_4(T_A)=12$, or $E_5(T_A)=13$.

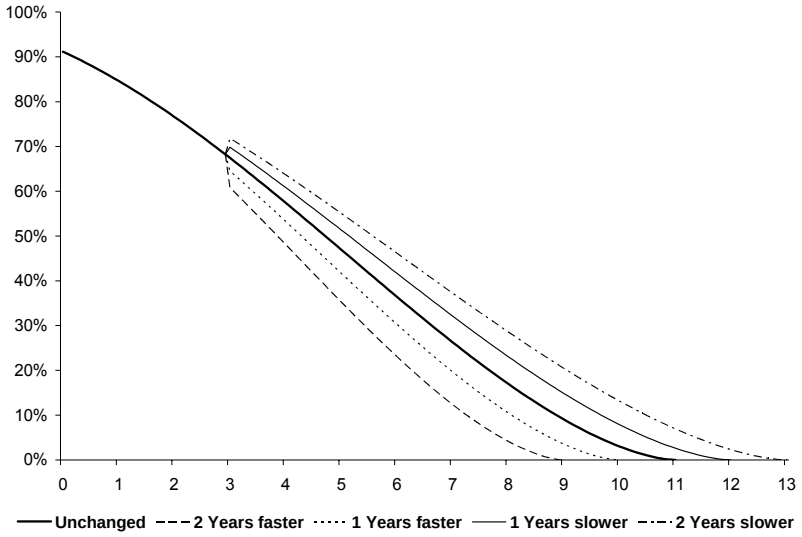

Figure 13.1: Technical risk adjustment for changes in project timing $E(T_A)$

Case 2:

The situation becomes different if, at some time during the course of the project, it becomes clear that the progress is either lagging behind initial expectations or is further advance than expected. At the same time, the expected date for the completion of the project is expected to remain unchanged. Such a situation can arise if more resources are allocated to a project that progresses slower than expected to make up for a delay that already took place. To model such a behavior, changes have to be made to the basic function (7.10) modeling the technical risk of a project.

If the new information requiring the adjustment of the formula arrives at $t=t_{up}$ and the project is off schedule by a delay factor d, (7.10) can be rewritten as (13.1) for all $t>t_{up}$.

$$TR_{up}(t) = \left(\frac{\cos\left(\left(\frac{11-t_{up}}{E(T_A)-t_{up}} \right) * (t-t_{up}) + 3 + t_{up} - d * \left(\frac{E(T_A)-t}{E(T_A)-t_{up}} \right) \right) \pi}{14} + 1}{2} \right)^{\frac{4}{5}} \qquad (13.1)$$

For all $t>t_{up}$, Figure 13.2 illustrates the behavior of the adjusted function (13.1) compared to the initial technical risk function (7.10). Illustrated are two adjustments made at $t_{up}=4$. In the first adjustment the project delay accounts for one year ($d_1=1$) at $t_{up}=4$ with an unchanged expected project termination date. In the second adjustment shown, the project is not delayed by one year at $t_{up}=4$ but rather ahead of schedule by one year resulting in a delay factor of $d_2=-1$.

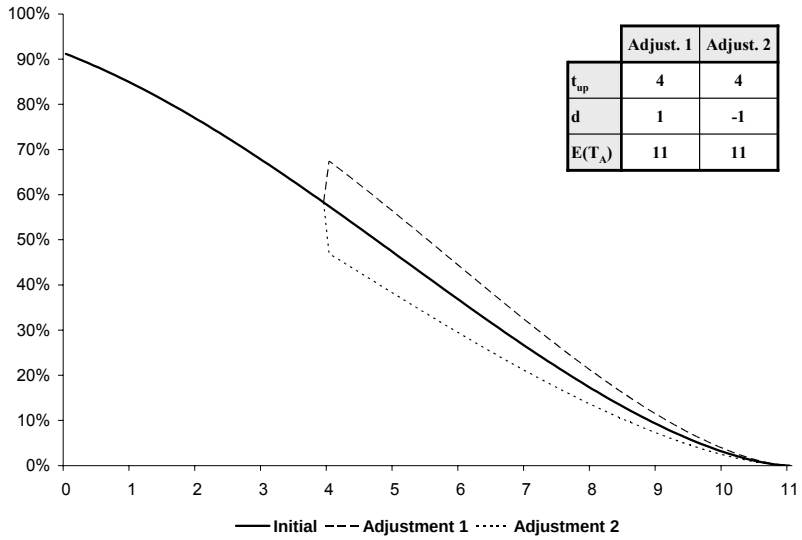

Figure 13.2: Technical risk adjustment - interim risk adjustments only

Case 3:

The remaining case described is a combination of a project delay[474] during the course of a project with a related adjustment in the expected project termination date $E(T_A)$. This type of situation can also be modeled using equation (13.1) for all $t>t_{up}$. Figure 13.3 illustrates two adjusted technical risk functions with an adjustment in $t_{up}=4$ compared to the initial case following (7.10) with $E(T_A)=11$. In the displayed cases the described project is either delayed by one year at t_{up} (adjustment 3) or one year ahead of schedule (adjustment 4). Despite the different project progress at t_{up}, both projects are expected to be completed two years ahead of schedule at $E(T_A)=9$.

[474] Project "delay" can also be an "advance", which is expressed by a negative delay factor d.

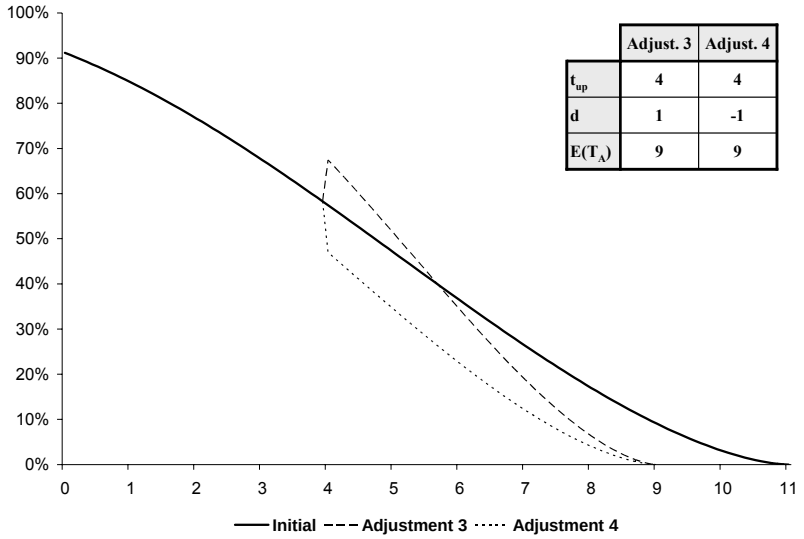

Figure 13.3: Technical risk adjustment - advanced project termination

As a last example Figure 13.4 shows two very similar adjustments as the one in Figure 13.3 with the only difference that the project is not expected to be completed ahead of schedule but rather delayed by two years resulting in the factor $E(T_A)$ to be changed from 11 to 13.

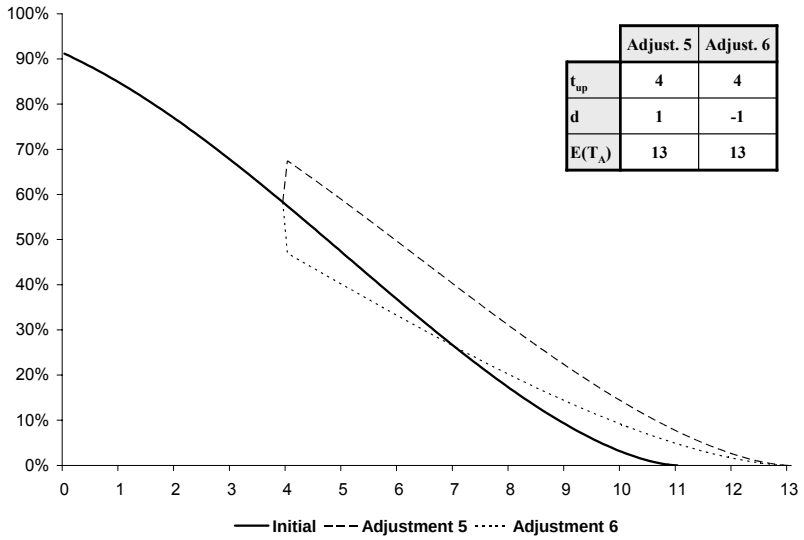

Figure 13.4: Technical risk adjustment - delayed project termination

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