Valuation in Life Sciences

Boris Bogdan · Ralph Villiger

Valuation in Life Sciences

A Practical Guide

With 92 Figures and 77 Tables

Springer

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Foreword

Capital, whether it originates from venture, public equity, private, or government sources, continues to be biotech's source of sustenance. In fact, access to financing can make or break a company, regardless of whether it has Nobel Prize winning science or a top-flight business school management team.

In order to attract capital there has to be a "value proposition" that is sufficiently engaging and well constructed that will not only capture the imagination of investors but also make them want to ultimately invest.

This book recognizes that there is no consent on how to apply valuation methodologies in life sciences. One of the complicating factors is that, compared to other industries, valuation of biotech innovation is much more demanding. The long 10-15-year development and clinical trials process still represents the main risks faced by any biotech company. Added to that is the fact that getting a drug across the regulatory goal line and receiving Food and Drug Administration approval (or other regulatory agency approval in the United States or elsewhere in the world) for marketing is no longer good enough. Since the biotechnology industry is not isolated from the major influences affecting the overall healthcare industry, the reality of de facto healthcare cost controls will mean a significant reduction in "peak sales" for individual drugs. Science will no longer be the deciding factor; payor agents will play a far more activist role via reimbursement criteria, co-payment arrangements and similar rationing technologies. Reimbursement planning starts with clinical planning.

At the dawn of the biotechnology industry, early investors had very few metrics with which to base and compare their investment decisions and valuations of such fledgling companies as Amgen and Genentech were "negotiated events". Investors bought into the hopes, dreams and expectations that the scientists and entrepreneurs were selling.

Fast forward to today and the industry is still extolling those same hopes and dreams that its innovation can make a difference…meet an unmet medical need with a breakthrough therapeutic; create better crops; improve the environment, or protect the population from the threat of bioterrorism.

By and large, the investment community and capital markets has liked what they have heard. For the comparative short 30-plus year history, this industry has attracted almost $400 billion. Capital continues to flow into biotechnology companies at incredible rates and this year alone we predict that a new milestone will be reached for the industry with $40 billion being invested in the United States alone. We have come a long way in a very short space of time.

Those of us who fund innovative, but relatively immature enterprises not only have to recognize the best-in-class companies but also understand how the future will unfold in the light of constant technology change. The maturing industry that is now melding its scientific entrepreneurship with the needs and culture of its larger commercial reality is an ever-increasing challenge. In the early days, the dream of an emerging biotechnology company was to become a fully integrated pharmaceutical company and lever its intellectual property portfolio into a stream of blockbuster drugs.

To demonstrate how dramatically this business model and landscape can change – the focus on a one-size fits-all blockbuster drug is a strategy that may have run its course. The best selling drug of 2020 is somewhere between the bench and pre-clinic trials … but who knows if big Pharma, as we know it, will develop it. The successful companies of the future will be those that marry both molecular diagnostics with targeted drugs and deliver effective personalized therapies. We are witnessing an unprecedented rate of evolution and transformation in the life sciences and healthcare. We are in an era of personalized medicine where the promise is compelling for the future of health care…personalized medicine offers earlier and more precise diagnoses, treatments tailored to the individual, reduction of side affects and adverse reactions to drugs, breakthroughs in treatment, and ultimately prevention of major diseases such as cancer, diabetes and Alzheimer's.

On the other side of the ledger the move to a more personalized, predictive and preventive medicine (the three "P's") world that will revolutionalize the health care system, as we know it today, is challenging pharmaceutical and biotechnology companies alike to adapt. Up until recently, their focus has been on the discovery of blockbuster drugs. Now, with the convergence of IT and genomics, smarter drug delivery and "labs" on a chip are moving us down an inevitable path towards targeted personalized medicines – away from "blockbusterology" – and spotting "early warning" signs of impending health problems. Science is leading into a promising realm of new technologies such as theranostics, responder/non-responder effect of biomarkers, molecular diagnostics and the re-emergence of genomics and proteomics companies in an era of tougher regulations governing the safety of drugs with payors looking to decrease the costs of health care.

Creating a successful and profitable biotechnology enterprise is therefore just as complicated as the genetic and cellular innovations that the company is trying to commercialize. Conservative estimates tell us that a biotech company will need close to $2 billion (according to recent estimates) and at least 12-15 years before any patient receives its novel drug therapy and returns on this massive investment can be generated. Along the way, the company will face many challenges: For its product – numerous and stringent regulatory hurdles; for the corporation – fickle financial markets; product competition; rapidly changing technologies; and difficulties in recruiting and retaining skilled staff. Taking all these factors into account small wonder that the chance of bringing a drug to market is about 1 in 1000!

Thus, as investors, we are taking a chance, it's true, but we view this as a very necessary investment in the future of mankind – and that gives us courage. Also, there is an opportunity for moving the science forward into commercialization, and for creating value. This, of course, requires a tremendous amount of due diligence and dogged research, but those of us who have stayed with this industry for decades know that the effort is well worth it.

While, as investors we have the courage to be part of a better future our investment decisions have to be tempered with reality and on arriving at appropriately calculated valuations of the company's worth … after all investment comes at a price to the entrepreneur. As a long-time investor in life sciences and someone who has been involved in the process of "valuation" for many years this is where the rubber meets the road in the deal making process. Tension on both sides of the negotiation table might be ameliorated if there was one agreed on set of rules about what a piece of technology or biotech companies are actually worth.

The claim is made that the process of valuation in biotechnology is one part science and one part art. I would argue that there is a third essential ingredient, and perhaps the most important, and that is passion. Without it the biotechnology industry, perhaps would never have come into being.

Any assistance that can help us figure out, in a more rational way, the complexity of the "value proposition" will help both communities at the bargaining table reach more realistic valuations is welcomed. A company's value lies in its potential to generate a stream of profits in the future. Profits can be generated from sales of drugs, services but also from upfront, milestone and royalty payments. All valuation exercises are based on determining a company's future, which requires many assumptions such as: the state of the market targeted and the potential share obtainable; the

company's intellectual property and its freedom to operate; third, the ability of management to deliver on the business plan; and fourthly, the absolute size of the financing and what's needed to get to the next value inflection point. There is no "magic bullet" when it comes to valuation and it has remained a "black box" process for even the most seasoned investment professionals.

The authors have, therefore, done an admirable job in setting out a roadmap for valuation in life sciences. They take us from this often times subjective operation to the more rational scientific process. The detailed worked examples are particular helpful in reducing the process into a more practical operation. This text will become a useful addition to the reference shelves of both the entrepreneur and investment professional alike and must reading for anyone contemplating raising investment capital.

G. Steven Burrill, November 2006
CEO, Burrill & Company
San Francisco

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Abbreviations

BLA	Biologics license application
CAPM	Capital asset pricing model
CNS	Central nervous system
CVS	Cardiovascular system
DCF	Discounted cash flows
DF	Discount factor
EMEA	European medicines control agency
ESOP	Employee stock options plans
EUT	Expected utility theory
FDA	Food and drug administration
GIT	Gastrointestinal tract
IND	Investigational new drug
IP	Intellectual property
IPR	Intellectual property rights
IRR	Internal rate of return
MCPM	Market-derived capital pricing model
M&A	Mergers and acquisitions
NCE	New chemical entity
NDA	New drug application
NME	New molecular entity
NPV	Net present value
PDE	Partial differential equations
PMA	Pre-market approval
rNPV	Risk adjusted net present value
ROV	Real options valuation
R&D	Research and development
VBA	Visual basic for applications
WACC	Weighted average cost of capital

Introduction

Valuation is a hot topic among life sciences professionals. There is no clear understanding on how to use the different valuation approaches and how to determine input parameters. Some do not value at all, arguing that it is not possible to get realistic and objective numbers out of it. Some claim it to be an art.

In the following chapters we will provide the user with a concise valuation manual, providing transparency and practical insight for all dealing with valuation in life sciences: project and portfolio managers, licensing executives, business developers, technology transfer managers, entrepreneurs, investors, and analysts. The purpose of the book is to explain how to apply discounted cash flow and real options valuation to life sciences projects, i.e. to license contracts, patents, and firms. We explain the fundamentals and the pitfalls with case studies so that the reader is capable of performing the valuations on his own and repeat the theory in the exercises.

The book is structured in five parts: In the first part, the introduction, we discuss the role of the players in the life sciences industry and their particular interests. We describe why valuation is important to them, where they need it, and the current problems to it.

The second part deals with the input parameters required for valuation in life sciences, i.e. success rates, costs, peak sales and timelines.

The third part outlines the principles of valuation. The reader gets an overview of the essential tools for valuation. The theory outlined lays the foundation of discounted cash flows and real options valuation, the two most common methods to quantify life sciences projects.

The fourth part is the core of the book and guides the reader through theoretical aspects and practical applications of valuation in life sciences. We discuss the differences and the usability of DCF and ROV in valuation of projects, license contracts, technologies, IP, and firms and calculate the case studies in a way that the user can adapt and reproduce them in his own spreadsheets.

The last part of the book contains Excel exercises the reader can use as a template for future valuations.

By the end of the book, the reader should have the knowledge to confidently apply valuation, strengthening his negotiation power and ability to take decisions.

The Life Sciences Industry

Academia

The majority of groundbreaking advances in science come from academic research. Since the universities are in constant lack of funding, a logical step is that they commercialise their research findings. There are two major ways in doing so: First, the scientist himself builds a start-up around his research, or second, the university licenses or sells the rights to the research findings to a third party. In both cases the university gets remunerated for the cession of IP rights, either with an equity stake in a start-up company, or with license payments over several years or even decades. Income from licensed IP, if successfully managed, can mean significant revenues to universities and research institutions. The key figures on licensing at the US universities, hospitals, and research institutions are listed below (source: Association of University Technology Managers (AUTM), 2005):

- In 1992 1229 licenses were executed compared to 4783 in 2004.
- Since 1980, 4543 companies were spun out of US universities, two third of them still active.
- The net licensing income increased from $218 million to $1,385 billion in 2004.

The figures confirm the trend of generating revenues from out-licensing IP. Next to tuition fees, state funding, and private donations, license income has become an important funding pillar for academia.

Biotech

After the burst of the biotech bubble in 2000/2001, the sector is slowly recovering. To the $602 billion global pharmaceutical sales in 2005, biotech companies are estimated to have contributed some 10% or $60 billion. The numbers below show that 2005 was a year of robust growth for the sector (Ernst&Young, 2006):

Table 1.1. New biotech drug approvals in the US

1985	1
1991	5
1995	16
2000	32
2004	40

- Revenues increase by 18% to $60 billion
- Industry net loss (public) decreased to $4 billion
- 32 new product approvals in the US

Products produced by the biotechnology sector ("biologics" = protein based therapeutics) are expected to show a long-term growth rate of 12 – 13% p.a. compared to the 5 – 8% p.a. growth of drug sales in general.

The global biotech financing has increased from under $20 billion in 2002, to over $35 billion in 2005, with the main growth stemming from license revenues and collaborations. Biotech is an essential source of drugs for the pharmaceutical industry. Apart from the rise in partnering revenues, the global venture capital investments into the biotech sector hit a new record high in 2005 with over $7 billion. As the sector starts to ripe, there are more initial public offerings (IPOs), raising $1,831 billion dollars in 2005, up from $251 million in 2002 (Burrill & Company 2005).

Despite the maturing of the biotech sector, the majority of companies is still years away from launching their first product and generating profits and therefore in a constant need for cash. Licensing agreements offer access to immediate cash for biotech and to innovative products for pharma and are likely to grow as a source of revenues for both

Pharma

New drug output, measured by marketing applications for new molecular entities has been on a steady decline since 1995, from 48 to 23 in 2003 (CDER, 2004).

17 years ago, the first drug achieved the US$ 1 billion sales mark (definition of a blockbuster drug); today there are over 60. Companies depend on the sales of an individual branded drug as we have seen with Lilly's loss of Prozac exclusivity in 2001, Bristol Myers-Squibb's loss of Taxol and Glucophage in 2001/2002, and Schering-Plough's loss of Claritin ex-

clusivity in 2002. Analysts forecast that pharmaceutical revenues could fall US$ 40 billion short of investors' expectations by 2007 due to patent expiries. More conservative estimates of drug sales lost to generics due to patent expiry range from US$ 7 billion in 2004 to US$ 17 billion in 2007 (Lehmann Brothers, 2003)

Several factors have caused a decline in R&D output in the pharmaceutical industry (Ma et al. 2004). First, drug discovery has relied much more on new genomic screening strategies in the recent past. A myriad of new targets have been found this way, but these targets are not clinically validated and thus have a much higher failure rate than existing targets. Zemmel and Ma estimate the success rate of validated targets to be 50% higher. Second, regulatory obstacles are increasing. Recent scandals like Vioxx force the FDA to review their approval policy and will most likely lead to tougher regulatory requirements, finally increasing the cost of drug development. Third, the landscape in drug development is changing. Treatments are getting more efficacious and numerous. With more than 5,000 companies in drug development to date, competition is fiercer; it requires better drugs to build a successful pipeline today than 20 years ago. Companies who missed the train struggle to get back on track.

The pharmaceutical sector has belonged to the most attractive industries over the last decade with yearly growth rates over 10%, but at present growth is slowing down. As the US, Europe, and Japan fight with rising health care costs and an increasing debt burden, the pharmaceutical industry experiences much more price pressure and will hardly be able to maintain current growth rates. On the other hand, new markets are opening up. India and China offer a population of more than 2 billion persons. Enforcement of patent laws will allow fast growth in this area.

In the future, Biotech will play an essential role in fuelling the pipeline of big pharma. According to Ernst&Young, 66 biotech–pharma mergers took place in Europe in 2005 alone (Ernst&Young, 2005). The trend of in-licensing products from biotech and acquiring attractive companies will strengthen and might reach a point where, according to Novartis, 50% of the company's products will derive from licensing.

Valuation

The Role of Valuation

Today, most academic institutions have an office for technology transfer, but only few of them possess the abilities to negotiate sustainable license

income. The standard way to value a project relies on experience and gut feeling; often the first best offer is accepted. Later, when the project proves to be better than anticipated, the university tries to renegotiate deal terms. With simple and small deals this is negligible, but once a university starts to handle large contracts, small mistakes in the legal and financial structure of the deal mean a difference of millions of dollars to the university.

Research institutions with a long-standing licensing experience often have capable people with sound knowledge on valuation and deal structuring in their technology transfer office. These institutions succeed in generating a respectable share of their research funding through licensing; other institutions of similar size, but with inexperienced personnel, do not make hardly any money with their inventions.

But even experienced licensing staff struggles to attribute the right value to a complicated license contract, as the contracts often include options and sublicensing clauses. The valuation is demanding and can only be performed using advanced methodologies, as we will show later. Nevertheless, a clear understanding of the basics of valuation helps to value most of the license contracts with a rational framework and generates a sound negotiation position for universities.

Biotech is often academia's counterparty and must therefore be able to value the same contracts. In the following situations, biotech has to deal with valuation:

- Fund raising
- Licensing
- Portfolio management
- M&A

Biotech often faces the question of the company's value. When seeking to raise funds, as every biotech does, it has to be sure how much stake to give away in return of cash. Venture capitalists are tough partners in negotiations; a sound idea of the own company's value is the prerequisite for the founders to keep a respectable stake in the company.

Licensing is the second situation where valuation plays a central role for biotech. Dealing with big pharma, biotech has to know the value of its compounds. While big pharma has experts for valuation and negotiation, in the biotech company the same person is in charge of fundraising and finding licensing partners. As these deals are vital for biotech, the company's management should not underestimate the importance of valuation. Pharma will not start negotiating without a solid valuation, based on thor-

ough due diligence, showing the leeway of the negotiations; Biotech should follow that example.

The third application of valuation to biotech is portfolio management. For advanced biotech companies, knowing which projects generate value, and which do not, is key to success. In this regard, we should mention that those companies that only have one product in their pipeline do not need to value it. Abandoning the project would mean closing the company. M&A and IPOs are usually a smaller problem for biotech. Normally by that stage, companies have their advising investment bank performing the M&A and the IPO. But even an experienced investment bank does not guarantee the right valuation. The executive management of the biotech should at least understand and agree on how the bank generated the proposed value.

Pharma, most often negotiating with biotech, encounters valuation in the same situations as biotech, sitting on the other side of the negotiation table. While biotech, being a young industry, often does not have the capabilities in valuation, pharma has its licensing, business development, or M&A team with all the necessary skills.

Current Problems in Valuation

At present, there is no consensus on how to apply valuation in life sciences. Due to inconsistent description and application of the different methods and input parameters, people feel insecure when applying valuation. Compared to other industries, valuation in life sciences is more demanding due to the inherent complexity and length of R&D. Main concerns are the choice of the right valuation method, the methodology itself, the input parameters and the interpretation of the results.

Valuation methods and methodology. There are two major quantitative valuation approaches applied in the sector, DCF and real options. While DCF has been the gold standard for years, real options valuation is gaining grounds and is regarded as a possible alternative in life sciences. Both methods have their advantages and drawbacks. DCF, when applied to early stage projects, generally yields negative values; nevertheless the industry is profitable. Consequently, managers do not trust their valuations and disregard the recommendation retrieved from the valuations. Projects in early development are continued despite their negative DCF values. Often this translates into a general refusal of quantitative methods. As soon as it comes to licensing and M&A, the companies urgently need a valuation method that displays the correct value of early stage projects.

Real options valuation on the other hand has been developed to overcome the shortfalls of DCF. It is still regarded as too complex and highly theoretic, compared to the easy to use DCF method. Today, there is no standard on how to apply the method to life sciences valuation. A multitude of different explanations and forms of real options do not facilitate its acceptance. This is partly attributable to the often repeated claim that real options should be treated like financial options. In fact, real options are just an expansion of DCF taking into account real flexibility of the management. The inappropriate use of the Black-Scholes formula, the discount rate, or the volatility are a root for disagreement on real options and hinder a broader use of the method. Too many eye-catching but apparently wrong case studies severely harmed real options valuation's image. Properly understood and applied, the method represents the reality much better than DCF does, assuming that estimated input parameters for the valuation can change over time and that the management can react to this. We will discuss the advantages and pitfalls of both methods in the life sciences sector and propose when and how to use DCF or real options.

Input parameters. Apart from the problem of using the right methodology, there is no consensus on how to define the essential input parameters in life sciences valuation. Mainly four parameters are problematic:

- Discount rate
- Costs
- Success rate
- Peak sales

The discount rate is not only a problem in life sciences; it is also a problem in valuation in general. It is the most important input factor with extreme impact on the valuation results. Unfortunately, the discount rate is to a large part not observable and relies mainly on theoretic models. Past and present methods to assess the discount rate have failed to generate consistent numbers. The CAPM, which has served as a basis for the determination of the discount rate for almost five decades, does not deliver usable results for most life sciences companies. Moreover, it is of no use for early stage companies, not publicly listed. New methods like the market derived capital pricing model (MCPM) have evolved, but again do not yield applicable results in life sciences. We will outline alternative methods to define the discount rate.

The second parameter posing difficulties are the costs. People not involved in everyday valuation will find it difficult to estimate the right costs of clinical trials and preclinical research, as well as of the post approval phase. There are useful public sources for industry data that are often not known. Problematic is furthermore the differentiation between costs for small companies like early stage biotech and costs for big pharmaceutical companies. A thorough discussion of the essential numbers for the life sciences sector will equip the user with a set of numbers for life sciences valuation.

The success rates, like the discount rate, have a tremendous impact on the valuation. Success rates and discount rates deal with risk and how to account for it in the valuation. People struggle with quantification of risk. The success rates need to be carefully chosen and adapted to the different valuation methods and sectors. A special chapter will explain in detail the success rates and the implications on DCF and real options valuation.

Peak sales, like the costs and the success rates, are a major value driver in the valuation, but hard to estimate. The assessment of sales potential for a product ten years from market is most often not more than a good guess. There needs to be a consistent way in how to define the sales figures, that unfortunately does not exist today. The reader will learn how to handle situations where peak sales are not predictable and practically apply the theory to the case studies.

Interpretation of results. Because of the above-discussed pitfalls, valuation results are not considered reliable and are not comparable. Ideally, valuation should yield reproducible numbers with the different methods allowing the user to base decisions on the outcome. Today this is not the reality. The case studies will instruct on the significance of the results and the sensitivity of the valuations on manipulation of input parameters.

The goal of the book is to serve as a roadmap for valuation in life science. The reader will know when to use the different valuation methods, how to choose the right input parameters, and most importantly, the reader will understand how to use the valuation results.

The reader can use the book to learn the fundamentals without prior knowledge in finance, valuation, or life science. Valuation professionals can focus on the theoretical and practical part to deepen their existing expertise and to practice. The book includes advanced chapters for professionals seeking advanced modeling concepts. These chapters should fuel new ideas in the industry.

Fundamentals in Life Sciences

In the following chapter the reader learns more about the data required for valuation in life sciences companies. We first discuss drug development and then medical device development. The chapter shall serve as a reference for those readers not familiar with life science. For reasons of clarity, we have not included all publicly available data, but have generated a combination the user can apply to valuation.

Drug Development

Drug Discovery

Drug discovery following basic research can in most cases be broken down into four phases: Target identification, target validation, lead identification, and lead optimisation. In the following we briefly describe each phase for those readers not familiar with the topic.

Target identification: Biological research studies the basic cellular processes in the healthy and pathologic state. By comparing these states, disease responsible actors are identified as possible drug targets. These targets are mainly proteins, such as cell surface receptors. Once a target has been selected, its interacting partners, biologic, and biochemical function is examined. A disease model is then set up and studied. Cultured human cells or animals such as mice serve as model.

Target validation: In search for the suitable target, each target for a given disease is compared to others and its potential in regulating biologic processes is assessed. The most promising targets are selected for further drug development.

Hit identification: In the next step, compounds acting on the selected target and leading to the looked-for change are discovered and characterized. Usually large libraries consisting of thousands to millions of molecules are used. Compounds interacting with the target, leading to the looked-for

change, are selected, if present in the library. The identified compounds are called leads.

Lead optimisation: Lead optimisation is the stage during which medicinal chemists attempt to improve primary leads to achieve the best compromise between improved activity, bioavailability and safety. Often during this same stage of development, lead prioritisation studies are conducted in living organisms (in vivo) and in cells in the test tube (in vitro) to compare various lead compounds and how they are metabolised and affect the body. Once the optimised lead is chosen, it is taken to the last stage prior to human testing, the preclinical studies.

Clinical Trials

Preclinical Testing: Once a lead compound is selected, its safety has to be tested in animals before human testing takes place. Preclinical tests in animals are designed to study the effect of the drug and its metabolites in the living organism. Toxicity, metabolic pathways, and excretion are studied in detail. Preclinical studies are needed to see if the drug can safely be tested in humans, or if it causes dangerous toxicity. Due to the poor predictive value of current animal model, previously elaborated hypothesis on the mechanism of action often fail in this phase. It might be necessary to reformulate the drug, costing a lot of time.

When preclinical testing is done, several drugs that seemed promising are abandoned; the further development is stopped due to problems of poor absorption, toxicity or simply because the drug doesn't work.

Clinical phase 1 trials: Phase 1 is the first phase of drug testing in humans. Phase 1 is conducted in a small group of healthy volunteers (20-80) and is designed to evaluate safety, dose range and side effects. The same questions as in preclinical testing are now assessed in humans. Absorption of the drug (bioavailability) into the blood stream is studied, as well as the mechanism of action in men. This involves the assessment of biochemical and physiological effects of the drug, including the correlation of action and effect of the drug with its chemical structure. Furthermore, the safety profile of the drug is monitored and side effects are carefully studied and documented. A license, which is granted upon study of preclinical data, is required to start human drug trials. In the USA the Federal Drugs Agency (FDA), in Europe the European Medicine Controls Agency (EMEA) is responsible for approval of human testing. In the US prior to starting human

clinical trials, an investigational new drug application (IND) must be filed to the FDA. Only if the IND is approved, clinical trial can start. In most countries, an independent committee, periodically reviewing results to ensure proper conduct and respect of ethical issues, monitors human trials. If the drug shows no serious side effects and no toxicity, it can be taken to phase 1I trials. Phase 1 trials are often the endpoint for new drugs, as many fail to meet the expectations in men.

Clinical phase 2 trials: In phase 2 trials, the drug is studied in a group of people (100-300) having the disease to be treated. Clinical phase 2a studies are small studies to define the dose; phase 2b studies are designed to prove effectiveness. The goal of phase 2 trials is to show the proof-of-concept of the drug, i.e. that it is effective in the treatment of the target disease. Nevertheless, pharmacodynamics and pharmacokinetics need to be assessed again, as the drug effect might differ in the patient group from healthy volunteers. Special attention is needed in patients with impaired renal or liver function concerning the accumulation of the drug or its metabolites. Another factor to be considered are the interactions between the drug under investigation and concomitant medications. In this stage, the drug might not show the wished effects in the patient group, which may mean the drug has to undergo modification or reformulation. However, in addition to all the absorption and excretion questions the drug also has to demonstrate a clear efficacy in the target patient group. New drugs often do not show a clear benefit over existing treatments in terms of efficacy, safety or delivery and will therefore have less chance to be approved by regulatory authorities and fail when marketed. Thus, most companies decide not to continue to develop a drug with poor efficacy at this point in testing.

Clinical phase 3 trials: If the drug looks promising at this stage, it is taken forward to large-scale phase 3 trials. The drug is tested in a large group of patients (500-20,000) with the condition to be treated. The main aim of this phase is to confirm the effectiveness of the treatment, to disclose any side effects, and to establish the right dosage for the future patient treatment. Questions to be answered are how effective the drug really is, whether it is more effective than other competing treatments on the market, and finally how should the patient labelling be.

Approval Phase: A company files a new drug application after successful clinical trials. The FDA or EMEA reviews the data and decides if the company is granted a marketing approval. Possibly, the regulatory author-

ity asks for further clinical trials or even rejects marketing approval. The time for reviewing the drug ranges from 1 to 2 years.

Phase 4 trials: Phase 4 trials are conducted after the drug has been launched. These trials give more information about long-term safety and efficacy of the drug. Alternative formulations, different dosage or new patient populations are tested.

Value Drivers

Cost

In a recent study on the cost of drug development, DiMasi et al. estimate that it costs US$ 802 mn (year 2000 dollars, capitalised costs) to bring a new drug on the market (DiMasi et al. 2003). This figure includes all costs, including drug failures, and is a capitalised instead of discounted perspective. Therefore, it is not appropriate as a starting point to estimate future expenditures in drug development. We cannot assume that a small biotech company will spend a couple of hundred million dollars to finally bring a drug to market. In the following, we will discuss the costs of drug development in more detail based on real life figures.

Lead optimisation: The costs for lead optimisation are very variable and depend on the size of the company. A smaller company spends US$ 0.5-6 mn (average US$ 2.5 mn), while large pharmaceutical companies spend US$ 3-8 mn (average US$ 6 mn).

Preclinical costs: The preclinical costs are again highly variable and depend as well on the company size. Small drug development firms spend US$ 1-9 mn (average US$ 3 mn), while the big pharmaceuticals spend 5-11 mn (average US$ 7 mn).

The costs for the clinical phases encompass all necessary expenses to conduct the trials, including project management, drug supplies, toxicology, investigator fees, or study design. The costs outlined below are an average and vary according to the different disease groups, as certain studies are inherently more complex than others. Nevertheless, the costs are a good approximation to be used for the purpose of the valuation. Adjusting the patient number per phase for the different disease groups allows getting a more precise estimate of the costs. The costs furthermore represent a full clinical trial investigation. It is possible to conduct all those trials at less cost. Also, the costs for big pharma are higher than outlined below. DiMasi

can be used as a source for big pharma drug development costs. His figures are not representative for young companies. A rule of thumb proposes that the drug development costs for biotech are a factor five smaller than what big pharma spends for the same phase.

Clinical phase 1 costs: The costs for an average phase 1 trial based on 100 patients excluding drug supply and non-clinical costs amounts to US$ 2 mn. If we include all costs, the expenditures for the phase 1 are US$ 4-5 mn.

Clinical phase 2 costs: Phase 2 costs for clinical expenditures are US$ 7-8 mn, and US$ 10-11 including non-clinical costs. This number is based on a trial with 300 patients. Smaller phase trial may cost less than $ 5 mn.

Clinical phase 3 costs: The clinical phase 3 is the most expensive phase as it involves the largest number of subjects. Average costs range from US$ 10-50 mn for the clinical trial costs and US$ 30-60 mn including non-clinical costs.

Approval costs: The approval cost including submission in the US and Europe are in the range of US$ 3 mn.

The table below summarises the complete drug development costs for a small to medium-size biotech/pharma company. Of course, these costs can vary considerably. The data below is therefore only a rough estimation what a complete clinical trial programme could cost for an average drug (Source: Avance).

Table 2.1. Drug development costs

Phase	Cost
Lead Optimisation	US$ 2-3 mn
Preclinical Phase	US$ 2-3 mn
Clinical Phase 1	US$ 1-5 mn
Clinical Phase 2	US$ 3-11 mn
Clinical Phase 3	US$ 10-60 mn
Approval	US$ 2-4 mn

Success Rates

Even though the pharmaceutical industry has a long-standing history of drug development, the numbers describing the success of the projects are well kept and not accessible. There are a number of publications on the

topic, most of which derive from the TUFTS Centre for the Study of Drug Development and which base mainly on data provided by big pharma.

The success rate is the chance that a project entering a development phase reaches the next phase. Success rates are assessed per phase and, once the drug is in clinical development, depend on the disease group. There are also major differences between the success rates of chemical and biological drugs.

The success rates for lead optimisation are 70%, and 65% for preclinical development for the average drug, independent of the disease group.

Combining the different publicly available publications on success rates, we get the following numbers (DiMasi 2001, Kola 2004, Avance).

Table 2.2. Drug development success rates

Disease Group	CP 1	CP 2	CP 3	Approv	Cumul.
Arthritis/Pain	76.9%	38.1%	78.1%	89.1%	20.4%
CNS	66.2%	45.6%	61.8%	77.9%	14.5%
CV	62.7%	43.3%	76.3%	84.4%	17.5%
GIT	66.8%	49.1%	71.0%	85.9%	20.0%
Immunology	64.8%	44.6%	65.2%	81.6%	15.4%
Infections	70.8%	51.2%	79.9%	96.9%	28.1%
Metabolism	47.8%	52.0%	78.9%	92.8%	18.2%
Oncology	64.4%	41.8%	65.4%	89.7%	15.8%
Ophthalmology	66.0%	39.0%	64.0%	92.0%	15.2%
Respiratory	63.4%	41.1%	59.9%	76.9%	12.0%
Urology	50.0%	38.0%	67.0%	79.0%	10.1%
Women's Health	39.0%	42.0%	48.0%	59.0%	4.6%

In the table *CP* means clinical phase, and *cumul.* stands for the cumulative success rate from beginning of clinical phase 1 to reach the market. The cumulative success rates in the table correspond to the figures published by DiMasi where available (DiMasi 2001).

The attrition rates for biologicals are at present much lower than for new chemical entities but recent trends indicate that they approach the ones of new chemical entities. We therefore suggest using the figures in the table for the purpose of valuation.

The reasons for failure in drug development have been described by DiMasi (DiMasi 2001). The abandonment for drugs with their first IND filing from 1987 to 1992 happened due to the following reasons:

Table 2.3. Reasons for abandonment of drug development

Economics	33.8%
Efficacy	37.6%
Safety	19.6%
Other	9.0%

The primary reasons to terminate a drug development project are lack of efficacy and safety, both technical reasons, and lack of profitability of the project. The latter reason, accounting for a third of all drug development terminations has important implications to valuation. A prominent example of economic abandonment is Novartis halting the development of NKS104 (pitavastatin) during Phase II trials. We will discuss this in more detail in the chapter on Basics in life sciences valuation.

Novartis Halts Cholesterol Drug Development

Saturday, December 17, 2005 13:00 IST Basel

Novartis has decided to stop the development of NKS104 (pitavastatin), a lipid-lowering agent in phase II for the treatment of elevated total cholesterol, after data from recent investigational trials showed the compound was no longer competitive enough for Novartis to invest further resources. The company intends to seek licensing partners for this compound.

As a result, Novartis intends to record an impairment of USD 266 million in the fourth quarter of 2005 to fully write off the remaining value of this asset. The European rights to this compound were acquired under a licensing agreement from Kowa. Novartis already recorded an impairment of USD 66 million in the third quarter related to the acquired and capitalised marketing rights for NKS104, informs a company release.

Novartis AG is a world leader in pharmaceuticals and consumer health. In 2004, the group's businesses achieved sales of USD 28.2 billion and pro forma net income of USD 5.6 billion.

Source: pharmabiz.com

Time

Drug development time depends like the success rates on the disease group and the chemical/biological properties for the drug. Below is a table summarising the different average phase lengths for the average drug (Source: Avance).

Table 2.4. Duration of drug development

Phase	Length
Lead Optimisation	20-40 months
Preclinical	10-12 months
Clinical phase 1	18-22 months
Clinical phase 2	24-28 months
Clinical phase 3	28-32 months
Approval	16-20 months

Table 2.5. Disease category average sales

Category	Sales
Anti-infectives	US$ 385 mn
Blood	US$ 981 mn
Bones & Joints	US$ 127 mn
Cancer	US$ 488 mn
CNS	US$ 746 mn
CVS	US$ 466 mn
GIT	US$ 792 mn
Inflammatory	US$ 571 mn
Metabolic	US$ 803 mn
Ophthalmologics	US$ 272 mn
Pain	US$ 693 mn
Respiratory	US$ 646 mn
Skin	US$ 98 mn
Urology	US$ 690 mn
Women	US$ 514 mn

Peak Sales

There are different definitions of peak sales. We refer to the maximum sales the drug will reach in its life cycle as peak sales. The peak sales number is the net sales the company makes with the drug.

The peak sales from existing drugs can be clustered into disease group sales. Table 2.5 gives an overview of the most recent average sales for the major disease groups.

Table 2.6. Disease category median sales

Category	Sales
Anti-infectives	US$ 265 mn
Blood	US$ 302 mn
Bones & Joints	US$ 127 mn
Cancer	US$ 344 mn
CNS	US$ 422 mn
CVS	US$ 145 mn
GIT	US$ 299 mn
Inflammatory	US$ 349 mn
Metabolic	US$ 371 mn
Ophthalmologics	US$ 157 mn
Pain	US$ 274 mn
Respiratory	US$ 213 mn
Skin	US$ 69 mn
Urology	US$ 685 mn
Women	US$ 386 mn

The numbers might seem high, but the reader has to keep in mind that first, only the sales of successful drugs are published, second, drugs that do not seem profitable are abandoned during development, third, the average sales are distorted by a few blockbuster drugs lifting the average figure, and fourth, that the sales figures of small population drugs are often not published.

If we want to have a sales figure that does not include the unlikely scenario of reaching blockbuster drug status we take the median sales of the drugs currently on market (cf. Table 2.6).

For early stage compounds, we recommend to use the median sales as an estimate for potential peak sales. This serves as the basis for conservative valuations. If there is a clear sign that the drug might reach the extremes of the sales distributions, i.e. become a blockbuster, the average number can be used as the estimate for future peak sales. At later stages in development, the sales estimate can be calculated in more detail with a bottom-up approach.

Medical Device Development and Approval

Development and Approval in Europe

In the European Union notified bodies (NB) play a similar role for medical device development as the FDA in the US. The NBs are controlled organizations that can review medical devices in development and issue a CE-mark, necessary for certain devices for marketing approval. Once a medical device has obtained the CE-mark, it can be marketed in the entire European Union. In the US, the manufacturer of a class III device (see below) must prove that the device is safe and effective, usually requiring a large randomised prospective clinical trial. In Europe, the manufacturer most show that the device is safe and its use is as intended by the manufacturer. This usually can be demonstrated in a small clinical trial involving less than 50 patients (Kaplan et al. 2004). This major difference between the US and Europe makes it much more costly to receive marketing approval in the US.

Development and Approval in the US

The FDA regulates the medical device development in the US. Devices have different pathways to approval based on their classification:

- Class I: General controls: crutches, band aids
- Class II: Special controls: wheelchairs, tampons
- Class III: Pre-Market Approval (PMA): heart valves (known to present hazards requiring clinical demonstration of safety and effectiveness) – OR – not enough known about safety or effectiveness to assign to Class I or II

Class I devices are the simplest devices, posing the smallest risk and require only general controls.

Class II devices are of moderate risk. They require a 510(k) Pre-Market Notification prior to marketing.

Class III devices are of high risk. They usually require a PMA prior to marketing. There are only a small number of Class III preamendements 510(k) devices in the US. 40 to 50 PMAs are approved each year in the US. If the FDA defines a device as Class III device, that type will always be a class III device, except if the FDA approves a reclassification petition and down-classifies the device. All competitors that develop similar products have to follow the PMA process in order to market their device in the US.

The 510(k) Premarket Notification. A 510(k) application demonstrates that a new device is substantially equivalent to another device that is legally on the market without a PMA. If FDA agrees that the new device is substantially equivalent, it can be marketed. Clinical data are not required in most 510(k) applications; however if clinical data are necessary to demonstrate substantial equivalence, the clinical studies need to be conducted in compliance with the requirements of the IDE regulations, IRB review and informed consent (21 CFR parts 812, 56 and 50, respectively).

The 510(k) process is a relatively rapid and flexible approval process. The goal of the 510(k) process is: "*Demonstration of Substantial Equivalence to a device that was on the U.S. market prior to May 28, 1976, or to a device that has already gone though the 510(k) clearance process."* A PMA device cannot serve as a 510(k) predictive device.

Clinical data might be required to demonstrate substantial equivalence to a predictive device. The trials are in most cases smaller and simpler than most PMA clinical trials.

The Premarket Approval Application. PMA is necessary to market a device that is not substantially equivalent to a device marketed in the US approved under 510(k). The PMA process is more complex than the 501(k) process and the review time with about one year much longer. Unlike most 510(k), a detailed manufacturing section is required. Prior to the final approval of the PMA, the device manufacturing facility must be inspected and approved.

The PMA process includes clinical trial that must meet the following requirements:

- Well controlled investigations
- Partially controlled investigations
- Objective trials without matched controls
- Well documented case histories conducted by qualified experts
- Report of significant human experience with a marketed device from which it can be concluded that there is reasonable assurance of safety and effectiveness of a device under its condition of use.

The vast majority of PMA studies are designed as well controlled studies, with randomised patient groups. International data can be used for the PMA approval if it follows the 21 CFR 814.15 guideline. The study must:

- Have been conducted in accordance with the declaration of Helsinki, or other ethical procedures, whichever is stricter
- Utilise a patient selection similar to a U.S. patient selection.
- Utilise a standard of care and medical practice similar to that in the U.S.
- Must be performed by competent investigators
- Generate data, including source documentation, that are available for audit by FDA.

Data on medical device development is not readily accessible and there are no published success rates, durations or costs for the different types of medical devices. Valuations for medical devices require more work in terms of defining the input parameters.

Basics of Valuation

Introduction

All companies deal with valuation from time to time. Capital budgeting, company and asset valuation, or value based management rely on valuation.

Two approaches are the foundation of valuation, discounted cash flow valuation and relative valuation. The first one is a bottom-up approach where the present value of an asset's future cash flows is calculated, the second determines the value of an asset by comparing it to similar other assets.

While relative valuation is well applicable by common sense, DCF needs considerable understanding of the relevant input parameters. As DCF is a vital approach to valuation in life sciences and the basis of decision tree analysis and real options valuation, it is worthwhile to discuss in detail how the method is properly applied.

We discuss in the following chapters the reasoning behind DCF and how to define the input parameters to value an asset. We also discuss the current problems to this valuation approach, such as the problem of risk and uncertainty, and some methods that try to overcome these problems.

Fundamentals

Cash Flows

The cash flow is, as its name describes, money that flows in or out of a company. Cash flows can be classified into:

- Cash flows from operations: Cash flows from day-to-day, income-producing activities.
- Cash flows from investing activities: Net cash flow from investing activities, defined as divestments minus investments.
- Cash flows from financing activities: Net cash flow from financing activities. Issue of new debt and equity minus repayment of debt, minus equity return, minus payment of dividends.

- Change in liquidity: Liquidity at the end of a period minus the liquidity at the beginning the same period.

The cash flows of a company are presented either in the statement of cash flows or in the accounting statement of cash flows. The latter is useful to see the change in accounting cash and differs from the statement of cash flows mainly in the interest expense. Below is Virtual Corp.'s statement of cash flows for one accounting period:

Table 3.1. Virtual Corporation statement of Cash Flows

Cash Flow of the Firm	('000s)
Operating Cash Flow	$200
Capital Spending	(100)
Additions to net working capital	(50)
Total	$50
Cash Flow to Investors of the Firm	
Debt	$45
Equity	$5
Total	$50

Extracting the valuation relevant cash flows from these statements is not always straightforward. For the purpose of the valuation theory outlined in this book, we will therefore not refer to accounting cash flows such as depreciation or to terms like additions to net working capital. We assume that all investments are immediately depreciated. Nevertheless, the final valuation result remains with both approaches the same.

The essential input for any valuation are the cash flows. We have to identify and estimate all relevant cash flows in terms of:

- Size
- Time
- Probability

Cash flow size. A cash flow is either positive, i.e. a revenue, or negative and therefore an expense, with an absolute size. A negative cash flow is either noted with a negative sign or between brackets, i.e.$ 50 expense is $ – 50 or $ (50).

Time of cash flows. We need to define the time when a cash flow occurs as the time influences the value of money. The discount rate accounts for this.

Probability of cash flows. Once we know the size and the time of a cash flow, we have to estimate the probability of it. A cash flow that is certain has more value than a cash flow that is uncertain.

We will learn in the following chapters, that valuation is the process of defining the cash flows size, time, and probability, the risk adjusting and netting of all relevant cash flows and finally calculating the net present value by discounting. Once we have exactly identified and described all cash flows for the valuation, the major part of the work is done.

Discounting

In valuation we compare cash flows that:

- occur at different points in time,
- are not accurately predictable in their size,
- occur with different likelihood.

The first point alludes to the time value of money, the second to the uncertainty of the estimate, and the third to the risk that the cash flow occurs at all. Discounting takes full account of time value and uncertainty. Probabilities (or success rates in the life sciences context) cover the shortfall risk.

Time value of money. The concept of time value bases on the fact that people prefer a dollar today to a dollar tomorrow. A dollar today has more value than dollar in the future. To keep its value, money must accrete. This value increment is called interest. Somebody investing a dollar in a project wants to get more than the dollar he invested after one year, because he could also have put his money on the bank and earn interest on it.

Interests are generally compounded annually. An interest rate of 5% means that the investor of $ 1,000 earns after one year $ 50 of interest. After another year we earn 5% of the meanwhile $ 1,050, ending up with $ 1,102.50. This example shows that compounding of interests has an impact on the final amount. In the second year, the investor receives not only 5% of the initial amount, but also 5% on the interests he earned in the first year.

We determine the risk free interest rate by taking the yields of treasury bonds of the US or the EURO zone. The risk free interest rates depend on

the maturity of bonds and vary from country to country. Usually, interest rates rise with increasing maturity. In Japan, interest rates are at the moment low (0%-2%), while they are higher in Europe (1%-5%) and in the United States (3%-7%). The numbers depend on the state of the economy in these countries and are subject to fluctuations. For valuation purposes, we will take interest rates of bonds with long maturities, i.e. 10 to 30 years.

Risk. Next to the time value, discounting reproduces the risk of the investment and the willingness of the investor to take risk. We estimate future costs and revenues to a certain degree, but the real cash flow can be higher or lower than our initial estimate. This uncertainty is typical for predictions. However, people tend to dislike under-performance or loss more than they do like over-performance or gain. They are willing to pay a fee in order to avoid any shortfalls. Insurances base their business on this asymmetric attitude called risk aversion.

Discounting must now compensate not only for the loss of value over time, but also for the impending difference between the expected and the actual return. Consequently, uncertain investments should reward the investor at a higher rate than safe investments, as it is more likely that the actual return is closer to the expected return E(R).

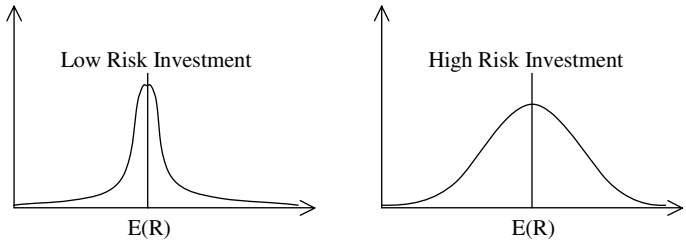

Fig. 3.1. Expected return of assets with different risk profile

The valuation can reflect this increased return expectancy by adding a spread on top of the rate that displays the above-described value loss over time. This spread depends on the uncertainty of the cash flow estimates and can range from 0% up to 20%. Typically, companies use a spread between 5% and 8%.

Discrete and continuous compounding. Discounting is one of the most technical parts of valuation. It is worthwhile to spend some time to get the technicalities right. We differentiate between discrete compounding and continuous compounding. Discrete compounding pays the interests ac-

crued over a period T-t at the end of the same period. With r being the annualized interest rate an amount of money S_T becomes:

$$S_T = S_t \left(1 + r_{dis}\right)^{(T-t)} \tag{3.1}$$

Continuous compounding assumes that interests are paid out and reinvested continuously, i.e. the investor earns at every moment already interests on the interests earned in the previous glimpse of time. Continuous compounding yields therefore a higher interest. After a time period *t* with interest rate *r* the amount *S* becomes, if continuously compounded:

$$S_T = S_t \exp\left(r_{con}\left(T - t\right)\right) \tag{3.2}$$

Unlike interest calculations where we have to calculate an amount we will receive in the future, discounting is used to determine the present value of a future amount. Instead of moving forward in time, we now move backward in time. This leads to the following discrete and continuous discounting methods, *r* being the discount rate:

$$S_t = S_T \left(1 + r_{dis}\right)^{-(T-t)} \tag{3.3}$$

$$S_t = S_T \exp\left(-r_{con}\left(T - t\right)\right) \tag{3.4}$$

Usually interest and discount rates refer to the discrete method, using one year as reference period. The continuous rate r_{con} that corresponds to the discrete rate r_{dis} can be found with the following relationship:

$$r_{con} = \ln\left(1 + r_{dis}\right) \tag{3.5}$$

The Cost of Capital

The discount rate of a firm corresponds to the average rate at which the stakeholders want their capital to accrete. A company has two major classes of stakeholders, debtholders or bondholders, and shareholders. Both require compensation for the risk of their investment into the company. Bondholders typically receive the principal of the bond. Only in the case of default of the company, they can lose up to the full amount invested. The spread of the bond that comes on top of the risk free rate must offset this risk. The spread depends on the likelihood of the company defaulting. Rating agencies like Standard & Poor's, Moody's, or Fitch give their opinions on the trustworthiness of companies. According to these ratings, the return rates of the bonds are determined. These bond returns then correspond to the

cost of debt, i.e. the minimum rate a company must achieve to satisfy the demands of their bondholders.

The rate required by the shareholders is called cost of equity. Unfortunately, this parameter is not observable. Several theories have evolved to determine the cost of equity. After this section, we will present the capital asset pricing model and the market-derived capital pricing model as two representatives.

Once we have determined cost of debt and cost of equity, we can compute the average cost of capital of a company. The debt part of the company must accrete by the cost of debt, the equity part by the cost of equity. An important property of debt is its tax-deductibility. This makes debt even cheaper capital. Taking account of the ratio between bond- and shareholders and the tax advantages of debt the cost of capital, or in this case the weight-adjusted cost of capital (WACC), becomes (with D being the market value of debt, E equity, and T the tax rate):

$$WACC = \frac{D}{D+E} r_D (1-T) + \frac{E}{D+E} r_E \tag{3.6}$$

The capital invested in a project must appreciate at least at the discount rate, otherwise the company cannot satisfy the expectancies of its stakeholders. This is the reason why the discount rate is often called hurdle rate.

Capital Asset Pricing Model

One way to determine the cost of equity is the capital asset pricing model. This model differentiates between diversifiable and non-diversifiable risks. The non-diversifiable risks are generally denoted as market risk, the diversifiable risks as asset specific risk. We assume that there exists a portfolio that is only exposed to market risk, all diversifiable risks cancel each other out. This portfolio is defined by the modern portfolio theory by Harry Markowitz (Markowitz 1952) and optimises the risk-return ratio (Sharpe ratio). The portfolio is called market portfolio. The return of an asset can then be described as follows:

$$r_{asset} = \beta\, r_{market} + \underbrace{\left(r_{asset} - \beta\, r_{market}\right)}_{\varepsilon} \tag{3.7}$$

r_{market} is the return of the market portfolio that is solely exposed to the non-diversifiable market risk. The factor β indicates by what extent the asset is exposed to the market risk. ε then represents the diversifiable part of

the asset's risk. Note that β is chosen such that ε is completely independent of r_{market}, i.e. there is no correlation between ε and r_{market}. Note that r_{market} and ε are random variables and are only predictable to a certain degree.

While an investor can reduce or even avoid his exposure to diversifiable risks by holding a large and well-diversified portfolio, he cannot reduce the non-diversifiable risks. He only must be rewarded for the non-diversifiable part of the asset's risk. The average return the investor therefore claims, i.e. the cost of equity if the asset is a share, is the risk free rate plus a spread on top, proportional to the non-diversifiable risk he accepts to bear. The reward for taking the market risk is called market risk premium. Unfortunately, this measure is not observable and might even be perceived differently by each investor. However, people generally accord that the market risk premium corresponds to the excess of the market portfolio over the risk free rate, $\hat{r}_{market} - r_f$, where $\hat{r}_{market}$ denotes the average return of the market portfolio. $\hat{r}_{market} - r_f$ is exactly the reward the market pays for bearing the market risk. Consequently, the cost of equity an investor claims for an equity investment is:

$$r_E = r_f + \beta \underbrace{\left(\hat{r}_{market} - r_f\right)}_{market\ risk\ premium} \tag{3.8}$$

It remains to define the parameters r_f, β, and the market risk premium. The risk free rate should not pose major problems. For the market risk premium one can use the historic excess performance of the market portfolio compared to risk free investments. Unfortunately, the theoretic market portfolio is not known, therefore we don't know $\hat{r}_{market}$ either. A generally accepted bypass is to assume an index as the S&P 500 or FTSE100. $\hat{r}_{market}$ then becomes the historical performance of the chosen index. Finally, we have to determine β. This measure is defined by:

$$\beta = Corr\left(r_{asset}, r_{market}\right)\frac{\sigma_{asset}}{\sigma_{market}} = \frac{Cov(r_{asset}, r_{market})}{\sigma^2_{market}} \tag{3.9}$$

Hence, β equals the correlation between the returns of asset and market multiplied with the ratio of their volatilities. A correlation of zero means that the asset is completely independent of the market portfolio and has no market risk component, consequently the β is zero as well. A correlation of one on the other hand means that the asset fluctuates in exactly the same way as the market portfolio, a correlation of minus one means that the asset moves exactly opposite to the market.

Drawbacks of CAPM. The CAPM method is the most widely used way to determine the cost of equity. However, it has major flaws. First, it relies to a great extent on the knowledge of the market portfolio. The market portfolio is the portfolio that maximises Sharpe's risk-return ratio in the universe of all possible investment opportunities, including not only equity and debt markets, but also commodities and illiquid and not transparent markets such as real estate, private equity, art, or even wine. Nobody knows the market portfolio; therefore, we cannot use it as a reference for calculation purposes.

Second, all measures in the CAPM are prospective. The β and the risk premium relate to the future. The β of an asset is a notoriously unstable parameter. Historic and future β do not have to be identical. Even historical β depend strongly on the chosen observation period. This instability renders the determination of the cost of capital arbitrary. Often it is possible to achieve any cost of capital simply by choosing an adequate observation period for β and the market risk premium.

Third, β intentionally captures solely the non-diversifiable part of risk. The argument goes that the investor can diversify and is therefore not rewarded for diversifiable risks. However, very few investors would agree with this, and especially within the private equity universe, investors have large parts of their fortunes invested in one single company, effectively impeding a sufficient diversification. Furthermore, the company or asset specific risks have an impact on the business of the company. It is little consolation for a company and its investors facing financial distress that the risks causing this situation are diversifiable and therefore should not have been included in any valuation anyway. Diversifiable risks can have significant impact and should therefore be included in the valuation. This is particularly true for life sciences companies as we will see further down.

Market-Derived Capital Pricing Model

The market-derived capital pricing model (McNulty et al. 2002) tries to overcome the major flaws of CAPM. First, it does not rely on an unobservable risk factor like the market portfolio. Second, MCPM uses explicitly prospective and observable parameters, and avoids reliance on arbitrarily measured parameters like β. Third, and most importantly, MCPM accounts for all risks of a company, whether they are diversifiable or not, trying to reflect better the risk perception of managers and investors.

The fundamental idea of MCPM is that shareholders should at least earn the cost of debt. We assume that shareholders insure this rate of return with a put option. The cost of equity then equals the cost of debt plus the

annualised cost of the put option. As a consequence of this definition, the cost of equity depends on the time horizon. The put option has the forward price of the share at the cost of debt as strike price.

$$r_E(T) = r_D + \frac{put\left(1,(1+r_D)^T,T\right)}{\frac{1}{r_D} - \frac{1}{r_D(1+r_D)^T}} \tag{3.10}$$

The put option uses 1 as the value of the underlying, the forward price $(1+r_D)^T$ as the strike, and T as maturity.

In many cases, MCPM yields intuitively better results than CAPM. MCPM however is not free of problems. First, the requirement that shareholders should be able to insure a return that is equivalent to the cost of debt lacks a stringent argumentation. Why should shareholders be able to avoid the downside while keeping all the upside? Second, the put option uses a prospective or implied volatility. This is only applicable if options are traded, i.e. when the company has already a respectable market capitalization. For smaller or even unlisted companies the prospective volatility is a very delicate measure. Unfortunately, the cost of equity is relatively sensitive to this parameter. Third, the cost of equity depends on the chosen time horizon. The authors calculate with a time horizon of five years, however, it is not clear how this is determined.

While being an interesting and in many cases plausible alternative to CAPM, MCPM is difficult to apply to small companies. Furthermore, the diversifiable risk is included in the cost of debt and the volatility, leading to some double counting and consequently to a too high cost of equity. As a remedy, one could use the risk free rate instead of the cost of debt.

Uncertainty

Cash flows are linked to two different natures of uncertainty. The first uncertainty concerns the accuracy of the estimate. We do not know in advance, how large a cash flow will be. Many factors like competition or regulation influence the actual size of the cash flow. This uncertainty can be negative, if for instance a competitor launches a better product. But the uncertainty has also an upside; imagine that the product sells better than anticipated, or costs are lower than expected.

The second nature of uncertainty is the technical uncertainty. It is not known in advance, whether a cash flow will happen at all. The reason for

uncertain cash flows is usually caused by failure and quantified by attrition rates. Attrition rates are purely value destructive. If a cash flow has only a probability p to happen, then you cannot count with the full cash flow, but only with its expectation, i.e. p times the cash flow. For valuation purposes, a cash flow must always be multiplied with its probability to happen. This requirement becomes clear when playing head or tales. Assume you win one dollar with heads and you do not win anything with tales. Obviously, you will win half a dollar on average, which is exactly 50% of the dollar, i.e. the probability times the cash flow. However, if you play just once, you either win or you do not. But if playing already two times, you have 25% chance to win two dollars, 50% chance to win one dollar, and 25% to win nothing at all. You are already more likely to win the average sum. If playing ten times, you have a chance of more than 65% to win 4, 5, or 6 dollars, i.e. close to the average. The more often you play, the more likely you win exactly the average value of the game.

Technology projects like in life sciences have the same property. The more projects a company has, the more likely it will end up with the number predicted by the success rates. The figure displays how many projects will succeed, assuming a company has 100 projects and each has a success rate of 10%. Clearly, the most likely scenarios are clustered around the average value of 10 projects. With 200 projects the picture gets even clearer. Finally, if the company were perfectly diversified, i.e. if it would have thousands of projects, it could exactly realise the success rates.

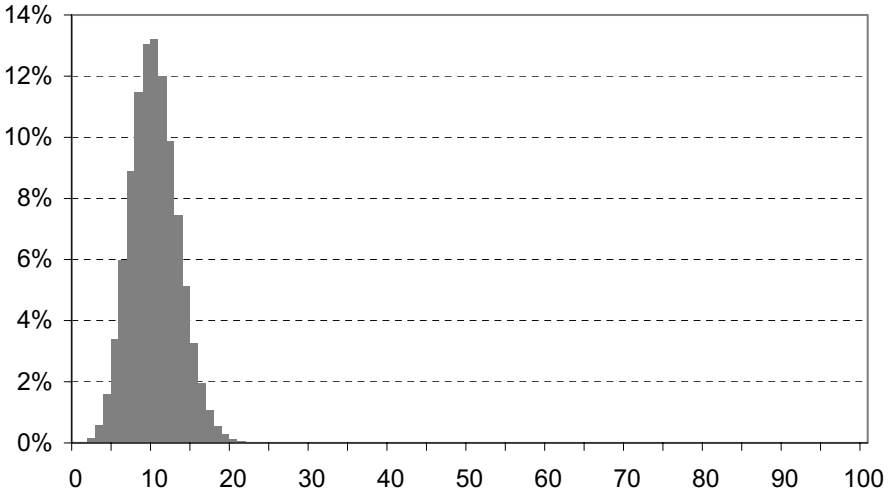

Fig. 3.2. Distribution of success with 100 projects

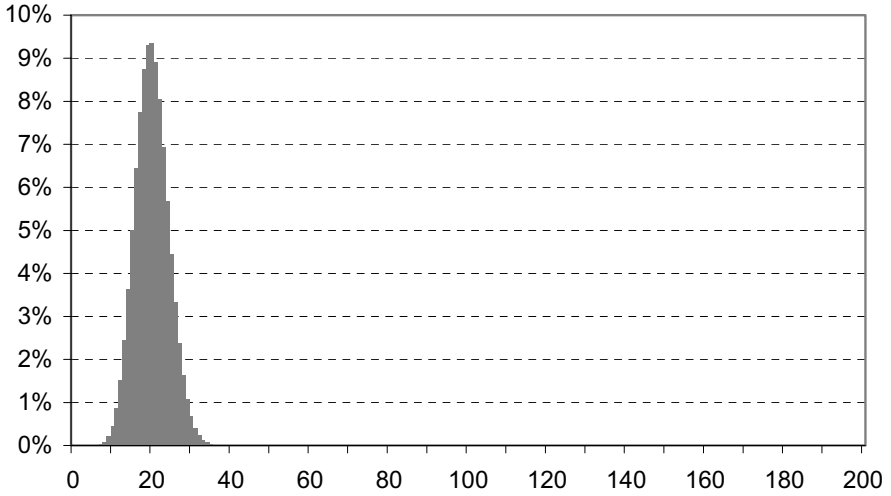

Fig. 3.3. Distribution of success with 200 projects

No company is perfectly diversified. To the contrary, most companies depend on the success of a few projects. In the extreme case we have a one-project company that will either be a success or a complete failure. The value of the company then extremely depends on the success of the project. If the project succeeds, the uncertainty is resolved and its negative effect can be excluded, i.e. we do not have to multiply the cash flows by the success rate linked to that uncertainty. This will lead to a jump in value in the order of *(1-p)/p*. Assume V to be the value after the uncertainty has been resolved. Consequently the value just before should be around p *times* V. The value increase is therefore:

$$\frac{V - pV}{pV} = \frac{1 - p}{p} \tag{3.11}$$

If the project turns out to be a failure, the value drops to zero. The value of a company or a project is just a measure of the average outcome. After negative results related to one important project, people blame valuation not to have predicted the value drop that has occurred meanwhile. Such statements are based on a misconception of valuation. A sound valuation does not predict winning or losing, but it quantifies the odds. Playing or investing many times, one realises the odds, just like in the casino, where in the long run the bank always wins.

Nevertheless, it is impossible to be perfectly diversified, as show the two figures for companies with 100 and 200 projects. Although scientific uncer-

tainty, as represented by success rates, is diversifiable, no company or investor will achieve a degree of diversification where the value is certainly realised. This would be perfect diversification. Consequently, every investor wants to be rewarded for this risk despite its diversifiable nature. CAPM does not account for this portion of risk, exactly because of its diversifiability.

Valuation Methods

Discounted Cash Flows Valuation

We have learned in the chapter on discounting that we can calculate the value of future cash flows back to today by discounting them. We then receive the present value of the cash flows. The discounted cash flow valuation is finally nothing else than netting the present value of all future cash flows. The result is the net present value (NPV) of the cash flows. The terms DCF and NPV are therefore equivalent. If we furthermore adjust the cash flows with the probability (risk) that they occur, we get the risk adjusted net present value (rNPV). In the following we will use the term DCF for the method to calculate the risk adjusted net present value.

The rNPV is calculated with the following formula:

$$rNPV = -I_o + \sum_{t=1}^{T} \frac{rCF_t}{(1+r)^t} \tag{3.12}$$

I_0 = Investment into the project at time 0 (=CF_0)
rCF_t = Risk adjusted cash flow at time t
r = Discount rate
T = Endpoint of the project (if today is $t = 0$, T = duration of the project)

In order to illustrate how to use the DCF valuation, we now calculate the rNVP of the project *Supersolution*. The project is still in development for one year. The investment for the development is due today and amount to $ 100,000. After one year, we have a 50% chance that the project passes the development phase and will finally be launched. The launch, including marketing and production expenses, amounts to $ 500,000. After the launch, the project generates the following revenues: Year 2 $ 100,000, year 3 $ 200,000, year 4 $ 300,000, year 5 $ 200,000, and in the final year 6 $ 100,000. Once the project is on the market, the expenses are 10% of the revenues. The company developing the project applies a discount rate of 15% to value all its investments:

Table 3.2. rNPV calculation of project Supersolution

Year	0	1	2	3	4	5	6
Expenses	($ 100,000)	($ 500,000)	($ 10,000)	($ 20,000)	($ 30,000)	($ 20,000)	($ 10,000)
Revenues			$ 100,000	$ 200,000	$ 300,000	$ 200,000	$ 100,000
Net CF	($ 100,000)	($ 500,000)	$ 90,000	$ 180,000	$ 270,000	$ 180,000	$ 90,000
Probability	100%	50%	50%	50%	50%	50%	50%
Risk adjusted CF	($ 100,000)	($ 250,000)	$ 45,000	$ 90,000	$ 135,000	$ 90,000	$ 45,000
Discount	100%	87%	76%	66%	57%	50%	43%
rpCF	($ 100,000)	($ 217,391)	$ 34,026	$ 59,176	$ 77,187	$ 44,746	$ 19,455
rNPV	($ 82,801)						

To calculate the risk adjusted net present value of the project we:

1. List the expenses (negative cash flows) for each year.
2. List the revenues (positive cash flows) for each year.
3. Net the cash flows.
4. Risk adjust the discounted cash flows with the success rate.
5. Discount the cash flows by multiplying the risk adjusted net cash flows with the discount factor. The result is the risk adjusted present cash flows (rpCF).
6. Sum the risk adjusted present values of all cash flows. The result is the rNPV, the risk adjusted net present value of all cash flows.

The discount factor is calculated in the following way:

$$DF = \frac{1}{(1+r)^t} \tag{3.13}$$

The risk adjusted net present value of the project is ($ 82,801). The company should therefore not invest in the project. In general, projects that yield a positive value should be continued, those with a negative value abandoned. We will discuss in the chapter on portfolio management how to decide which projects to halt and which not.

Internal rate of return (IRR). The project above yields a negative value if we value it with a discount rate of 15%. The rate of 15% is the hurdle rate the company applies to decide if projects should be continued or abandoned. Projects that give a positive rNPV when discounted with 15% have a return that is higher than the demanded 15%. These projects pass the hurdle rate and are continued. We now calculate for our example the dis-

count rate that yields exactly a project value of zero. The resulting discount rate is the internal rate of return of the project.

$$rNPV = -I_0 + \sum_{t=0}^{T} \frac{rCF_t}{(1+IRR)^t} = 0 \tag{3.14}$$

The IRR of our project is 4.58%. At this discount rate the project yields a value of zero. The figure below displays the relation between the discount rate and the rNPV:

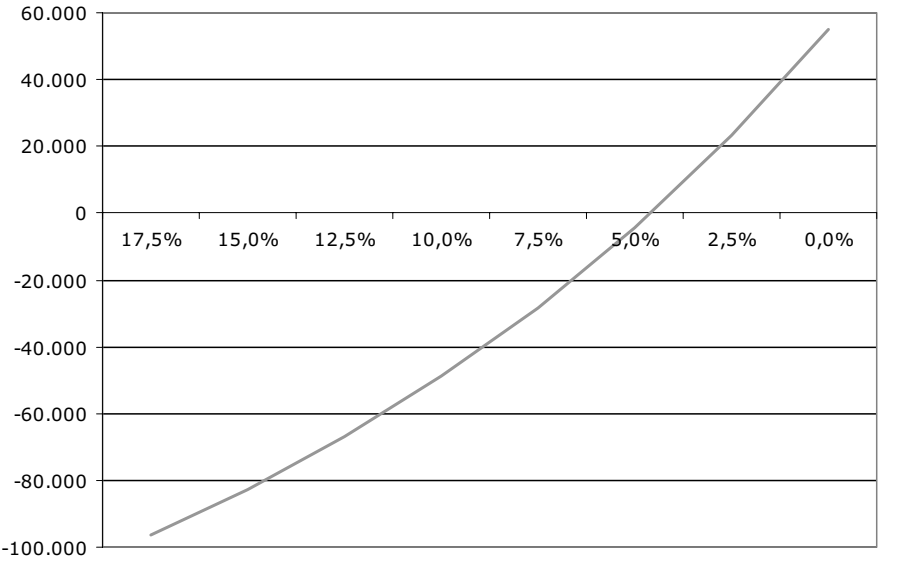

Fig. 3.4. Influence of discount rate on project value

The internal rate of return is therefore the exact calculation of the return of a project. The money invested into the project above therefore accretes with 4.58%. As long as the IRR is below the discount rate, the project has a negative value.

Real Options

General Aspects

DCF convinces by its simplicity. Nevertheless, this simplicity is only achieved at the cost of some strong hypothesis. In the DCF method we assume that the market does not change, i.e. once we have fixed our estimate

of the peak sales, we do not question this number anymore. One can argue that the estimated peak sales correspond to the average of what we can expect. Whatever happens, there is about the same probability that the actual outcome lies above or below the estimated number. On average, the sales equal what we have predicted. So why not just calculate with the estimated peak sales?

This reasoning bears two dangers. First by assuming one scenario, i.e. the average, we run the risk to take this number for granted. This can lead to over-reliance on this scenario that is still only a vague estimate. Second, the reduction of the future to just one scenario avoids considering alternatives in case the estimate turns out to be wrong or must be adjusted due to new information. This would correspond to a static management unable to react to a changed marketplace. Of course, this does not mean that managers who use DCF just twiddle their thumbs. Even with DCF, you can revaluate the project once some value drivers change. This is common practice and does not depend on the valuation method. However, DCF does not take into account this practice. DCF values the project as if the management takes a one-time go or no go decision. It would be reasonable to assume that the company alters its plan if one critical measure deteriorates or maybe improves way above expectations. The company has various options at hand: it can scale down the project, put it on hold, halt it completely, or in the good case accelerate or expand it. The management constantly decides what to do in order to increase value. In some scenarios, although not in the most probable ones, management takes actions that differ from the initial project plan. DCF does not consider this managerial flexibility.

The real options approach takes into account that some decisions in a project's or company's life can or even must occur at a later stage depending on future market conditions. These can be fundamentally different from current market conditions; therefore, future decisions can only be anticipated to a certain degree. Consequently, management has to maintain flexibility to react to changes. This flexibility is used either to increase profits or to avoid losses. Either way it generates value. If a project includes such options where the management can influence the ongoing of the project, this should flow into the valuation process. Flexibility is always used to increase the value of a project or company, therefore a valuation method that captures this flexibility returns a superior value than one that does not. This value creation is not captured by DCF valuation.

The novelty of real options valuation compared to DCF is that some future decisions about the ongoing of the project or company are conditioned on the respective market conditions and not vaguely anticipated. In real options theory the development of a project or company is depending on the changing market conditions, while in DCF the course of the project is predefined, no matter what happens.

In order to correctly model the decisions, it is necessary to model the conditions, or parameters, they depend on. For this, real options theory makes use of the extensive research in the field of financial options that deal with the same issues. The market fluctuates and it is not sure from the beginning what payoff a holder of a derivative will incur at expiry.

While in financial derivatives the different ways to execute are predefined, management has to recognise the different ways how to adapt the company's business to the changed environment. Finally, it does not suffice to recognise that the company can still adapt its decisions at a later moment in time. We also need to quantify this flexibility. Some projects might have several probable alternatives and consequently, flexibility is important and represents a considerable part of its value. Other projects are unlikely to be redirected, mostly clearly profitable projects; their inherent flexibility is almost worthless. We must model the different ways to react to a changed market environment. These different reaction types define the different embedded real options in a project or a company. The existing literature provides six categories of real options based upon the types of managerial flexibility:

- Option to defer
- Option to expand or contract
- Option to abandon or license
- Option to switch
- Option to stage investments
- Option to grow

Option to defer. An investment cannot be recuperated anymore once it is triggered. Hence it should only be triggered if the subsequent revenues are expected to be higher. The option to defer is finally a trade-off between risk and return. Investing immediately gives the company earlier, less discounted, revenues. Waiting might resolve some uncertainty about the market. For some projects it might be advisable to wait although they have a positive NPV due to their risk profile that might better be cleared prior to

investing. An option to defer is specially valuable if the project outcome is highly uncertain and the investment irreversible. But waiting involves also the risk of loosing the first mover advantage. Therefore, in a competitive environment the option to defer might be worth less. Costs to keep the option alive, e.g. renting costs, have a negative impact on its value as well.

Option to expand or contract. Options to expand or contract incorporate the possibility to change the existing scale of the project according to the market movements. A company may build production facilities in excess of the expected demand. The company may incur additional revenues in times of high demand. On the other hand the company should engineer their plants in a way that they can be partially shut down in periods of low demand, reducing the fix costs. Testing a new market with a scout product and expanding if the test run proves successful is another example of this option type.

Option to abandon or license. If a project fails to meet the expectations and is even deficitary, the company's management should consider abandoning the project, possibly avoiding losses. The technology of the project might be licensed and the infrastructure sold. The company can recuperate a salvation value. The more reversible the investments, the higher the salvation value.

Option to switch. A company can reconsider its production location and switch to a cheaper place. It is also imaginable that a production plant will be modified in order to fabricate another product. In these cases the company switches either the production costs or the sales revenues.

Option to stage investments. Some projects require a staged investment. The firm resolves in every subsequent stage further uncertainties. Based on the learned facts, the project is revaluated and consequently continued or abandoned after each phase. These staged investments are modeled as compound options. After each period the company has the option to continue or not. Continuing corresponds to the acquisition of a new option. A staged investment process is common to R&D projects and to start-ups.

Option to grow. Growth options are the most common and most widely cited real options. A company is supposed to have the possibility to expand its activities to other countries, to other clients, or to other products, if the initial activity proves to be successful. In a first stage the company resolves uncertainty about the market conditions, such as product acceptance, demand, and price politics. Once these doubts are removed, the company

decides whether it is worth to expand – to grow – or not. Finally growth options are nothing else than staged investments. But normally growth options are considered to be just a one-stage option, while R&D real options are multi-stage options.

As we will see later, real options valuation in life sciences mainly requires the option to abandon a project once it is not profitable anymore. Other options, e.g. options to grow or options to switch, are useful in certain instances but not for everyday valuation.

We have already mentioned that it is the duty of the management to recognize the multiple options that the company holds in its hands and react to them. Different strategies offer different options. Real options valuation must then be used to compare the different strategies. As we see later, real options are not only a strategic tool for value aspects, but they also provide important information about risk and liquidity management.

Nevertheless, there are also some dangers attached to the real options approach. So-called options and later opportunities should not be misused to justify any kind of investments. Real options still demand a thorough valuation process; they can be worth less than the initial investment to acquire the option. Furthermore, projects tend to create their proper dynamics and might be difficult to abandon. It is not sufficient to change the valuation method from DCF to real options; it is necessary to adapt the entire decision taking process to this new method. Real options assume that the management takes a decision in the future based on the best available information according to rational decision criteria. The valuation loses its justification if the management does not stick to this practice anymore. Eventually real options valuation is more a strategic than a valuation tool; it is a new way of management.

We have mentioned above that the options – or the flexibility linked to them – represent a value that does not go into the DCF valuation. Usually real options valuation returns a higher value than DCF. This does not mean that the project is suddenly worth more if valued with real options. The project is still the same. And even when the management uses DCF, it revaluates a project periodically and adjusts its hypothesis. But the DCF valuation does not take this periodical revaluation into account; a revaluation that might trigger new investments or the abandonment of the project. DCF simply omits an aspect of the project life. In some cases this leads to a missed opportunity. We discuss this aspect in further detail in the following chapters. Finally, we can oppose DCF and real options valuation in the following manner:

Table 3.3. Comparison of DCF and real options

	Advantages	Disadvantages
DCF	Easy to implement and to understand	Misses the value of flexibility and market uncertainty
	Standard in all sectors of the economy	Not suitable for risk management
Real Options	Captures market uncertainty and the management's ability to react	Relies on more hypothesis and requires more data
	Suitable for risk management	Technical
	Improves strategic thinking if properly understood	

Resolution Methods

Financial mathematics offers four different methods to value an option:

1. Formula (closed form solution)
2. Trees
3. Simulations
4. Finite differences

All methods yield the same result, but the ways to get there are different. We discuss the methods with focus on their applicability to the valuation of real options. Some methods have been developed for special purposes and do not necessarily suit the requirements of real options valuation. First, the assumptions of real options are relatively modest compared to financial options. Second, the users of real options valuation most often do not have the required mathematical knowledge to apply the approach in practice. The complexity of the valuation method should therefore be as simple as possible, but not any simpler. No rocket science is required. Above all, the method should show the particularities that are considered in real options valuation and should not hide them in complicated algorithms. The decision takers need an efficient, explanatory and understandable tool, not a scientific high-end black box. The managers must be able to defend and explain their decisions without a long monologue about assumptions and technicalities. The valuations should support them in the communication of value and risk of a certain investment. We will now investigate the four valuation techniques with these thoughts in mind.

Formulae. Formulae are well suited for the valuation of simple call and put options determined by five input parameters (underlying, strike, maturity, interest rate, and volatility). Unfortunately, it is virtually impossible to capture the complexity of real options in project valuation with a closed form formula. The complexity quickly surmounts the mathematical knowledge of most users and ends up being a black box. Finally, it is not helpful to use a formula, as the real option framework should not only serve to generate a number, but also as a managerial instrument to visualise possible scenarios and the impact of revaluations and decisions. We will further discuss the applicability of formulae to real options in the chapter about the differences between real options and financial options.

Trees. Trees are a simplistic model of future market movements and are broadly used to value financial options. Binomial trees subdivide the time to maturity in small time steps and assume that in each time step the market, or in what we will see later, the peak sales, can go both up or down, each scenario with a certain probability.

Binomial trees are best spanned in a way that after a step up and a step down the market is in the same state again. We call this type of tree a recombinant binomial tree. Usually the tree is spanned until the time of option expiry, the time steps can be chosen to satisfy the accuracy requirements, yearly, quarterly, monthly, or even daily. Normally, the smaller the time steps, the more accurate the final value. The option value is obtained by calculating the tree back from the final leaves to the root. At expiry, the option value is clear if the market state is known, and the tree precisely indicates the market state for every leave. After that, we place ourselves in a node one time step before expiry. From there, we have to deal with a

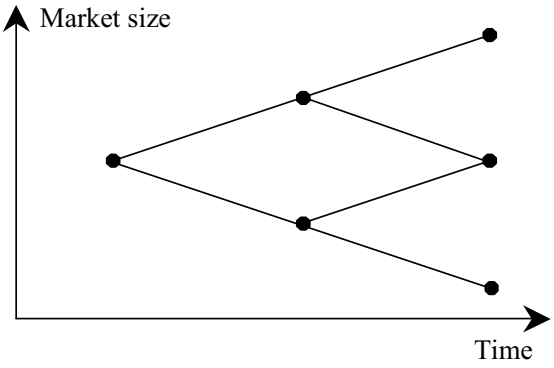

Fig. 3.5. Recombinant binomial tree

simplified situation: We have just two possibilities, whereof we know the probability. Being able to deal with such simplified situations, we can value the option for each possible situation at every time step before expiry. Working back the tree time step by time step, we finally reach the root node of the tree. By subdividing the initial problem into clearly arranged situations, we can calculate a value for the option.

Trees are easy to understand. They visualize what can happen to the market. While a formula yields a value in a magic way, the link to the value drivers is missing. A tree allows comprehending how and when a value driver impacts the value. Everyone resolving a tree has no problems to say how the final value is built up.

Simulations. Simulations follow an even simpler concept than trees. We determine the future beforehand, e.g. we assume certain peak sales numbers, and then attribute a value to the option given that future. This is repeated many times with an algorithm that randomly chooses the outcome. The simulated scenarios must on average correspond to the assumed probability distribution. Once all scenarios are simulated, there is no uncertainty anymore. Every manager can tell how much an investment is worth if he already knows the future. The simulations return not only an average value of the option; they also give a good impression about the uncertainty of the value and are therefore an excellent risk measurement tool.

Fig. 3.6. Simulation paths

Simulation techniques can very well deal with more complicated assumptions, but struggle with some special option structures called path-dependency. Nevertheless, simulations enjoy great popularity in the financial world and are well suited for real options valuation. Unfortunately,

simulations require programming expertise and are thus often too complex. We will give some guidelines on how to use simulations in a separate chapter on simulations.

Finite Differences. Option valuation has first been approached using a mathematical concept called partial differential equations (PDEs). PDEs are a very flexible concept that can deal with many additional hypotheses. They however only display characteristics and properties of the option value, e.g. how it behaves by modifying some parameters, but do not provide the value. For simple hypothesis it is possible, to derive the option value out of a PDE; most of the times however this is impossible. Similar to binomial trees, finite differences subdivide the problem into small concise subproblems. While it is impossible to predict the value development on a large scale, finite differences use PDEs to forecast the value development on a small scale. Finite differences are widely used in engineering, biology, or even meteorology; they are extremely powerful to make forecasts, but require a high degree of proficiency with mathematical concepts and programming.

Table 3.4. Comparison of resolution methods

Method	Advantages	Disadvantages
Formula	Easy to use	Calculation process not visible
	Fast	Only for simple option structures simple assumptions
	Sensitivities	
Trees	Easy to understand	Rigid
	Visualisation	
	can deal with more complicated options	
Simulations	Easy to understand	Time consuming
	Visualisation	Problems with path dependency
	Can deal with more complicated assumptions	
Finite differences	Can deal with more complicated assumptions	Calculation process not visible, hard to understand
	Can deal with more complicated options	Technically demanding

For real options valuation of biopharmaceutical projects trees are most suitable. A simple formula cannot cope with the project structure. We will also discuss simulations but omit finite differences because of their complexity.

Binomial Tree Valuation in Real Options

We will show in the following chapters in detail how to apply binomial trees to real options valuation. It is essential that the reader understand how to construct the tree and how to use it in the valuation. It will be the basis in all subsequent chapters dealing with real options. The application of the Black-Scholes formula to real options valuation will be discussed in a separate chapter.

Using a tree, we model the market development, i.e. possible changes of the sales revenues. While we know the market state today, we are already uncertain about the market state after one time step, let's say next month.

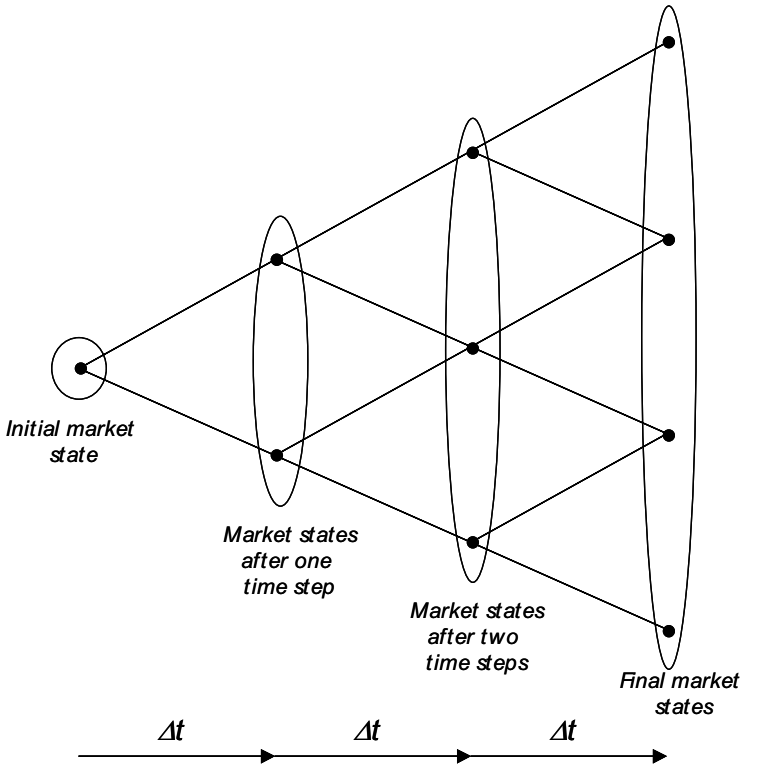

Fig. 3.7. Binomial tree

The market can either improve or deteriorate. The up- or down-steps of the tree reflect this. The further we go into the future, the less certain we are about the forecast. The tree therefore widens the farther we move in time. Each node represents another market state for the corresponding time. The end nodes represent market states at the final time point of the tree.

In real options valuation we model the market up to the last decision point of the project we want to value. We then place ourselves in each of the end nodes, i.e. at the time of the last decision and assume a market that corresponds to the node. The market state in the end node gives us all future cash flows, revenues and expenses. This situation is no different than if we just have to decide without any further uncertainty and can be calculated using standard DCF valuation for all future cash flows of the project after the last node of the tree. In some end nodes the market state might be so bad that the DCF value is negative, i.e. the expected revenues do not provide enough compensation for the necessary investments. In these states, we abandon the project. Consequently, we put the value of the project to zero by abandoning it, because there are no future cash flows anymore. Putting the value to zero instead of keeping the negative NPV corresponds to the option to abandon. In these states, the project value is increased from a negative value to zero, while in the other states where the project is profitable, the values are kept the same. The average value of all scenarios is therefore higher than without putting the negative values to zero. This difference in value is directly linked to the option to abandon, which avoids losses and is the source for the different values in DCF and real options valuation.

In a next step we place ourselves in the nodes one time step before the nodes we have just solved. The uncertainty in these states is not too complex. There are just two possibilities, either we reach after one time step the upper state or the lower state, in our case the upper or lower end node. For both scenarios we know the probability and the value of the project in these states – we have just calculated them. We can therefore take the expectation of the project values, discount it and account for the cash flows that are due in this very time step. Assessing the value for each node at that time step, we have already calculated the values for the final two layers of the tree. Applying the same procedure to each previous layer we can work back the tree to its root. Finally, the value of the project corresponds to the value calculated for the root node, because this is exactly the time and market state of today.

We will now explain each step of the tree valuation outlined above in detail and illustrate it with an example.

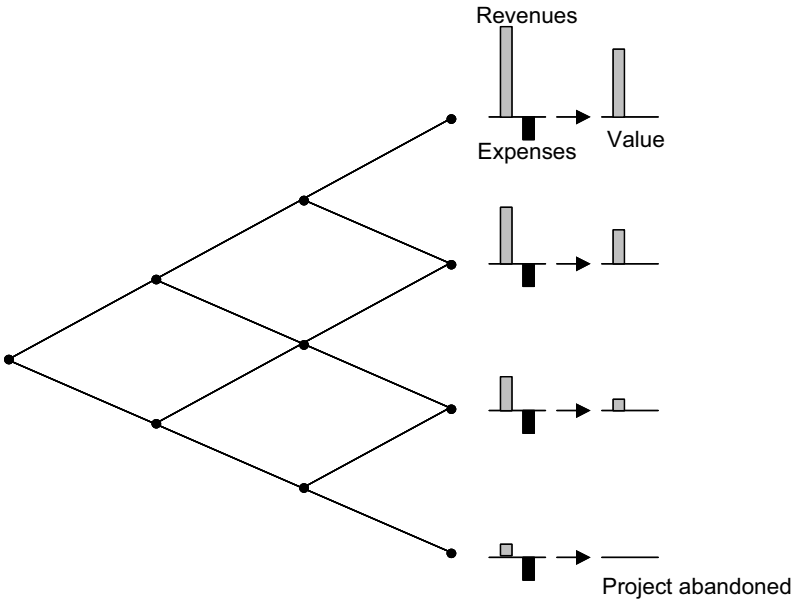

Fig. 3.8. Calculation of end nodes

Step 1: Determine the project parameters, i.e. the underlying S, growth rate μ, volatility σ, the time step size Δt, the expenditures, the success rates, and the duration of the project. Before constructing the tree, we have to fix the input parameters of the project for the valuation. Not all are already relevant for the tree; but it is better to define the parameters before starting to set up the Excel sheet.

We first define the underlying of the binomial tree, *S*. In most cases the underlying of the tree is the peak sales or the market state. Once we have the peak sales, we estimate their growth rate and their uncertainty, i.e. their volatility. If we know all characteristics of a project, i.e. all test results of the development; we can more or less accurately determine the peak sales at the time of launch. Before, i.e. during development, many factors have an impact on the estimated peak sales. New knowledge on application, safety and efficacy, a change in the competitive environment, e.g. another company launches a similar product, or an economic downturn, influence the estimate of the project's peak sales *S*. We do not know how all these risk factors will evolve, but we assume that first, the general market for the medication is going to grow at the growth rate μ and second, the volatility of the peak sales estimate *S* is σ. The volatility is a measure of uncertainty, i.e. the exactness of our peak sales estimate today. The more uncertain the

peak sales estimate today is, the higher is the volatility of the estimate. We will further discuss volatility in the chapter on life sciences valuation. Finally, we determine the project related parameters, i.e. the duration of the different phases, the success rates and costs of the phases.

In our example, we assume that a company develops a product. The product first has to pass two development phases, where it is tested on feasibility and other concerns like compatibility with other products, compliance with regulation or safety. We estimate the peak sales to be $ 150,000. The volatility of our estimate is 30%. The project is at the start of the first development phase that lasts 2 years. We now decide whether to go ahead or not, depending on the project value. After two years, the project will finish phase 1 testing with a success rate of 75%. Again, depending on the outcome of phase 1 testing and the market conditions at that time, we will perform another valuation; we will only start phase 2 testing if the project has a positive value. Phase 2 testing lasts 1 year and will be successfully completed in 80% of the cases. The costs for phase 1 and phase 2 testing are $ 25,000, and $ 30,000, respectively. If the project passes phase 2 testing successfully, we will value the project again. Depending on the valuation, we will launch the project. The costs to launch the project are $ 150,000 and are due at the beginning of the fourth year. Our company discounts the project at a rate of 15%. We are looking at 5 years of sales. The operating margin is 50%.

Table 3.5. Project characteristics

Estimated peak sales	$ 150,000
Volatility	30%
Margin	50%
Discount rate	15%
Time on market	5 years
Phase 1 testing	
Duration	2 years
Success rate	75%
Costs	$ 25,000
Phase 2 testing	1 year
Success rate	80%
Costs	$ 30,000
Launch costs	$ 150,000

Step 2: Spanning the Tree: With the assumptions made in step 1 we can proceed to spanning the tree. The underlying, in our case the peak sales estimate, move either up or down during the next time step Δt. But on average the estimate move to $Se^{\mu \Delta t}$ (or to $S(1+\mu)^{\Delta t}$ if μ is discretely compounded). As another condition we want the tree to recombine, i.e. the market gets to the same state after a down- and then an up step as after first an up- and then a down-step.

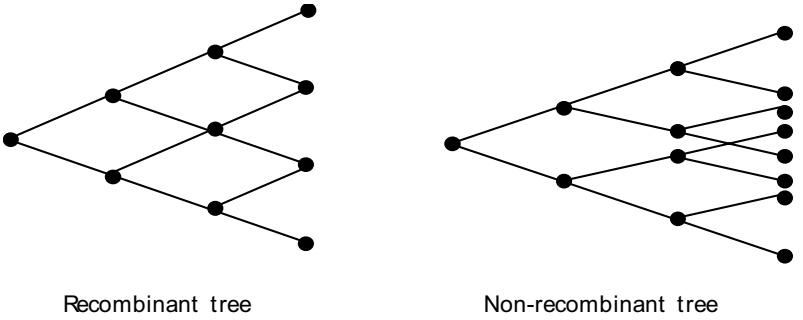

Fig. 3.9. Recombinant vs. non-recombinant tree

As we see in the figure, this feature reduces the complexity of our tree considerably. The size of the up and down step is determined by the volatility and by the time interval. The higher the volatility is, the larger is the angle between the branches. The formulae are displayed in the box below. If we design the tree in the way shown in the box, all the conditions are fulfilled. The average value after the time step Δt is $pS_u + (1-p)S_d = Se^{\mu \Delta t}$. Due to the condition $d=1/u$, the tree is recombinant and the uncertainty σ is correctly implemented in the tree. Therefore, we can build a tree with these relationships from now until the last decision point.

The choice of the time step influences the accuracy of the valuation. The shorter the time step, the more accurate the valuation, but the more fastidious the calculation. For real option purposes time steps of one, three or six months, in some cases even of one year are sufficient.

$$STEP\ up: \quad u = e^{\sigma\sqrt{\Delta t}} \tag{3.14}$$

$$STEP\ down: \quad d = \frac{1}{u} \tag{3.15}$$

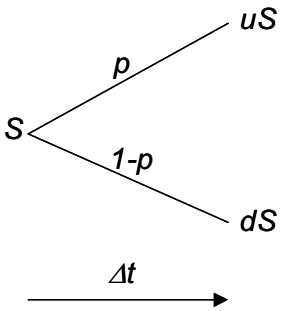

Fig. 3.10. Step up and step down

$$PROBABILITY up:\ p = \frac{e^{\mu\Delta t} - d}{u - d} \qquad (3.16)$$

$$PROBABILITY down:\ 1 - p \qquad (3.17)$$

We now span the tree for our example. For simplicity, we use time steps of one year. The estimated peak sales today are $ 150'000, the growth rate is assumed to be zero, and the volatility of the estimate is 30%. Using the formula of the box below, we now calculate the step size for each year.

$$u = e^{\sigma\sqrt{\Delta t}} = e^{30\%\sqrt{1}} = 1.35$$

$$d = \frac{1}{u} = \frac{1}{1.35} = 0.74$$

$$p = \frac{e^{\mu\Delta t} - d}{u - d} = \frac{e^{0\cdot 1} - 0.74}{1.35 - 0.74} = 43\%$$

In year two we expect the peak sales estimate to change with the probability p to 1.35 times the initial sales estimate of $ 150,000, resulting in $ 202,479. With a probability of 1-p, the estimate goes down by 0.74 to $ 111,123. The probabilities for the step up, p, and down, 1-p, are again calculated according to the formula in the box. We receive for p 43%, and for 1-p 57%. This means that in every year we expect our sales estimate to increase by the factor 1.35 with a probability of 43%, and to decrease by the factor 0.74 with a probability of 57%. As we have already outlined, the changes in the peak sales estimate derive from the changes of the market, e.g. new information

about the project in terms of applications, safety, or customer acceptance. This flexibility of the estimated sales figure is an important difference to DCF, where we assume that the estimate once fixed, stays constant during the entire project life. Obviously, it is more realistic to assume that an estimate of future sales figures is subject to change and fluctuation. We later see how this is applied to life sciences projects.

The figure below displays the tree spanned to the market entry of the product. The figures in the top of the boxes are the estimated peak sales, and below the probabilities to reach that state.

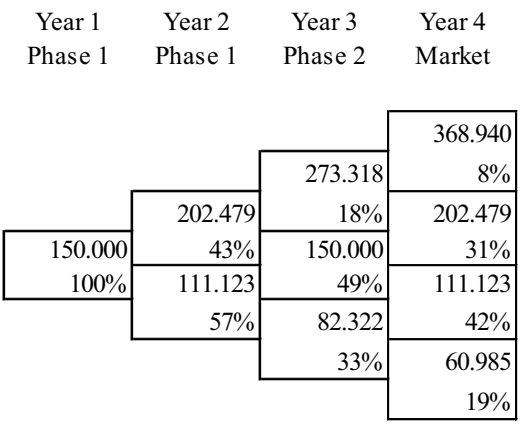

Fig. 3.11. Binomial tree displaying market states and their probabilities

We see that in the best case our peak sales estimate is $ 368,940, but we expect to reach that number at the time of market entry only in 8% of all cases. The worst case, $ 60,985, is reached with a probability of 19%.

The following figure exhibits a tree modelling a market of initial 100 units, an annual growth rate of 0% and an annual volatility of 40%. We chose 6 months time increments. After 5 years the tree allows 11 different states of the market, the range lasts from 6 to 1,692. At first sight this seems to overweigh the high values and therefore a positive market development. If we take a closer look at the tree, the numbers keep their justification.

If an ant walks along the tree, always from the left to the right, then there are 1,024 different paths at the ant's choice (there are 10 points where the ant has to chose to go up or down – between two possibilities – hence there are 2^{10}=1,024 different paths). But only one path ends at the very top – if the ant each time choses to go upwards. On the other hand, there are many more

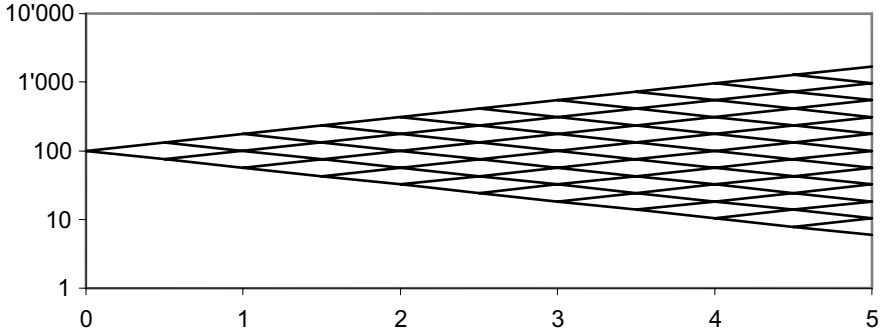

Fig. 3.12. Tree for a five years' period

possibilities to reach one of the middle states. The ant is supposed to go upwards with a probability of 49% and downwards with a probability of 51% – these are the tree parameters that correspond to a growth rate of zero, a volatility of 40%, and a time step of 0.5 years. The different number of paths and their probability induces different weights (probabilities) for each end state. The following graph displays this relationship. The fact that it is slightly more probable that the market goes down at each node (51%) shifts the probability curve on the graph a bit to the left.

The possibility that a medication, whose peak sales are estimated today at $ 100 mn, would reach peak sales of $ 1,692 mn in five years seems not realistic. Nevertheless one can argue that it is possible, though not realistic, that competitive products suddenly deal with severe problems; the

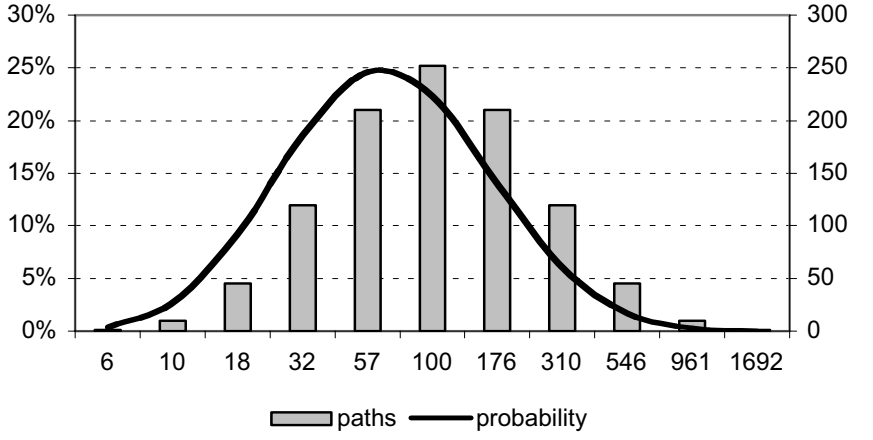

Fig. 3.13. Frequency and probability of different end states

applications of the drug is consequently expanded to other diseases or the efficacy exceeds anything ever seen and a major demand for this kind of drug arises. This way the medication could become a blockbuster. Roche experienced a similar scenario with the threat of the avian flu pandemic. This sudden change of market state let sales of Tamiflu rise from CHF 330 mn in 2004 to CHF 1,558 mn in 2005. Still this scenario is comparable to winning the lottery, but someone finally wins it. The tree considers that by attributing a minimal probability to this end state. The most probable end states are 57, 100 and 176 with more than 65% of probability all together. On first sight some end states of the tree might seem unrealistic, but the tree captures exactly the probabilistic hypotheses. The more unrealistic a state is, the lower the probability attributed to it by the tree.

Step 3: Solving the end states. After having set up the tree we now solve the tree from the end where no uncertainty is left, i.e. where the decisions can be taken according to clear criteria. The tree puts you into hypothetical states at the final decision points, i.e. at the end nodes of the tree. In each state, the tree gives you a best estimate of the potential of the project, if this state were actually achieved. With this input, we are able to calculate the value of the project. We know the future payoff of the project, as the end node tells us the size of the peak sales and there are no more decision points ahead. Using these peak sales along with the expenditures to launch and market the project; we can calculate the net present value of the project at the end node. Next we decide whether to invest or not according to the value of the DCF calculation: Invest if the discounted (and probability-adjusted) future revenues exceed the investments, abandon otherwise. This way the value of the project is necessarily positive, as all projects with a negative rNPV are not continued. The project either is profitable, i.e. the revenues are higher than the expenses, or the project is abandoned, in which case the value is zero. This is the first implementation of the option idea. Nobody would voluntarily make losses; one rather exercises the option to abandon the project and floors the future losses to zero. The value of the DCF calculation is now attributed to all end nodes in the tree. In all cases where we have a negative value we put the end node value to zero. Resetting the value to zero is only done when we are at a decision point, i.e. start of a new phase, here the market phase. In our example we start with solving the most upper node, with expected peak sales of $ 368’940. The sales will be constant for 5 years and then stop. We now have to find the value for this end node by multiplying the yearly sales with the margin of 50%, and then discount them back to the date of launch, i.e. beginning of year 4.

Table 3.6. Calculation of NPV in the end nodes (in $)

	Year 4	Year 5	Year 6	Year 7	Year 8
	Market	Market	Market	Market	Market
Discount	100%	87%	76%	66%	57%
Sales	368,940	368,940	368,940	368,940	368,940
Operating Profit	184,470	184,470	184,470	184,470	184,470
DCF	184,470	160,409	139,486	121,292	105,471
NPV	**711,129**				
Sales	202,479	202,479	202,479	202,479	202,479
Operating Profit	101,239	101,239	101,239	101,239	101,239
DCF	101,239	88,034	76,552	66,567	57,884
NPV	**390,276**				
Sales	111,123	111,123	111,123	111,123	111,123
Operating Profit	55,561	55,561	55,561	55,561	55,561
DCF	55,561	48,314	42,012	36,533	31,767
NPV	**214,188**				
Sales	60,985	60,985	60,985	60,985	60,985
Operating Profit	30,493	30,493	30,493	30,493	30,493
DCF	30,493	26,515	23,057	20,049	17,434
NPV	**117,549**				

The table above represents the calculation of the net present value of the project's operating profit at the time of launch for the end nodes. We first calculate the operating profit from the sales figures for each year. In a next step we discount these operating profits with the discount factor corresponding to the respective year. The discount factors are calculated with the formula (3.13). We then sum up the discounted yearly operating profits. The results for the four different states are displayed as the NPV. Now we still have to take the decision if we launch the product or not. We therefore subtract the expenses from the net present value of the operating income and receive the following numbers, displayed in bold for each scenario (see Table 3.16).

We see that only in the case of the lowest end node we do not launch the project. The future income would not payoff for the launch expenses and the project would not be profitable. For all further calculations we set the

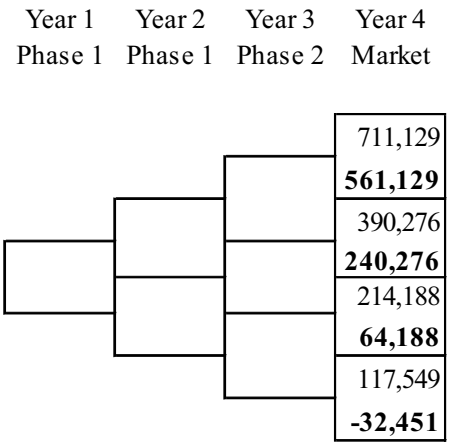

Fig. 3.14. Project value in the endnodes

value of this box to zero, as we do not proceed in this node, avoiding the expected losses.

Step 4: Working back the tree to the previous phase. We now place ourselves in one node right before an end state. This node represents a state Δt before the last decision point. What happens between then and the decision point, i.e. the end node of the tree where we already have the value? First, the results of phase 2 will be known. This is crucial for the ongoing of the project; a negative result corresponds to the end of the project. Second, the market potential is going to fluctuate, either a step up or a step down in the tree. Third, the time simply advances by Δt, this forces us to discount future cash flows by this time difference.

We consider these three points for the calculation of the project value at our specific node:

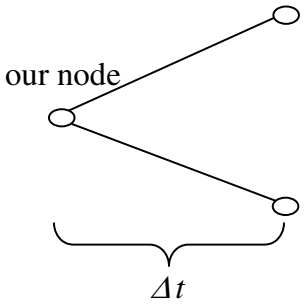

Fig. 3.15. One time step in the binomial tree

1. The results are part of a project's technical uncertainty. The outcome is not known in advance. We can only make use of statistical success rates. We then adjust the project value by this probability.
2. The tree reflects the market uncertainty, there are two end states following our node. The expected value of the project in our state is therefore the average of the project value at the two following end states.
3. Finally the whole value must be discounted for the time interval Δt.

If V_T^{up} and V_T^{down} are the project values of the two consecutive end states, then the value $V_{T-\Delta t}$ of the project at our node can be expressed in the following way:

$$V_{T-\Delta t} = \underbrace{P}_{1}\underbrace{\left(pV_T^{up} + (1-p)V_T^{down}\right)}_{2}\underbrace{\frac{1}{(1+r)^{\Delta t}}}_{3} \tag{3.18}$$

P is the statistical success rate of the phase, p the probability of the step up. Now we calculate the project value for all nodes at T-Δt with the formula above. Then we have to go another time step back to the nodes at T-$2\Delta t$. Note that if between T-Δt and T there is no end of a phase, i.e. if we are in the middle of a phase, we do not have to account for a failure of a phase. This must only be done at the very last time step of a phase. The value $V_{T-\Delta t}$ is therefore:

$$V_{T-\Delta t} = \underbrace{\left(pV_T^{up} + (1-p)V_T^{down}\right)}_{2}\underbrace{\frac{1}{(1+r)^{\Delta t}}}_{3} \tag{3.19}$$

Step (1) drops out, only the expectation (2) and the discounting (3) enters into the calculation. Applying this scheme we work back the tree to the root, carefully considering the difference in the calculations at nodes where we take decisions, i.e. after test phases, and where not. We calculate the value for the tree, starting with the most upper node for year three. According to the formula, we get:

$$V_3^{273} = 80\%\left(43\% \cdot 561{,}129 + 57\% \cdot 240{,}276\right)\frac{1}{1+15\%} - 30{,}000$$

$$V_3^{273} = \underline{\underline{232{,}134}}$$

We repeat the same for the other two nodes:

$$V_3^{150} = 80\%(43\% \cdot 240{,}276 + 57\% \cdot 64{,}188)\frac{1}{1+15\%} - 30{,}000$$

$$V_3^{150} = \underline{\underline{66{,}781}}$$

$$V_3^{82} = 80\%(43\% \cdot 64{,}188 + 57\% \cdot 0)\frac{1}{1+15\%} - 30{,}000$$

$$V_3^{82} = \underline{\underline{-10{,}998}}$$

As we are again at a decision point, the negative value in the lowest node is set to zero, because we do not continue the project in this case and therefore avoid the losses. This actually means that the lowest point at launch is never reached, because the project would already be abandoned beforehand.

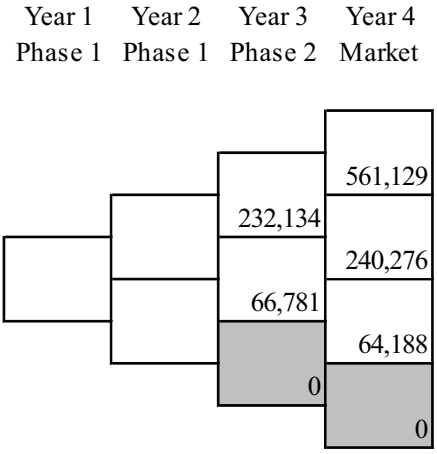

Fig. 3.16. Calculating back the tree to year 2

Step 5: Working back the tree to the root. The resolution of the rest of the tree is now a repetition of the previous steps. At each start of a phase you decide at each node, if it makes sense to continue the project. For this you compare the value of the project you have obtained in the above-described way with the costs of the phase. Replace the previous project value either with the positive difference between value and investment or put it to zero in case the difference is negative and the project consequently abandoned. Again, this is the implementation of an option in the valuation process. Then work back one time step and adjust for the technical uncertainty of the previous phase (1) as well as you take the expectation (2) and discount

all values for another Δt (3). After that, you work back to the start of the previous phase by only averaging (2) and discounting (3). Move back to the root of the tree applying these steps for each phase. In our example, for year 2, where we do not have any decisions to take, we calculate the following:

$$V_2^{202} = 75\% \cdot (43\% \cdot 232{,}134 + 57\% \cdot 66{,}781)\frac{1}{(1+15\%)}$$

$$V_2^{202} = \underline{\underline{89{,}445}}$$

$$V_2^{111} = 75\% \cdot (43\% \cdot 66{,}781 + 57\% \cdot 0)\frac{1}{(1+15\%)}$$

$$V_2^{111} = \underline{\underline{18{,}534}}$$

The expenses for the phase 1 are triggered at the beginning of year one. We can now calculate the value for the root node the same way as we have calculated the value for year 3.

$$V_1^{150} = (43\% \cdot 89{,}445 + 57\% \cdot 18{,}534)\frac{1}{(1+15\%)} - 25{,}000$$

$$V = \underline{\underline{17{,}357}}$$

The tree then looks the following:

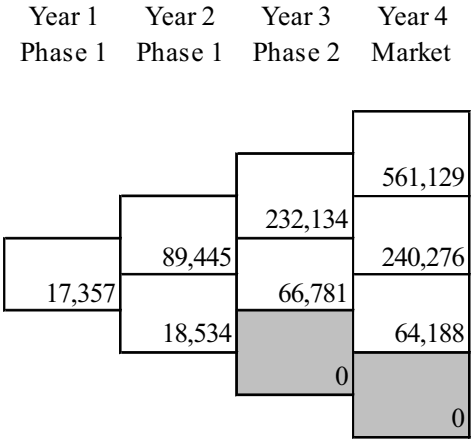

Fig. 3.17. Tree solved up to the root node

The root node value represents the real option value of the project today. The project has a real option value of $ 17,357.

Difference Between Real Options and Financial Options

In the following chapter we discuss the difference between real options and financial options and the implications on using the Black-Scholes formula for real options. The chapter is intended for readers interested in advanced discussions of real options and is not fundamental for the following chapters of the book.

Real options owe their name to their similarity to financial options. Almost every introduction to real options compares an investment opportunity with a financial call option. This suits to explain the general concept of real options. Unfortunately, virtually all literature about real options only concentrates on the second word of the name, "options". The word "real" is not only a descriptive of the different area of application – real economy vs. financial economy – it is also an important statement about the very nature of these options and has significant impact on quantification.

We start with a short explanation of the fundamentals of financial option pricing, i.e. about hedging. Then we elucidate the difference between real and financial options and explain its influence on valuation.

Financial option valuation. The concept of financial option valuation has been introduced by Fisher Black and Myron Scholes with their seminal paper in 1973 (Black 1973). Since then, the basics haven't changed significantly. They have shown that a financial option is replicated with a portfolio of the underlying and a bond. This allows mitigating all risk. And since the portfolio is without risk, it must earn the risk free rate, otherwise there would be an arbitrage opportunity.

The simplest way to visualise this concept is by means of a binomial tree. First, we model the fluctuations of the underlying of the option. We assume that the value of the underlying can go up or down during the next time step. Assuming today's value of the underlying being S, after one time step it can be either uS or dS, with u denoting the up step, and d the down step. Each scenario, the up or the down step, has a certain probability p or $1\text{-}p$.

The parameters u, d, and p should be set in a way such that they model correctly the underlying's fluctuation. In the Black-Scholes concept it is usually assumed that the underlying follows a geometric Brownian motion with growth rate μ (also called drift) and volatility σ. We give two examples of parameter sets u, d, and p that model correctly a geometric Brownian motion with parameters μ and σ.

The table below summarises the parameters to model the fluctuation of the underlying:

Table 3.7. Parameter sets for binomial trees

	Set 1	Set 2
u	$e^{\sigma\sqrt{\Delta t}}$	$e^{\mu\Delta t+\sigma\sqrt{\Delta t}}$
d	$e^{-\sigma\sqrt{\Delta t}}$	$e^{\mu\Delta t-\sigma\sqrt{\Delta t}}$
p	$\frac{e^{\mu\Delta t}-e^{-\sigma\sqrt{\Delta t}}}{e^{\sigma\sqrt{\Delta t}}-e^{-\sigma\sqrt{\Delta t}}}$	$\frac{1-e^{-\sigma\sqrt{\Delta t}}}{e^{\sigma\sqrt{\Delta t}}-e^{-\sigma\sqrt{\Delta t}}}$

Second, we define the replicating portfolio. The portfolio consists of the option, a portion Δ of the underlying (We use the notation Δ for consistency with the literature. Don't confuse Δ with the time increment Δt). The remaining part is allocated to a risk-free bond, which we can neglect in what follows. Δ is chosen such that, no matter what happens to the underlying, the return of the portfolio is the same. This is achieved with the following reasoning (V, V_{up}, and V_{down} representing the value of the option at the different nodes of the binomial tree):

$$V_{up} + \Delta uS = V_{down} + \Delta dS \tag{3.20}$$

Solving for Δ we get:

$$\Delta = -\frac{V_{up} - V_{down}}{uS - dS} \tag{3.21}$$

Valuation of financial options

1. Model the underlying
2. Build a replicating portfolio
3. Calculate the expected risk-free discounted value using risk-neutral probabilities

Third, we have to find a way, how to value the option. From the fact that the portfolio has by construction always the same value after one time step in all nodes of that time, we conclude that it is risk free. A risk free asset or portfolio must earn the risk-free rate r_f, otherwise we would have an arbitrage opportunity.

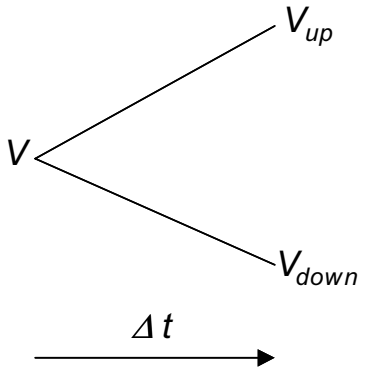

Fig. 3.18. Time step in option valuation

It would now be easy to deduce the value of the option from the values of the option at the leafs of the tree. The value of the option however is not equal to the expected and discounted future value of the option, because we cannot consider the option alone but only in conjunction with the replicating portfolio (otherwise we would not have a risk-free asset). Let us therefore define a fictive number q such that:

$$V = e^{-r_f \Delta t}\left(qV_{up} + (1-q)V_{down}\right) \tag{3.22}$$

The purpose of the introduction of q is a valuation algorithm that can focus on the option alone instead of always having to consider the replication portfolio. We have to stress that the introduction of q is a trick. Using the postulated property of q, the fact that

$$V + \Delta S = e^{-r_f \Delta t}\left(V_{up} + \Delta uS\right) \tag{3.23}$$

and the definition of Δ we can deduce the value of q.

$$V_{up} + \Delta uS - \Delta S e^{r_f \Delta t} = qV_{up} + (1-q)V_{down} \tag{3.24}$$

$$q = \frac{V_{up} - V_{down} + \Delta S \;\; u - e^{r_f \Delta t}}{V_{up} - V_{down}} \tag{3.25}$$

$$q = 1 - \frac{u - e^{r_f \Delta t}}{u - d} = \frac{e^{r_f \Delta t} - d}{u - d} \tag{3.26}$$

Using q according to its definition we can now calculate the value of the option V in a simple way:

$$V = e^{-r_f \Delta t}\left(qV_{up} + (1-q)V_{down}\right) \tag{3.27}$$

q is sometimes called risk-neutral probability, because its use corresponds to a discounted expectation, using q as probability within the tree and discounting at the risk-free rate. Note that usually discounting something uncertain at the risk-free rate is not accepted, because investors want to be rewarded with a risk premium. Nonetheless, in the case of financial option valuation this is allowed because it is only a trick. In fact, we discount the whole portfolio at the risk free rate, and the whole portfolio does not fluctuate.

The risk-neutral probabilities for the above mentioned parameter sets are:

Table 3.8. Risk free formulae for binomial tree

	Set 1	Set 2
u	$e^{\sigma\sqrt{\Delta t}}$	$e^{\mu\Delta t+\sigma\sqrt{\Delta t}}$
d	$e^{-\sigma\sqrt{\Delta t}}$	$e^{\mu\Delta t-\sigma\sqrt{\Delta t}}$
q	$\frac{e^{r_f\Delta t}-e^{-\sigma\sqrt{\Delta t}}}{e^{\sigma\sqrt{\Delta t}}-e^{-\sigma\sqrt{\Delta t}}}$	$\frac{e^{(r_f-\mu)\Delta t}-e^{-\sigma\sqrt{\Delta t}}}{e^{\sigma\sqrt{\Delta t}}-e^{-\sigma\sqrt{\Delta t}}}$

We recognise especially from parameter set 1 that using risk-neutral probabilities corresponds to a change of the underlying's drift parameter μ to r_f. In mathematical terms we have changed the underlying's real-world probability measure to its risk-neutral probability measure. But remember, this is only a trick for the purpose of the valuation, the underlying still follows a geometric Brownian motion with parameters μ and σ, whether there are some options or not.

Real options valuation. We now follow the same steps and quantify real options. First, we model the uncertainty of the underlying. This can be either estimated revenues of a product, the gold or oil price, or another economic metric. For simplicity let us assume that the underlying follows equally a geometric Brownian motion with parameters μ and σ. Second, we build the replicating portfolio. This now leads us to the very difference

between real options and financial options. While financial options are a contract that defines rights on a traded asset in a liquid market, real options are business opportunities. The decision to seize such opportunities depends on an economic metric, the underlying of the real option. This underlying however can be a virtual number, an estimate, e.g. the estimated revenues of a not yet developed product, or a share of a specific market the company considers expanding in. Most often the underlying is not tradable, which makes it impossible to build a replicating portfolio. In the case of commodity companies like mines or petrol companies, the underlying is traded in a liquid market. Nonetheless, the question we have to ask is not "Can we build a replicating portfolio?" but rather "Do we build a replicating portfolio?" If we do build a replicating portfolio, then we can use the valuation of financial options as described above. If we do not, then we cannot use the valuation of financial options, because the fundamental concept of replication is not respected. We have to keep in mind that financial options are valued as part of a risk-free portfolio, and only this justifies the use of the risk-free rate in the risk-neutral probabilities. If you valued real options with risk-neutral probabilities you would value something you do not have, namely a business opportunity that is hedged. Even oil companies and mines may only apply risk-neutral valuation if they hedge their real options. Hedging the business opportunities would correspond to pocket in the value of the business opportunity and then hedging it until the end of the life cycle. This would be real arbitrage, a very smart way to run a business. Unfortunately, we have not heard of any company doing so. The reason might be simple: Real options model the uncertainty of some value drivers. But there are still a lot of other factors not built in the model and not hedgeable, and managers cannot trust their models such that this would justify large financial transactions to hedge their business opportunities. For the moment, it seems that the model risk outweighs the business risk.

But, let us return to the standard real options that cannot be replicated anyway. We have to acknowledge that we must not use the elegant valuation method that applies to financial options. So, the second point of financial option valuation cannot be executed. Consequently, the third point that is based on the second cannot be respected either. So what can we do?

Let us go back to the actual meaning of "real options". Real opportunities are business opportunities that require decisions in the future. Until then, some value relevant parameters can fluctuate. The decision will eventually be based on the parameter set that is encountered at the time of decision. Hence, in contrast to other valuation methods, using real options we just model some additional decisions that influence the course of the project. Typically, these decisions are abandonment or expansion. The

decisions and the subsequent scenarios occur with some probability. These probabilities depend on the probability distribution of the decision driving parameters. It is therefore straightforward, first, to model the fluctuation of these decision relevant parameters, second, to anticipate for each possible scenario what management would decide, and third, to calculate the expected value of all these scenarios. In the binomial tree, this means that the value of the real option can be described by:

$$V = e^{-r_a \Delta t}\left(pV_{up} + (1-p)V_{down}\right) \tag{3.28}$$

We notice two differences with respect to financial option valuation. First, we use the real world probability p that models correctly the likelihood that either the one or the other scenario occurs. Second, we use the risk-adjusted discount rate r_a instead of the risk-free rate r. Since the value of the option fluctuates with the underlying, the option holder faces some risk, which he wants to be rewarded for. Again, the financial option was part of a risk-free portfolio, so there was no risk that would have to be compensated.

In this context, real options valuation is nothing else than a risk-adjusted expectation. Risk-neutrality or change of probability measures like for financial options lack any justification. The difference between real options and other valuation methods lies solely in the modelling of future decisions and their underlying drivers.

Some authors try to bypass this apparent inconvenient that avoids the direct application of Black-Scholes by assuming that the real option can be hedged. They suppose that there is a traded asset that could be used to replicate the real option. This hypothesis is called market asset disclaimer (MAD). MAD is about as useful to plan your agenda assuming the week has eight days because you are short in time. The planning might work fine, but at the latest on the eighth day reality will wake you up. In corporate finance the investors' wake-up call uses to be little tender.

Consequences. All formulae from quantitative finance are considered to be applied to financial option valuation. Therefore, we have to adapt them prior to using them for real options valuation. In the case of the binomial tree we have to use the real-world probabilities and use the risk-adjusted discount rate when working back the tree.

Black and Scholes' partial differential equation (Black et al. 1973) has to be modified in the following sense:

$$V_t + \mu S V_S + \frac{1}{2}\sigma^2 S^2 V_{SS} - r_a V = 0 \tag{3.29}$$

For the financial option version of this PDE we have to replace μ and r_a with r. This formula can be derived by using the Hamilton-Jacobi-Bellmann equation.

The well-known and often used option formula, equally derived by Black and Scholes, must read:

$$V = Se^{(\mu - r_a)t} N(d_1) - Ke^{r_a t} N(d_2) \tag{3.30}$$

$$d_1 = \frac{\left(\mu + \frac{1}{2}\sigma^2\right)t}{\sigma\sqrt{t}}, d_2 = d_1 - \sigma\sqrt{t} \tag{3.31}$$

Conclusion. Black and Scholes derived an elegant method to value financial options as part of a risk free portfolio. Consequently, they could discount at the risk-free rate and use risk-neutral probabilities. In contrast to that, real options cannot be, or, equally important, are not hedged. This implies that real options valuation simply becomes an expectation calculus discounted at the risk-adjusted rate.

If you use risk-neutral valuation for real options and you do not hedge, you value something you do not have – a business opportunity as part of a risk-free portfolio – instead of something you have – a business opportunity with real risks.

Valuation in Life Sciences

In the following part we discuss how the theory outlined in the previous chapter is applied to valuation in life science. First we look at some special aspects, i.e. discounting, volatility and peak sales prediction, and then move to the actual valuation. We start with the valuation of standard projects and then gradually move to the more complex problems. Every section includes a case study to illustrate practically how to use the theory. The exercises in the last part of the book complement the cases.

Discounting

Theory and Reality

Discounting contains two components, time value and risk. While the time value of money in life sciences is not different to any other industry, the risk of drug and medical device development is special. Life sciences companies principally face technical risks, concerning efficacy and safety of a project. This technical risk is diversifiable. Investing in a large number of companies ensures that the ratio between success and failure corresponds to the industry-wide success rate. The worse the diversification, the more dependent is the portfolio on the success of single projects, with a one-product company being the extreme. Unfortunately, these scientific risks are not reflected in the discount rate if calculated with CAPM. The for drug development companies is on average rather low, in some cases even zero. The subsequent CAPM discount rate is therefore in the range of the risk free rate and the market return, typically between 5% and 10%. The argument goes that the technical risk is already incorporated in the valuation by the use of success rates. Nevertheless, non-diversification is a special kind of risk that can critically affect daily business. MCPM takes care of non-diversification. The discount rates calculated with MCPM are similar to the CAPM rates for large pharmaceutical companies. This is in line with what we have discussed above; large pharmaceutical are well-diversified and they do not depend excessively on the success of few pro-

jects. MCPM then indicates discount rates between 30% and 40% for smaller biotech companies that do not have any product on the market.

The discount rates observed in the market, either in valuations for private capital rounds or in analysts' reports, show a picture in between the two presented theories. While the discount rate of diversified companies comes close to the theoretical cost of capital calculated with CAPM, less diversified and earlier stage companies have to pay their investors a spread to the CAPM rate. Nevertheless, this spread is not as high as MCPM suggests. This confirms our caveats regarding CAPM and MCPM.

The following table displays published discount rates used by companies.

Table 4.1. Discount rate comparables

Company	Discount Rate		Source
Lilly	18.75%	Rate to discount acquired IP R&D	Annual Report 2004
Actelion	15%	Integrated drug development company with one major marketed product	Annual Report 2004
AstraZeneca	Risk free rate	Risk neutral valuation	Annual Report 2004
AstraZeneca	8%	Projects partnered with AZ	Cash offer by AZ for CAT
CAT	12.5%	Projects owned by CAT	Cash offer by AZ for CAT
Genentech	16%-19%	1999	Webpage
Genentech	20%-28%	1990	Webpage
MedImmune	11.3%	Fully integerated drug development company	Annual Report 2004
Berna Biotech	9.9%	Vaccine company, CAPM + small company spread	Merger memorandum Crucell-Berna Biotech by PWC
Merck KGaA	7%-7.6%	Chemical company with pharma business	Annual Report 2005
Schering	13.5%	Region Europe	Annual Report 2005
Schering	14.25%	Region USA	Annual Report 2005

Proposed Framework

The most critical risk of drug development companies is doubtlessly high attrition. MCPM accounts for this issue, even if in a rather intuitive way.

We do not agree with the MCPM idea that shareholders must be able to insure against possible losses. We therefore approach the discount problem in a way that considers the very basic challenge of discounting: the inclusion of risk aversion.

Table 4.2. Risks of a drug development company and how to consider them

Risks	Shared by the industry	Company specific
Description	Daily business risk, mainly operational	Characteristic exposures of a company like attrition or sales numbers/potential of single products
Modeling	Difficult, because mostly soft factors	Attrition is modeled with success rates, market risk is modeled with binomial trees or simulations
Effect on discount rate	Base business risk that must be rewarded	Company specific risks that depend on the pipeline of the company
Part of discount rate	Base rate	Spread
Quantification	CAPM applied to industry index	EUT applied to pipeline

We decompose a company's risk map into risks every company has to deal with and risks that are specific for a company, like a fingerprint of the company. The first category includes financial market risks like interest rates or exchange rates, employee turnover, human errors, war, and other operational risks. Apart from financial risks, it is almost impossible to model these risks. Most operational risks are soft and remain not quantifiable. Nevertheless, these risks are well reflected in an index and CAPM can be used to calculate the discount rate that compensates for this kind of risks.

Company specific risks include attrition, cluster risks due to over-reliance on one technology, and market risks linked to single projects or markets the company operates in. These risks are well suited for quantitative modeling, even if this is a challenging undertaking. The spread we have to add for this company specific risks must be calculated on the basis of a quantitative model. The less diversified a company, the riskier it is and the more an investor wants to be compensated for taking this risk. The theory that deals with taking risks and how to compensate for risks is called

Expected Utility Theory. Analysing the company specific risks using EUT allows calculating a corresponding discount rate that accounts only for the modeled risks. The model can then be calibrated on the market. This discount rate has to be added to the base rate we have calculated using CAPM. The final discount rate then becomes:

$$discount = risk\ free\ rate + spread(CAPM) + spread(EUT) \quad (4.1)$$

Correctly implemented, such a model allows the quantification of a company's risk profile. Intuitively, a company that has further advanced projects has a more favourable risk profile than an early stage company. Similarly, a company with licensed projects is a less dangerous investment than a company that conducts all projects on its own, putting positive cash flows much more at risk. A quantitative model like the one described above delivers the following discount rates (see Table 4.3).

The table describes the projects in the pipeline (column 1-4) and the corresponding discount rate (column 5). The more advanced a pipeline is, the lower is its discount rate. We can also see that licensing reduces the discount rate. The risk profile is furthermore affected by the disease category;

Table 4.3. Discount rates (Source: Avance)

Project 1	Project 2	Project 3	Project 4	Discount
NDA ($ 500)	Ph. 3 ($ 500)	Ph. 2 ($ 500)	Ph. 1 ($ 500)	12.0%
NDA ($ 300)	Ph. 3 ($ 300)	Ph. 2 ($ 300)	Ph. 1 ($ 300)	12.0%
Ph. 3 ($ 500)	Ph. 3 ($ 500)	Ph. 1 ($ 500)	Ph. 1 ($ 500)	13.4%
Ph. 3 ($ 300)	Ph 3 ($ 300)	Ph. 1 ($ 300)	Ph. 1 ($ 300)	13.8%
Ph. 3 ($ 500)	Ph. 2 ($ 500)	Ph. 1 ($ 500)	Ph. 1 ($ 500)	15.1%
Ph. 3 ($ 500, lic)	Ph. 2 ($ 500, lic)	Ph. 1 ($ 500, lic)	Ph. 1 ($ 500, lic)	14.2%
Ph. 3 ($ 300)	Ph. 2 ($ 300)	Ph. 1 ($ 300)	Ph. 1 ($ 300)	16.7%
Ph. 3 ($ 500)	Ph. 1 ($ 500)	Prec. ($ 500)	Prec. ($ 500)	17.3%
Ph. 3 ($ 500, lic)	Ph. 1 ($ 500, lic)	Prec. ($ 500, lic)	Prec. ($ 500, lic)	15.3%
Ph. 3 ($ 300)	Ph. 1 ($ 300)	Prec. ($ 300)	Prec. ($ 300)	18.5%
Ph. 2 ($ 500)	Ph. 1 ($ 500)	Prec. ($ 500)	Prec. ($ 500)	19.3%
Ph. 2 ($ 500)	Prec. ($ 500)	Prec. ($ 500)	Prec. ($ 500)	19.5%
Ph. 1 ($ 500)	Prec. ($ 500)	Prec. ($ 500)	Prec. ($ 500)	19.9%
Ph. 3 ($ 500)	Ph. 1 ($ 300)			19.5%
Ph. 3 ($ 500)	Ph. 1 ($ 300)	Prec. ($ 300)		19.2%
Ph. 3 ($ 500)	Ph. 1 ($ 300)	Prec. ($ 300)	Prec. ($ 300)	18.4%

success rates vary across disease categories. A company specialised in cardiovascular diseases has a lower discount rate than a company with a comparable pipeline in women's health, because success rates for CV drugs are higher. The discount rate also depends on the number of projects in the pipeline.

Volatility

The volatility is an input parameter for real options valuation. It is generally understood as an indicator of the underlying's uncertainty. Since real options valuation is a descendant from financial options valuation we first look at the definition and measurement in finance. Then draw up the particularities of volatility in drug development projects.

In quantitative finance the volatility is usually measured as the standard deviation of the daily returns (or better: log-returns) of an asset. The standard deviation indicates by how much the asset price fluctuates in a certain time. A volatility of 0 corresponds to an asset with no uncertainty, i.e. the asset is completely predictable. The higher the volatility, the less predictable the asset. Indices like the Dow Jones or FTSE 100 have a relatively

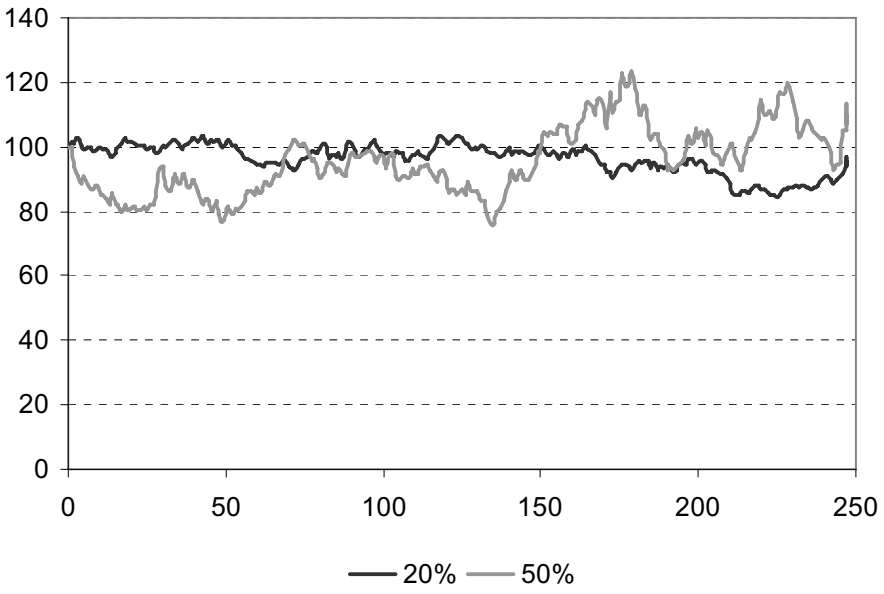

Fig. 4.1. Two simulated stock price curves using different volatilities

low volatility (10%-20%) because of their diversification. Single shares on the other hand are affected by company specific events and can have considerably higher volatilities. Volatilities of 50% to 80% are not rare for biotech companies.

The volatility measures the fluctuations or the uncertainty of an asset and its price. If the volatility refers to the past changes of the share price we call it historical volatility. In the continuation we are more interested in the future volatility, a measurement of the expected changes of the share price. In general we can say that the volatility is driven by the change of appreciation of the asset's price by the investors. Various factors influence this appreciation:

1. Uncertainty about results and performance of the company
2. Risk profile of the company
3. Appreciation of the industry of the company and the market in general

An exporting company depends naturally on foreign exchange rates. Oil companies depend on the oil price. And all companies depend on the way they seize business opportunities, business scandals and their corporate governance. Some components of the volatility can be attributed to the market and the industry, others are particular to the company. The volatility of a biotech share is mainly driven by the uncertainty of future clinical trials. A positive result leads may let the share price sky rocket, a negative result can mean the end of the company.

In real options valuation we require the volatility of the underlying, i.e. the expected peak sales. An analysis of this volatility is jeopardised by the natural life cycle of a product that clearly motivates a large part of changes in sales numbers. An analysis of the volatility must therefore distinguish between changes due to the sales curve and changes due to a changed market potential. Factors different from natural growth and the life cycle that influence the sales numbers comprise:

1. General state of the economy
2. Competition
3. Regulation

The volatility of a drug is influenced by the drug characteristics and its position in the market. Fashion drugs (nice to have drugs) depend more on the purchasing power of patients than life saving drugs (need to have drugs). The rise of new competition can seriously impact the sales num-

bers of a drug. Alternatively, competitors might lose sales due to newly discovered side effects. National health care policies can boost or slow down the sales numbers. Furthermore, we have to consider that a first-in-class drug is likelier to receive competition with improved efficacy, less side effects or increased application convenience. Nevertheless, the uncertainty of sales is rather moderate once the drug is on the market. We estimate the post-development volatility of a drug between 10% and 20%.

The above discussed volatility measures the change of the sales potential assuming that the drug and its qualities is known. The volatility that matters for real options valuation describes the uncertainty of the peak sales estimate before commercialization, i.e. when some properties of the drug are still not fully known. The peak sales estimate obviously also depends on the same factors like the post-development volatility, but there are some additional risk drivers. The clinical development reveals important information concerning safety, efficacy, dosage, further applications and patient convenience and allows a benchmarking to other therapies. All these factors can have a positive or a negative impact on the sales potential of the drug. Once clinical development is finished, these issues are well explored. The pre-commercialisation volatility is therefore higher.

We know that in drug development about 30% of all abandonment is caused by economic reasons, i.e. lack of profitability (Dimasi 2001). This is exactly what real options model: the ability to halt a project because it does not make any economic sense. We can therefore adjust the volatility in a way that for a standard drug development project 30% of abandonment is economically motivated. This leads to a volatility of 25% to 35%. Accounting for special factors that impact the estimation of peak sales like a novel mechanism of action, an undeveloped market for a new indication, or a clear competitive environment, we finally arrive at a range of 20% to 50% volatility for the peak sales estimate. The upper end representing a novel approach with many uncertainties concerning indication and target population.

Peak Sales

The estimation of peak sales raises difficulties when preparing the input parameters for valuation. With early stage projects it is virtually impossible to estimate the peak sales. This uncertainty gets resolved with the progression of the project trough development. In the following, we discuss how to predict the sales for projects corresponding to their development stage.

Obviously, very early in project development we do not have a clear picture of the future sales potential. We often not even know what exact disease we can treat with the compound. This is especially true for cancer drug development. Even though there are signs when testing the drug in animals, the indication for clinical testing will only get evident after clinical phase 1. The sales estimate has always to be as precise as possible and justifiable. It is not believable to predict the peak sales of a cancer drug in preclinical testing based on the number of subjects that will receive the drug once it is on the market. In preclinical testing one often does not even know in which cancer the drug might be efficacious. But we can say that the drug might reach the average peak sales of the most similar comparable basket of drugs that are currently on the market. I.e. if we are looking at a new cytotoxic drug, we can put together the subset of all cytotoxic drugs on the market today and use this figure as a comparable. Of course, the sales figure needs to be projected into the future. We have to consider competition and the behavior of the disease. For a drug that is even further back in development we could simply use the average sales of all drugs that are currently on the market. In this situation we argue that we do not know enough about the drug, but the most closely comparable reference is the average drug today on the market. We always take the best comparable for early stage projects. If we want to make a conservative estimate for the future peak sales we take the median sales. This way we diminish the influence of a few blockbusters on the peak sales figure.

We can also estimate the peak sales with a top down approach. We define the size of the market, e.g. market for anti-hypertension drugs. Then the future market share of the drug is estimated, e.g. first year 2%, second year 3% etc. Important is to predict the market size, it the market is growing, shrinking and by how much each year. Already modest growth rates at the time of drug development mean enormous changes. E.g. a drug is in clinical phase I, estimated time to launch are 8 years. The current market size is $ 800 mn, growing by 4% each year. The predicted market share of the drug in the first year is 5%. At time of marketing, the market size will be $ 1.18 bio, and the predicted market share $ 60 mn, instead of $ 40 mn (5% of $ 800 mn), a 50% increase.

Once the project advances, we learn more about the details on the drug, its safety and efficacy profile, and its anticipated indication. We know what is the best dosing schedule and we can define a price for the drug based on the current drugs approved on the market today. This approach is called bottom-up and needs considerable due diligence, but allows to pre-

dict more precisely the sales potential. The estimate gets much more imprecise if we are looking at a first in class device or drug where we cannot foresee how the regulatory authorities will handle the drug labeling and how the insurers will reimburse the drug.

Project Valuation

In this section, we explain how to value life sciences projects. The theory on project valuation will lay the grounds for the subsequent chapters; license contract, IP, and firm valuation follow the same principles.

In the following, we designate drug or medical device research and development prior to market launch as projects, once on the market as products. The time to market can range from months to years. Typically, there are still future cash flows occurring related to the project, and the projects can be subject to attrition, i.e. being unsuccessful or simply being stopped.

Project valuation matters for:

1. Project managers negotiating the budget.
2. Portfolio managers reviewing the pipeline.
3. Business developers and licensing managers negotiating a license or collaboration deal
4. Investors selling or buying companies.
5. Analysts reviewing companies.

Projects managers have to apply for their budget on a regular basis. Budget debates tend to be highly political and the project managers compete with each other to get as much money as possible. Naturally, they want to present their projects as priority to the company, i.e. as more valuable than the competitor projects. A project manager must therefore understand what parameters drive the projects value and find good justifications why those should be so favourable in his project.

Business developers and licensing managers need to value a potential project for licensing from two sides. First, they have to value the project as if it would be developed as a proprietary drug in-house, in this case as a project. The licensor's value is the minimum price of the license contract; the licensee's value the maximum price. Second, they have to value the license contract with the proposed license terms to make sure they get a fair deal,

i.e. the price of the license contract must lie between the lower and upper limit. We will discuss the implications of valuation to licensing and negotiation in the next sections.

Portfolio managers on the other hand do not have any interest in an optimistic valuation of the pipeline. They need to compare the projects in the pipeline objectively in order to optimally allocate resources, to put projects on hold, or even to abandon some. Because project managers have personal incentives in overvaluing their projects, portfolio managers must therefore critically question all parameters when reviewing the pipeline.

Investors have various motivations to value a project. Either they want to invest directly into a project or in a basket of projects, i.e. in a company. When investors invest in a company, they try to negotiate a low valuation of the company so they do not have to pay the full price for it. Venture capitalists for example are in the comfortable position to distribute money to clients looking for money. As they are in the dominant negotiation position, they can value the company below its real value and offer the money on a take-it-or-leave-it basis. This advantage disappears as soon as several venture capitalists compete for the offered stake. Once the investors want to sell their investment, they want to get the highest possible price. The valuation then needs to be at the higher end.

Analysts will value single projects to get the value of the entire company, just as investors do. They will not expose themselves when performing this task. Consequently, many analysts' recommendations are alike and provide no new information. An analyst glorifying a young company that goes bankrupt the next month will most likely have to look for a new position. On the other hand, an analyst that is wrong with his prediction but has followed the herd can claim to be at least not the only one.

The reader might be surprised about the view of optimistic, realistic, or low valuations. However, the fact that people have different goals when valuing a project leads to different values. A project will not represent the same value to the buyer or the seller. The fact that different interests influence the valuation result needs to be kept in mind when handling the numbers.

We will first discuss how projects are valued with DCF in theory and in the first part of case study 1. We will then look at how to value projects with ROV and discuss the second part of case study 1.

Project Valuation with DCF

To value a project we must first define all cash flows related to the project and then determine the applicable discount rate. Once these data are assessed, we can proceed to the actual valuation.

Cash Flows

Cash flows are characterised by *time*, *size*, and *probability* to occur.

Time. During research and development, cash flows are the costs of the individual phases. Mostly, these costs are spread over the whole length of a phase. Once the product approaches commercialisation, the company has to invest in preparing product launch, sales force, and production facilities. Launch costs can incur over several years, sometimes starting even earlier than launch. After launch, the cash flows are linked to sales revenues and operating expenses.

Size. All cash flows are negative to the exception of sales revenues and licensing revenues. The sales development is modeled by the peak sales estimate, the growth rate, and the sales curve. The peak sales estimate corresponds to the maximum sales revenue of the product if it would already be on the market today. A product first needs some time to achieve its maximum market share. Therefore we model the sales dynamics with a sales curve, starting at 0% and reaching 100% at the time when the product reaches its maximum market penetration. We account for the difference between today's market and the market at time of maximum penetration by applying a growth rate. The growth rate displays the annual average increase of the peak sales estimate due to economic, industry specific, and demographic growth.

$$revenue_t = \underbrace{SalesCurve_t}_{\substack{penetration \\ at\ time\ t}} \underbrace{(1+\mu)^{(t-t_0)}}_{\substack{growth \\ adjustment}} PeakSales \tag{4.2}$$

The sales revenues are reduced by the costs of goods, marketing, distribution, and administrative costs. These reductions are summarised in the operative margin.

Probability to occur. After each phase, it is possible that the project has to be abandoned. The success rate of each phase indicates with what probability the project continues to the next phase. This means that only the cash flows of the current development phase are certain, all others occur

with the probability that the previous phases are passed successfully. The cash flows of the second phase only happen with the probability that the first phase is successful, i.e. with the success rate of the first phase. The cash flows of the third phase then only happen with the probability that the first and second phase are successful, i.e. the success rate of the first phase times the success rate of the second phase. The cash flows related to commercialisation of the product happen with the probability that the project passes all prior R&D phases successfully.

We have now identified all cash flows related to the project to value and defined their time, size, and probability. The next input parameter that we have to determine is the discount rate.

Discount Rate

With the discount rate we account for the *time value of money* and the *risk.*

Time value. Typically, the time value of money is the risk free interest rate, which is the rate offered in state issued securities (e.g. T-Bills). The discount rate is composed of the current risk-free intertest rate and a risk premium on top of that.

Risk. Generally, risk summarises all sort of uncertainty regarding the cash flows of the project. These encompass technical uncertainty, i.e. the danger that the project must be halted at some stage, the fluctuation of sales revenues and foreign exchange rates, and other deviations from the valuation assumptions.

There is no generally accepted theory how to determine the discount rate. Some say that one should apply a different discount rate for every project, others argue for a uniform discount rate on company or portfolio level. It depends what the purpose of the valuation is. An in-licensed product will most often not be discounted with the in-house discount rate but with a higher one to take in consideration the information asymmetry. A portfolio manager will discount all projects with the same discount rate of the company to get a uniform valuation.

We propose a framework to define the discount rate as outlined in the section on discounting in life sciences. The number depends on the risk profile of the company, its pipeline, and its projects and allows a very good quantification of these parameters.

Valuation

Once we have assessed all input parameters, we can proceed to the actual valuation. Using the discounted cash flows method we must:

1. Adjust each cash flow by its probability to occur. This means that we multiply each cash flow with its probability (P).
2. Discount each cash flow back to the present or to the date we want to know the value for.
3. Sum up all discounted and probability adjusted cash flows to the net present value.

In mathematical terms this reads:

$$NPV = \underbrace{\sum_{t_i} \underbrace{\underbrace{(1+r)^{-t_i}}_{2} \underbrace{P_{CF_{t_i}} CF_{t_i}}_{1}}_{3}}_{} \tag{4.3}$$

If the net present value is positive, then the valuation suggests continuing the project. A positive value means that the internal rate of return of the project is higher than the hurdle rate, i.e. the discount rate. On the other hand, a negative value should lead to abandonment of the project, since the invested capital yields not the required return.

Case Study Project Valuation: DCF

Dr. Project Manager loves his cardiovascular drug research project he has just successfully carried trough preclinical testing. The results are encouraging and allow planning for the phase 1 clinical trial. Dr. Project Manager now has to apply for his budget. In order to convince the management that his project is worthwhile, he wants to value it. He knows that the mid-size pharma company he is working in has a very strong clinical research pipeline with good projects, but the company is lacking the cash to fund all of them. Dr. Project Manager wants to show that his project has a high value and an attractive return on investment (ROI). For this he follows the above- described schedule and first defines the cash flows with respect to size, probability, and time. Second, he determines the discount rate, and third, he proceeds to the actual calculation.

Cash flow size: *Dr. Project Manager draws up the budget for the next phases. As a starting point, he wants to figure out all the to bring the project on the market. After consulting his colleagues in the clinical trial and marketing department he comes up with the following cost assumptions for his project:*

Table 4.4. Project development costs

Clinical Phase 1	$ 9 mn
Clinical Phase 2	$ 22 mn
Clinical Phase 3	$ 80 mn
Approval	$ 3 mn
Launch	$ 120 mn

The launch costs include the construction of a new production plant and the establishment of a new marketing department. Still left is the estimation of the revenues the product will achieve. Dr. Project Manager thinks that based on the limited knowledge about the efficacy profile of the drug, it is not possible to predict the peak sales yet. He decides to look at all the comparable drugs that are now on the market and to calculate the average sales his project might achieve compared to the present market. The average sales for comparable marketed cardiovascular drugs in 2004 were $ 486 mn. It is still early to determine the sales with a bottom-up approach, therefore Dr. Project Manager opts for a comparative approach. However, he feels that the average number is too optimistic for his project. Therefore he prefers to use an estimate that is not distorted by the unrealistic scenarios to achieve a blockbuster. For this he can use either the median of comparable product sales or the most likely sales. He decides for the most likely sales to exclude too optimistic scenarios and the distortion by niche and under-performing products. The most likely peak sales amount to $ 241 mn. Dr. Project Manager is not sure whether the general market growth between 5% and 10% can be applied to his project. The market growth could very well be linked to the increasing number of therapies available, and for a single product, this market growth could have even negative substitution effects. He therefore decides to use a neutral 0% growth. After defining the peak sales, he still has to elaborate when the peak sales will be reached and when competition sets in. Again, due to limited knowledge on the project, he chooses to use the following standard sales curve for a drug with patent expiry after 12 years:

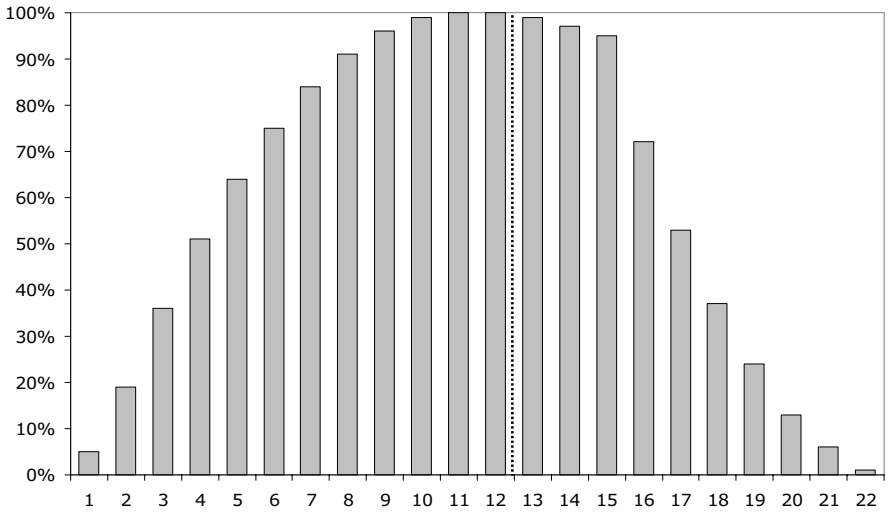

Fig. 4.2. Standard sales curve

Finally, Dr. Project Manager must reduce the sales revenues by the operating costs, which involve costs of goods, costs of marketing and sales, and some general and administrative costs. Whet will be left of the sales revenues is the operating margin. Colleagues from the financial department suggest him to use 65%.

Cash flows probability. *With this Dr. Project Manager has the size of the future cash flows. He now wants to know how likely they will occur. Therefore, he needs to find out the probabilities of passing the next development phases and obtaining regulatory approval. Studying the literature, he comes up with the following success rates (Kola et al. 2004):*

Table 4.5. Project success rates

Clinical Phase 1	*63%*
Clinical Phase 2	*42%*
Clinical Phase 3	*75%*
Approval	*95%*

Cash flows timing. *Having found the costs and the success rates, Dr. Project Manager still needs to define the timelines for the project. Again, he consults his colleagues and studies the literature. The timeline he assumes for his valuation are:*

Table 4.6. Development time

Clinical Phase 1	*1 year*
Clinical Phase 2	*2 years*
Clinical Phase 3	*3 years*
Approval	*2 years*

He assumes that the clinical costs are equally spread over the length of the phase; the costs for approval are due at the beginning of the approval phase. Launch costs are distributed over three years, one third before launch, one third in the first year, and one third in the second year.

Discounting. Dr. Project Manager decides now that his valuation will be based on a standard rNPV calculation. Therefore, he needs to define the discount rate he will apply to the calculations. Not sure about this, he considers if he should take a discount rate specific for his project, or the success rate the company applies generally. Still not smarter after having studied a textbook on valuation he calls up his friend Prof. Corporate Finance. The professor tells him that there is no sound theory on how to adjust the discount rate for project risks. However, he suggests using the company discount rate, as this is certainly lower and yields therefore a higher value. Dr. Project Manager therefore goes ahead with the company internally used discount rate of 14%.

Solution Case Study Project Valuation: DCF

Determination of cash flows. We deduce the cash flows from the assumptions and attribute them to the right period. The R&D expenses are spread uniformly over the length of the corresponding phase, except the expenses for filing an NDA. The launch costs are distributed over three years, one-third before launch, the other two thirds in the two first years of commercialisation. We then need to compute the sales revenues. In a first step we must know the peak sales in each corresponding year. The peak sales the product achieves in the market in *i* years from now are:

$$PeakSales(i) = PeakSales * (1+\mu)^i \tag{4.4}$$

In our particular case the growth rate is 0%. We therefore have the same peak sales estimate until launch. By way of example we assume the growth rate to be 5%, in that case the peak sales in year 9 would be:

$$PeakSales(9) = \$241mn * (1+0.05)^9 = \$373.87mn$$

To deduce the sales revenues from the peak sales we must multiply them with the sales curve:

$$Salesrevenues(i) = PeakSales(i) * Salescurve(i) \quad (4.5)$$

We are now only missing the operational expenses, defined as follows:

$$OpExpenses(i) = Salesrevenues(i) * (100\% - MARGIN) \quad (4.6)$$

This gives us the final table with all cash flows:

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
	Phase 1	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Approval	Approval	Market	Market
Sales curve									5%	19%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues									**$ 12 mn**	**$ 46 mn**
Operating expenses									**($ 4 mn)**	**($ 16 mn)**
R&D Expenses	**($ 9 mn)**	**($ 11 mn)**	**($ 11 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 3 mn)**	**($ 40 mn)**	**($ 40 mn)**	**($ 40 mn)**
	Year 11	**Year 12**	**Year 13**	**Year 14**	**Year 15**	**Year 16**	**Year 17**	**Year 18**	**Year 19**	**Year 20**
	Market	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**
Sales curve	36%	51%	64%	75%	84%	91%	96%	99%	100%	100%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues	**$ 87 mn**	**$ 123 mn**	**$ 154 mn**	**$ 181 mn**	**$ 202 mn**	**$ 219 mn**	**$ 231 mn**	**$ 239 mn**	**$ 241 mn**	**$ 241 mn**
Operating expenses	**($ 30 mn)**	**($ 43 mn)**	**($ 54 mn)**	**($ 63 mn)**	**($ 71 mn)**	**($ 77 mn)**	**($ 81 mn)**	**($ 84 mn)**	**($ 84 mn)**	**($ 84 mn)**
R&D Expenses										
	Year 21	**Year 22**	**Year 23**	**Year 24**	**Year 25**	**Year 26**	**Year 27**	**Year 28**	**Year 29**	**Year 30**
	Market	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**
Sales curve	99%	97%	95%	72%	53%	37%	24%	13%	6%	1%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues	**$ 239 mn**	**$ 234 mn**	**$ 229 mn**	**$ 174 mn**	**$ 128 mn**	**$ 89 mn**	**$ 58 mn**	**$ 31 mn**	**$ 14 mn**	**$ 2 mn**
Operating expenses	**($ 84 mn)**	**($ 82 mn)**	**($ 80 mn)**	**($ 61 mn)**	**($ 45 mn)**	**($ 31 mn)**	**($ 20 mn)**	**($ 11 mn)**	**($ 5 mn)**	**($ 1 mn)**
R&D Expenses										

Fig. 4.3. Calculation of project value

Probability of cash flows. For each year we compute the probability that the project is still alive. During the first phase the project is certainly alive. The second phase is only achieved if the first phase is successfully passed, i.e only achieved with the success rate.

$$Prob(Phase(i)) = Prob(Phase(i-1)) * SuccessRate(Phase(i-1)) \quad (4.7)$$

In particular we have for phase 1 a probability of 100%, for phase 2 a probability of 100%*63%=63%, then for phase 3 a probability of 63%*42*=26% and so on. We then calculate the risk adjusted net cash flows (rnCF); we sum up all cash flows of the same period and multiply with the probability that the project is still alive in that period.

$$rnCF(i) = Prob(i) * (SalesRevenues(i) - OpExpenses(i) - R\&DExp(i)) \quad (4.8)$$

For year 9 this is:

$$rnCF(9)=Prob(9)*(SalesRevenues(9)-OpExpenses(9)-R\&DExp(9)) \quad (4.9)$$

$$19\%*(\$12\ mn-\$4\ mn-\$40\ mn)=-\$6\ mn$$

Discounting of cash flows. We discount all risk adjusted net cash flows back to the valuation date; we now have the risk adjusted net present cash flows.

$$rnpCF(i)=rnCF(i)*(1+discount)^{-i} \quad (4.10)$$

Again for year 9 this would be:

$$-\$6\ mn*(1+0.14)^{-9}=-\$2\ mn$$

The risk adjusted net present value (rNPV) finally is the sum of all risk adjusted net present cash flows.

$$rNPV=\sum_i rnpCF(i) \quad (4.11)$$

	Length (y)	Costs	Suc. Rate
Phase 1	1	$ 9 mn	63%
Phase 2	2	$ 22 mn	42%
Phase 3	3	$ 80 mn	75%
Approval	2	$ 3 mn	95%

Launch costs	$ 120 mn
Peak Sales	$ 241 mn
Growth Rate	0%
Operating Margin	65%

Discount Rate	14%

	Year 1 Phase 1	Year 2 Phase 2	Year 3 Phase 2	Year 4 Phase 3	Year 5 Phase 3	Year 6 Phase 3	Year 7 Approval	Year 8 Approval	Year 9 Market	Year 10 Market	Year 11 Market
Sales curve									5%	19%	36%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues									**$ 12 mn**	**$ 46 mn**	**$ 87 mn**
Operating expenses									**($ 4 mn)**	**($ 16 mn)**	**($ 30 mn)**
R&D Expenses	**($ 9 mn)**	**($ 11 mn)**	**($ 11 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 3 mn)**	**($ 40 mn)**	**($ 40 mn)**	**($ 40 mn)**	
Success Rate	63%	100%	42%	100%	100%	75%	100%	95%	100%	100%	100%
Probability	100%	63%	63%	26%	26%	26%	20%	20%	19%	19%	19%
Risk adjusted net CF	**($ 9 mn)**	**($ 7 mn)**	**($ 7 mn)**	**($ 7 mn)**	**($ 7 mn)**	**($ 7 mn)**	**($ 1 mn)**	**($ 8 mn)**	**($ 6 mn)**	**($ 2 mn)**	**$ 11 mn**
Discount	100%	88%	77%	67%	59%	52%	46%	40%	35%	31%	27%
Net present CF	**($ 9 mn)**	**($ 6 mn)**	**($ 5 mn)**	**($ 5 mn)**	**($ 4 mn)**	**($ 4 mn)**	**($ 0 mn)**	**($ 3 mn)**	**($ 2 mn)**	**($ 1 mn)**	**$ 3 mn**

rNPV	**$ 2.9 mn**
IRR	**14.6%**

Fig. 4.4. rNPV project valuation

The spreadsheet summarises all calculations we have performed so far to calculate the rNPV of the project.

Project Valuation with Real Options

When calculating the net present value of a project using the discounted cash flow method; we determine the estimate of the future cash flows as if it were certain, with no room to fluctuate. We know that the estimate is not accurate; therefore we have to use a risk premium to remunerate for the uncertainty of the estimate. However, in the calculations we then assume that the size of the cash flows is fixed. Nevertheless, decisions along the project path depend exactly on parameters that may change in the course of time. Imagine that a competing project shows outstanding clinical results. This might impact our sales estimations; and maybe the sales estimations are even that low that they do not justify further investments in the project. Revaluing the project, management then decides to abandon it because of non-profitability. Such scenarios are not considered in the DCF framework. To get a realistic value of the project it is therefore reasonable to model the uncertainty of the parameters that influence project relevant decisions.

Life sciences projects have critical decision points at the beginning of each phase. The previous phase gave insight into the characteristics of the product, how it behaves with respect to efficacy, safety, and compared to competitive products. This allows drawing some conclusions on the market potential. If the market potential does not compensate for the coming investments, i.e. if the value of the project is negative, then the project is stopped.

Concretely, we should model the economic potential of the project, i.e. the estimated peak sales; the sales potential is most prone to uncertainty and has a crucial impact on the profitability of a project. We therefore have to assess, in addition to the parameters used in the DCF calculation, the volatility of the peak sales estimate. We have dedicated a special section to the determination of the volatility.

Real Options Valuation

We can now value the project. In a first step, we model the uncertain parameters, i.e. the peak sales estimate; we span a binomial tree from the date of valuation to the time of the last decision. In life sciences, this is mostly the date of filing a new drug application or launch. The time steps of the tree should be chosen in a way that they reflect the project plan. Often a project is scheduled in years, half years, or sometimes in quarters. In the second step, we value the project at each end node of the tree using the discounted cash flows method. Remember that if there are no decisions to

Real options valuation

1. Span a binomial tree for the peak sales estimate
2. Value the project in each leaf of the tree
3. Work back the tree to the root. For each time step do
   1. Take expectation of up- and down-step
   2. Apply success rate if necessary
   3. Discount for the elapsed time step
   4. Add cash flows
   5. Decide if it is a decision point

$$V_t = \underbrace{\max\left\{\underbrace{(1+r)^{-dt}}_{3}\underbrace{P_t}_{2}\underbrace{\left(pV_{up}^{t+dt} + (1-p)V_{down}^{t+dt}\right)}_{1} + \underbrace{CF_t}_{4}, 0\right\}}_{5} \tag{4.12}$$

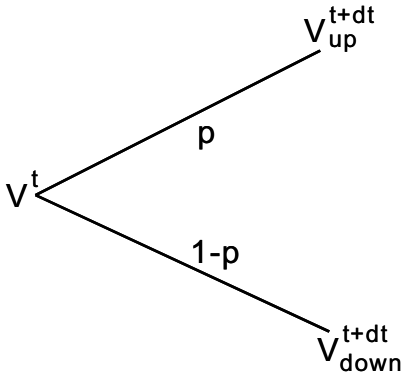

Fig. 4.5. One time step

make, DCF and real options yield the same value. The third step is working back the tree to the root node. The value of the project is then equal to the value we have calculated for the root node. Working back the tree means that we place ourselves in a node one time step back of the layer we have already valued. Consequently, we know the value of the project if it reaches either the upper or the lower state. To get the value for the state we have placed ourselves in we must complete five actions. First, we must take the expectation of reaching after the time step the upper or the lower state. Second, we need to account for the fact that the project

might not reach the next time step because of attrition. Note that for most of the time steps the transition probability is 100%. Only at the end of a phase, attrition becomes effective, i.e. completing a development phase. Third, We have to account for the time that elapses in this time step; hence, we have to discount the value. Fourth, we must add the cash flows that occur in this time step. The cash flows must not be probability adjusted. The attrition rates are already considered in action 2. Finally, fifth, we must decide whether it is worthwhile to continue the project in that node. Of course, this happens only at decision points, i.e. at the beginning of each phase. A project is usually continued if its value is positive. In case of a negative value, the project is abandoned and consequently its value in this node is set to zero. This fifth action is exactly where the option thinking comes in. We lift a negative value to zero, which is a value increase (by avoiding losses). Management makes use of its possibility to revaluate the project and abandons it if it is not profitable. Using the real option framework we assume that at each decision point in the future the management values the project according to the market state and abandons all projects with a negative value. This thinking is not part of the DCF approach.

For all nodes of the tree we have calculated the value of the project in that specific state, i.e. at that moment, with that peak sales estimate. The goal of the valuation is to find out the value of the project at valuation date with the given peak sales estimate. This is exactly the value of the root node. Note that this value could still be negative, or zero, suggesting abandonment of the project. To illustrate the steps of the real options valuation we continue with the case study.

Case Study Project Valuation: ROV

When Dr. Project Manager calls his friend Prof. Corporate Finance to ask about the discount rate he should best use, the latter also suggests him to use the real options valuation method. Prof. Corporate Finance argues that real options valuation is closer to the reality of a drug development project, since at the beginning of each phase management revalues the project and decides whether to continue it or not, just like in the present situation. This argumentation sounds fair to Dr. Project Manager and he decides to find out how much value management flexibility adds to his project.

Volatility. *The only parameter he has to determine in addition to the previous DCF calculation is the volatility. Dr. Project Manager remembers that the volatility is a measure of uncertainty, but is confused about the*

parallel use of volatility and success rates. Furthermore, he is not sure about how to determine the volatility. So, he calls up his friend once again. Prof. Corporate Finance explains him, that the volatility captures only the uncertainty of the peak sales and not of the whole project. A straightforward method to measure the volatility would therefore be calculating the volatility of adjusted drug sales. These might range from 10% to 20%. But Prof. Corporate Finance argues, that the volatility does not actually refer to the peak sales, but to the peak sales estimate. This is impacted during R&D by the clinical results that allow conclusions on the commercial performance of the drug. New information during R&D is not included in the volatility of marketed drug sales. He suggests to add an R&D spread on top of the volatility of marketed products of about 15%. Dr. Project Manager decides to use a volatility of 30%, representing an average risk profile (for a detailed description on how to calculate the volatility consult the section in Basics and Special Aspects).

Solution Case Study Project Valuation: ROV

Real options valuation with a binomial tree is done in three steps. First, span the tree, second, attribute a value to each end node, and third work back the tree to the root node.

Construction of the binomial tree. We model the underlying peak sales estimate with a binomial tree following the parameters μ*=0% (growth rate)* and σ*=30% (volatility)*. Still using yearly time steps this gives us:

$$u = \exp\left(\sigma\sqrt{dt}\right) = \exp\left(0.3 \cdot \sqrt{1}\right) = 1.35$$

$$d = \frac{1}{u} = \frac{1}{1.35} = 0.74$$

$$p = \frac{(1+\mu)^{dt} - d}{u - d} = \frac{(1+0)^{1} - 0.74}{1.35 - 0.74} = 43\%$$

Starting at valuation date we mount the tree to the final decision point, in our case beginning of NDA. NDA because we assume that this is the last decision point. We therefore model 6 time steps (1 year for phase 1, 2 years for phase2, and 3 years for phase 3). This gives us the following tree:

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Phase 1	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Approval
						$ 1'458 mn
					$ 1'080 mn	1%
				$ 800 mn	1%	$ 800 mn
			$ 593 mn	3%	$ 593 mn	5%
		$ 439 mn	8%	$ 439 mn	9%	$ 439 mn
	$ 325 mn	18%	$ 325 mn	18%	$ 325 mn	16%
$ 241 mn	43%	$ 241 mn	31%	$ 241 mn	25%	$ 241 mn
100%	$ 179 mn	49%	$ 179 mn	36%	$ 179 mn	29%
	57%	$ 132 mn	42%	$ 132 mn	34%	$ 132 mn
		33%	$ 98 mn	32%	$ 98 mn	30%
Legend:			19%	$ 73 mn	23%	$ 73 mn
Peak Sales				11%	$ 54 mn	16%
Probability					6%	$ 40 mn
						4%

Fig. 4.6. Binominal tree with probabilities and market states

	Year 7 Approval	Year 8 Approval	Year 9 Market	Year 10 Market	Year 11 Market	Year 12 Market	Year 13 Market	Year 14 Market	Year 15 Market	Year 16 Market	Year 17 Market	Year 18 Market
Sales curve			5%	19%	36%	51%	64%	75%	84%	91%	96%	99%
Peak Sales	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 m
Sales revenues			**$ 73 mn**	**$ 277 mn**	**$ 525 mn**	**$ 744 mn**	**$ 933 mn**	**$ 1'093 mn**	**$ 1'225 mn**	**$ 1'327 mn**	**$ 1'400 mn**	**$ 1'443 m**
Operating expenses			**($ 26 mn)**	**($ 97 mn)**	**($ 184 mn)**	**($ 260 mn)**	**($ 327 mn)**	**($ 383 mn)**	**($ 429 mn)**	**($ 464 mn)**	**($ 490 mn)**	**($ 505 mn**
R&D Expenses	**($ 3 mn)**	**($ 40 mn)**	**($ 40 mn)**	**($ 40 mn)**								
Success Rate	100%	95%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Probability	100%	100%	95%	95%	95%	95%	95%	95%	95%	95%	95%	95%
Risk adjusted net CF	**($ 3 mn)**	**($ 40 mn)**	**$ 7 mn**	**$ 133 mn**	**$ 324 mn**	**$ 459 mn**	**$ 576 mn**	**$ 675 mn**	**$ 756 mn**	**$ 819 mn**	**$ 864 mn**	**$ 891 mn**
Discount	100%	88%	77%	67%	59%	52%	46%	40%	35%	31%	27%	24%
Net present CF	**($ 3 mn)**	**($ 35 mn)**	**$ 5 mn**	**$ 90 mn**	**$ 192 mn**	**$ 238 mn**	**$ 263 mn**	**$ 270 mn**	**$ 265 mn**	**$ 252 mn**	**$ 233 mn**	**$ 211 mn**

	Year 19 Market	Year 20 Market	Year 21 Market	Year 22 Market	Year 23 Market	Year 24 Market	Year 25 Market	Year 26 Market	Year 27 Market	Year 28 Market	Year 29 Market	Year 30 Market
Sales curve	100%	100%	99%	97%	95%	72%	53%	37%	24%	13%	6%	1%
Peak Sales	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 mn	$ 1'458 m
Sales revenues	**$ 1'458 mn**	**$ 1'458 mn**	**$ 1'443 mn**	**$ 1'414 mn**	**$ 1'385 mn**	**$ 1'050 mn**	**$ 773 mn**	**$ 539 mn**	**$ 350 mn**	**$ 190 mn**	**$ 87 mn**	**$ 15 mn**
Operating expenses	**($ 510 mn)**	**($ 510 mn)**	**($ 505 mn)**	**($ 495 mn)**	**($ 485 mn)**	**($ 367 mn)**	**($ 270 mn)**	**($ 189 mn)**	**($ 122 mn)**	**($ 66 mn)**	**($ 31 mn)**	**($ 5 mn)**
R&D Expenses												
Success Rate	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	200%
Probability	95%	95%	95%	95%	95%	95%	95%	95%	95%	95%	95%	95%
Risk adjusted net CF	**$ 900 mn**	**$ 900 mn**	**$ 891 mn**	**$ 873 mn**	**$ 855 mn**	**$ 648 mn**	**$ 477 mn**	**$ 333 mn**	**$ 216 mn**	**$ 117 mn**	**$ 54 mn**	**$ 9 mn**
Discount	21%	18%	16%	14%	12%	11%	9%	8%	7%	6%	6%	5%
Net present CF	**$ 187 mn**	**$ 164 mn**	**$ 142 mn**	**$ 122 mn**	**$ 105 mn**	**$ 70 mn**	**$ 45 mn**	**$ 28 mn**	**$ 16 mn**	**$ 7 mn**	**$ 3 mn**	**$ 0 mn**

rNPV	**$ 2'870 mn**

Fig. 4.7. rNPV calculation of the uppermost end node

Valuation of the end nodes. We now attribute a value to each end node; we calculate the project value as if the project were at the beginning of the approval phase, with the estimated peak sales corresponding to the node. In the most optimistic case, we calculate the value of the project assuming that it reaches peak sales of $ 1,458 mn (field on the top right end). This seems to be an unrealistic case, but bear in mind that this state is achieved only if in each time step the peak sales estimate improved, i.e. with a probability of $p^6=0.6\%$. So, the probabilities of the tree already take care of the likelihood of each state. For the valuation of the project in each end node we have to go through all steps of the DCF valuation.

The value of the project in the uppermost end node is therefore $ 2,870 mn. This we do for every end node, yielding the following results:

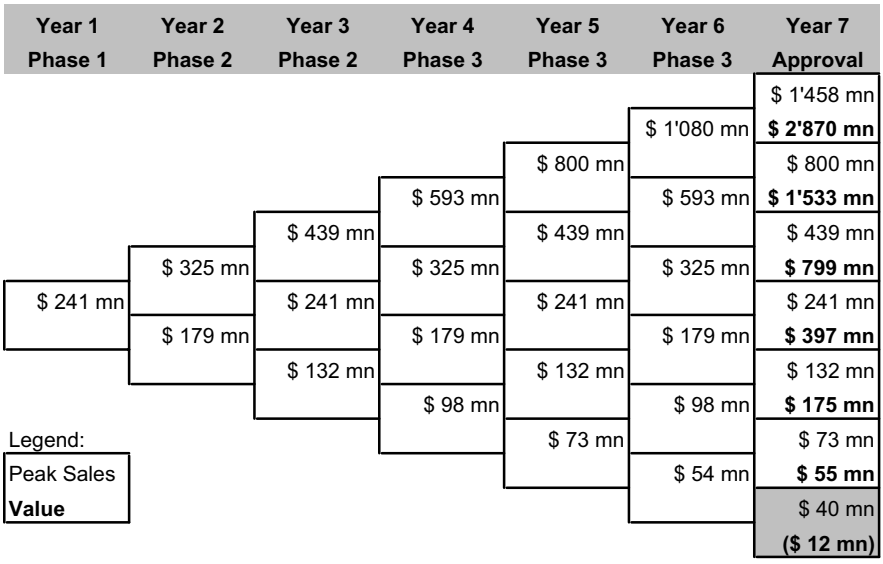

Fig. 4.8. Project value in the end nodes

Note that the value of the lowest end node is negative. This means that, if we estimate the project at the beginning of the approval phase to only achieve peak sales of $ 40 mn, we are better off abandoning the project, as it does not compensate for all the expenses that are still due. An abandoned project has a value of zero. We therefore replace the negative value with a zero.

Working back the tree. We now work back the tree. For this we have to go one time step back from the values we have already calculated. In the cur-

rent situation we have calculated all values for the beginning of the approval phase, we therefore place ourselves now in the last year of phase 3. For each state we have the possibility to reach either the upper or lower state in the following year with the respective probabilities.

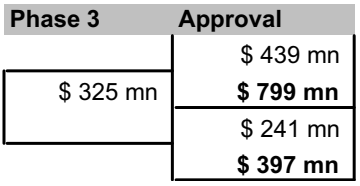

Fig. 4.9. Calculation of the value in one state

By way of example we calculate the value for the state with peak sales $ 325 mn. We know that after one time step the project will be worth either $ 799 mn with a probability of 43% or $ 397 mn with a probability of 57%. However, these probabilities only hold if the phase 3 trial is successful, i.e. in 75% of all cases. During the time step in consideration the company has to pay the last tranche of the phase 3 trial costs, $ 27 mn, and another year elapses, resulting in discounting the future values. Using the formula x, we can compute the value for the current state:

$$V_t = (1+r)^{-dt} P_t \left(pV_{up}^{t+dt} + (1-p)V_{down}^{t+dt} \right) + CF = \tag{4.13}$$

$$(1+0.14)^{-1} \cdot 0.75 \cdot (0.43 \cdot 799 + (1-0.43) \cdot 397) + 27 = 347$$

If the current state is a decision point, then we would also have to correct negative values to zero, corresponding to abandonment of the project in that state. Applying the above formula to all states and working back the tree time step after time step to the rote node, we can fill the tree with project values for each node (cf. Fig. 4.10).

We see that in phase 3 in the lowest state (grey field), the company abandons the project and in the approval phase if the peak sales amount to only $ 40 mn. The value of the project in these states is consequently zero. The value of the project at valuation date is $ 3.4 mn. Comparing this with the $ 2.9 mn DCF value we note that the possibility to halt the project if it has a negative value adds 17% of value in this case. Note that decision points are only at the beginning of the phases. In our case the project is abandoned in two decision points, beginning of phase 3 and at the beginning of approval phase in the lowest nodes.

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Phase 1	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Approval
						$ 1'458 mn
					$ 1'080 mn	**$ 2'870 mn**
				$ 800 mn	**$ 1'357 mn**	$ 800 mn
			$ 593 mn	**$ 835 mn**	$ 593 mn	**$ 1'533 mn**
		$ 439 mn	**$ 492 mn**	$ 439 mn	**$ 705 mn**	$ 439 mn
	$ 325 mn	**$ 112 mn**	$ 325 mn	**$ 411 mn**	$ 325 mn	**$ 799 mn**
$ 241 mn	**$ 50 mn**	$ 241 mn	**$ 217 mn**	$ 241 mn	**$ 347 mn**	$ 241 mn
$ 3.4 mn	$ 179 mn	**$ 37 mn**	$ 179 mn	**$ 179 mn**	$ 179 mn	**$ 397 mn**
	$ 2 mn	$ 132 mn	**$ 66 mn**	$ 132 mn	**$ 151 mn**	$ 132 mn
		($ 1 mn)	$ 98 mn	**$ 51 mn**	$ 98 mn	**$ 175 mn**
Legend:			**$ 0 mn**	$ 73 mn	**$ 43 mn**	$ 73 mn
Peak Sales				**($ 16 mn)**	$ 54 mn	**$ 55 mn**
Value					**($ 11 mn)**	$ 40 mn
						$ 0 mn

Fig. 4.10. Solving the tree to the root node

Case Discussion

Cash flows size. The determination of the peak sales in the case displays a common problem when valuing early stage projects. At the start of clinical phase one, it is often unclear what the indication of the drug might be if it reaches market. This is especially true in oncology, but also cardiovascular products like Viagra are used for other indications than initially planned. At this stage, we can often only roughly estimate what the drug might do, but not predict how many patients will be treated, and what the dosage and frequency will be. A comprehensive way to determine the sales in this case is to compare the drug to the most similar subgroup of drugs on the market today. In the example, we have simply chosen to look at all cardiovascular drug. We could also have taken a sample of antihypertensives, or beta-blockers. If we think that the drug we are developing could have the potential to also reach the extremes of the sales distribution of current drugs, we could use the average sales as a reference. If we think that our drug has not the potential to be a blockbuster, but is likely to be an average drug, we should to use the most-likely or the median peak sales as a reference. The number we get out of this approach, the comparable approach, is the sales estimate of the drug as if it were on the market today. This number can be extrapolated to the time of launch and to the time when peak sales should

be reached by estimating a growth rate and by assessing the impact of competitors with drugs currently in development. We will discuss below the problems with applying a growth rate to the sales estimate.

Cash flows probability. When we determine the probability of the cash flows we have to make sure not to base the numbers on gut feeling. There is no way in predicting the outcome of clinical trials. We have to base our valuation on average success rates conforming to our drug. Furthermore, we should always use the same source for the success rate when we want to compare the project to others. As we have described above, there are differences in the success rates depending on what sample the publication bases on.

Cash flows timing. The tricky part when determining the timing is to be realistic about the project and the sales development. Too often, drug development takes more time than anticipated. In our example, we have used round numbers for the purpose of illustration. These numbers are likely to be at the lower end of drug development duration and are likely to be exceeded. Also the sales curve for an individual drug is hard to predict. We think it is most suitable to use an average sales curve based on historical data as in our case. Obviously, this sales curve will depend on the disease group and classification of the drug (orphan).

Dicounting. As the project in our case originates from the company itself and is developed in-house, the company discount rate can be used. If the project were in-licensed or if a particular country risk were to apply, an adjustment of the discount rate could be discussed. Nevertheless, special care is needed not to subjectively manipulate the discount just to reach the desired valuation outcome. In order to compare projects it is important that the valuation approach and the input data are consistent, in particular the discount rate.

DCF vs. ROV. Using ROV instead of DCF, we assume that the estimated peak sales can change according to the volatility. The average of the estimated peak sales at the launch nodes is the same as the estimated peak sales in the DCF calculation. We therefore do not change the average predicted sales number in ROV, but we do allow the estimate to go up or down. Obviously, if the sales expectation falls below a certain point, the project is not profitable anymore, i.e. has a negative value. In ROV we model that the management halts the project, once its value becomes negative in the tree. The real option value is then increased by putting the

negative value at that node to zero, as the project is abandoned and future losses avoided. If we omit the option to abandon, i.e. if we keep the negative values, then the tree calculation yields exactly the DCF value, as shown in the figure below. This displays the consistency of the two values. The tree has been built with the condition that the expected (or mean) value development of the peak sales estimate equals the one we have supposed in the DCF approach. This was done by the use of the growth rate in the tree parameters *u*, *d*, and *p*. If we now use the same assumptions as DCF implicitly does, namely, that management continues the project except scientific attrition avoids it, then the value calculated with the tree should obviously be the same like the DCF value. It is exactly the ability of the management to react on a change of the situation, in our case a correction of the peak sales estimate due to new information about the product, its competition, and the market environment, that creates the additional value of real options valuation.

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Phase 1	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Approval
						$ 1'458 mn
					$ 1'080 mn	**$ 2'870 mn**
				$ 800 mn	**$ 1'357 mn**	$ 800 mn
			$ 593 mn	**$ 835 mn**	$ 593 mn	**$ 1'533 mn**
		$ 439 mn	**$ 492 mn**	$ 439 mn	**$ 705 mn**	$ 439 mn
	$ 325 mn	**$ 112 mn**	$ 325 mn	**$ 411 mn**	$ 325 mn	**$ 799 mn**
$ 241 mn	**$ 50 mn**	$ 241 mn	**$ 217 mn**	$ 241 mn	**$ 347 mn**	$ 241 mn
$ 2.9 mn	$ 179 mn	**$ 37 mn**	$ 179 mn	**$ 179 mn**	$ 179 mn	**$ 397 mn**
	$ 1 mn	$ 132 mn	**$ 66 mn**	$ 132 mn	**$ 151 mn**	$ 132 mn
		($ 4 mn)	$ 98 mn	**$ 51 mn**	$ 98 mn	**$ 175 mn**
Legend:			**($ 17 mn)**	$ 73 mn	**$ 43 mn**	$ 73 mn
Peak Sales				**($ 19 mn)**	$ 54 mn	**$ 55 mn**
Value					**($ 16 mn)**	$ 40 mn
						($ 12 mn)

Fig. 4.11. Real option value without abandonment of negative states

Sensitivity analysis. We now study the impact of various parameters on the valuation and discuss the implications on how to define them.

The following five parameters have a very high impact when an early stage project is at the money:

- Peak sales
- Growth rate
- Margin
- Discount rate
- Success rates

Peak sales. Naturally, peak sales must have an important influence on the value of a project, since they account for all positive cash flows. A 10% change in peak sales, i.e. a change of $ 24 mn, translates into a value change of about $ 4 mn. For a project that is right at the border of profitability as in our example, such a 10% change can lead to a value increase of more than 100%. If however we assume the project to be clearly profitable (or in the money) with annual peak sales of $ 486 mn, the same 10% change of peak sales increases the value only by 19%, or a peak sales increase of $ 49 mn translates into a value increase of $ 8 mn (cf. Table 4.7). The project is sensitive to peak sales, but even very high sales numbers are only partly translated into the absolute value of the project, while the costs for phase 1, as an example, are translated one to one into the value. E.g. an increase of $ 5 mn in clinical phase 1 costs will decrease the value by $ 5 mn.

Growth rate. As we have seen, the peak sales are an estimate of what the drug could reach if it were on the market today. Often, people adjust that number by adding a growth rate of 5-10%. The sensitivity analysis shows that a growth rate of only 1% increases the value by 200%, a growth rate of 2% by 500%. We therefore recommend not applying a growth rate at all if we work with the above-described comparable approach to determine the peak sales. It is hard to estimate what influence the industry growth rate has on a single product. The growth can be caused by demographic and pricing dynamics, in which case the growth impacts the sales figures of a single drug. But the growth can also be due to an increase in treatments, which would rather have a negative impact on a single product due to increased competition.

Margin. A 10% change in margin provokes exactly the same change as a 10% change in sales. Since we multiply each sales cash flow with the margin, we have exactly the same effect whether we modify the sales estimate or the margin by the same percentage. The following equation illustrates this:

$$SC(i)*(PS*(1+10\%))*margin=SC(i)*PS*(margin*(1+10\%)) \quad (4.14)$$

Discount rate. Like the growth rate, the discount rate has a tremendous effect on the valuation. A careful and consistent use of the discount rate is recommended and the rate should not be misused to manipulate the valuation result.

Success rates. The success rates immediately factor away a large part of the project value. If we look at the current phase, the success rate translates one to one in the valuation. As discussed above, this sensitivity calls for the use of published average success rates and forbids individual speculations about a project's success.

The parameters that influence the valuation most are not observable in reality: The growth rate and the discount rate. Already small subjective changes make valuations arbitrary and incomparable. We therefore recommend using those figures in a standardised way.

An interesting observation is that the volatility, contrary to the belief of many critics of ROV, does not have a large impact on the results.

If we consult the absolute changes in the example, we see that DCF is more sensitive to alterations of the input parameters. For this we have to understand that the real option value is actually the DCF value of the project plus the value of the flexibility to abandon the project.

$$\text{Real Option} = \text{DCF} + \text{Flexibility} \tag{4.15}$$

The flexibility is less valuable the less likely it is that management makes use of it. If now a change leads to an increase of the project value, the value of the flexibility decreases. Hence the total impact of the change is smaller for the real option value. The same is true for an input change that causes a value decrease. The project is then more likely to be abandoned because of economic reasons; the flexibility becomes more important. This increase in flexibility value partly amortises the value loss due to the input change.

We will now assess what impact changes of input parameters have on the same project if it is clearly in the money. We use peak sales of $ 486 mn (average sales) instead of $ 241 mn.

The valuation is especially sensitive to:

- Growth rate
- Discount rate

All other parameters have only a slight influence on the project as it is now clearly in the money.

Table 4.7. Sensitivity analysis

	DCF	Δ DCF	ROV	Δ ROV	Δ DCF-ROV
Base scenario	$ 47.88 mn	0%	$ 47.90 mn	0%	$ 0.02 mn
Peak Sales +10%	$ 56.82 mn	19%	$ 56.83 mn	19%	$ 0.01 mn
Peak Sales -10%	$ 38.95 mn	-19%	$ 38.97 mn	-19%	$ 0.02 mn
Launch Costs +10%	$ 47.07 mn	-2%	$ 47.08 mn	-2%	$ 0.01 mn
Launch Costs -10%	$ 48.70 mn	2%	$ 48.71 mn	2%	$ 0.01 mn
Growth Rate 1%	$ 62.75 mn	31%	$ 62.80 mn	31%	$ 0.05 mn
Growth Rate 2%	$ 80.12 mn	67%	$ 80.28 mn	68%	$ 0.16 mn
Margin +10%	$ 56.82 mn	19%	$ 56.83 mn	19%	$ 0.01 mn
Margin -10%	$ 38.95 mn	-19%	$ 38.97 mn	-19%	$ 0.02 mn
Discount +10% (15.4%)	$ 34.24 mn	-28%	$ 34.25 mn	-28%	$ 0.01 mn
Discount -10% (12.6%)	$ 65.04 mn	36%	$ 65.06 mn	36%	$ 0.02 mn
Volatility +10% (33%)	$ 47.88 mn	0%	$ 47.90 mn	0%	$ 0.02 mn
Volatility -10% (27%)	$ 47.88 mn	0%	$ 47.90 mn	0%	$ 0.02 mn
Success Rate C1 +10% (69.3%)	$ 53.57 mn	12%	$ 53.59 mn	12%	$ 0.02 mn
Success Rate C1 -10% (56.7%)	$ 42.20 mn	-12%	$ 42.21 mn	-12%	$ 0.01 mn
Costs C1 +10%	$ 46.98 mn	-2%	$ 47.00 mn	-2%	$ 0.02 mn
Costs C1 -10%	$ 48.78 mn	2%	$ 48.80 mn	2%	$ 0.02 mn
Success Rate C2 +10% (46.2%)	$ 54.71 mn	14%	$ 54.73 mn	14%	$ 0.02 mn
Success Rate C1 -10% (37.8)	$ 41.06 mn	-14%	$ 41.07 mn	-14%	$ 0.01 mn
Costs C2 +10%	$ 46.74 mn	-2%	$ 46.76 mn	-2%	$ 0.02 mn
Costs C2 -10%	$ 49.03 mn	2%	$ 49.04 mn	2%	$ 0.01 mn
Success Rate C3 +10% (82.5%)	$ 55.97 mn	17%	$ 55.99 mn	17%	$ 0.02 mn
Success Rate C3 -10% (67.5%)	$ 39.79 mn	-17%	$ 39.81 mn	-17%	$ 0.02 mn
Costs C3 +10%	$ 46.62 mn	-3%	$ 46.64 mn	-3%	$ 0.02 mn
Costs C3 -10%	$ 49.15 mn	3%	$ 49.16 mn	3%	$ 0.01 mn
Success Rate NDA +10% (100%)	$ 52.32 mn	9%	$ 52.34 mn	9%	$ 0.02 mn
Success Rate NDA -10% (85.5%)	$ 39.45 mn	-18%	$ 39.46 mn	-18%	$ 0.01 mn
Costs NDA +10%	$ 47.86 mn	0%	$ 47.87 mn	0%	$ 0.01 mn
Costs NDA -10%	$ 47.91 mn	0%	$ 47.93 mn	0%	$ 0.02 mn

We see that the difference between DCF and ROV completely vanishes when a project is clearly in the money. The probability that management has to make use of its flexibility to abandon the project is virtually zero, therefore no additional value can be attributed to the project in the real option framework. The larger differences for the growth rate differences stem from slight imprecision of the binomial tree method.

In contrast to DCF, ROV illustrates that the project might be abandoned due to a change in the peak sales estimate and sensibilises the management on this.

Simulations of Projects

Introduction

In this section, we give a short introduction to simulations and how to use them in Excel. Simulations are a very useful tool to appreciate the risk profile of a project or a company, but they are technically much more demanding than standard valuation. In order to exploit the full power of simulations we must write a code in a programming language. This is beyond the scope of this book; but we give an outlook to what can be done with simulations without programming.

Simulations are models of reality, imaginations of how it could be. While in the real world we only see one version of a random event – a dice shows only one number – we can simulate all possible outcomes. When simulating rolling a dice 1,000 times, we can see that on average one out of six times we get a one. But we can even retrieve much more out of the simulations. With what probability does an even number follow a three, or how often do we get two consecutive fours?

In life sciences, we have two different sorts of random events. First and most importantly, we do not know in advance the outcome of the trials. We can only estimate the chances of the trial to be successful; these are typically the success rates. Second, the peak sales estimate and later the peak sales themselves change over time. In reality, each trial will be either a success or a failure, and if the product reaches commercialisation, it will achieve some peak sales. While in reality we observe the results only a posteriori, we anticipate the results when we simulate. We generate randomly trial results and peak sales. Knowing the project's fate in advance, we can deduce what cash flows will occur at what time, e.g. if the project passes all phases up to phase 2 but fails in phase 3. We then would have to account for all phase costs until phase 3. Since in this scenario we would actually incur these expenditures, we have to account for them in full, without adjusting them for their probability. If we now discount all cash flows and sum them up, we obtain the value of this scenario. In the case of a phase 3 failure, it is a considerable loss, we spend the phase costs and the trial fails. Repeating this method many times, we will get scenarios where the project fails in the first phase, but also scenarios where the project reaches commercialisation. When correctly simulating the trial outcomes, the quantity of commercialisation scenarios corresponds exactly to the success rate that the project reaches the market.

Analysing the simulation results, we get a better idea of the project's risk profile. The results allow retrieving data like

- What is the probability of an IRR better than 30%?
- What is the scenario that will only be outperformed in 10% of all cases?
- What is the scenario we can outperform in 50% of all cases?
- What is the worst case scenario?

When running simulations on a portfolio or company basis, we can also check how well the pipeline is diversified; if it has some cluster risks, or how far the company value can possibly drop in case of the realisation of a very adverse scenario. We can also calculate a risk measure called value at risk (VaR) out of the simulation results. VaR(α) is the value drop which happens with a probability of α. In the portfolio simulation displayed in the figure below, the average value amounts to $ 2,860 mn. In 10% of all scenarios the value is lower than $ 2,150 mn. Consequently, the VaR(10%) amounts to $ 710 mn. We can also interpret the VaR like that: If we assume the mean value as fair, then the VaR corresponds to the negative mispricing that is exceeded in 10%.

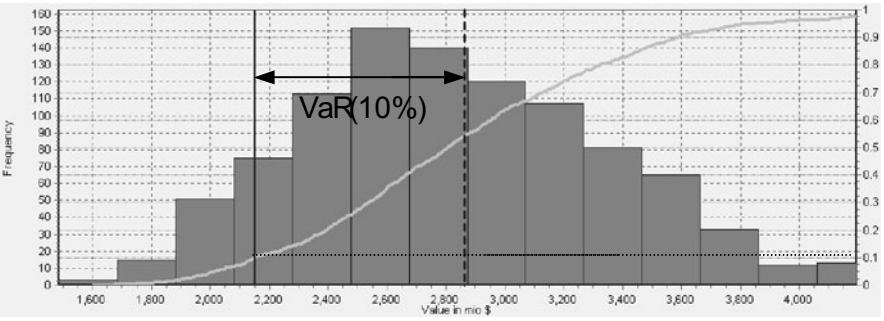

Fig. 4.12. Value at risk for a pipeline value (1,000 simulations, calculated with ri:val[1])

In the continuation, we will explain how we can generate random variables and how we can use them in simulations.

[1] ri:val is a valuation software developed by the authors and specially designed for the biopharmaceutical industry.

Theory

Excel offers a function *rand()* that generates random numbers in the interval (0,1). Each number in this interval is equally likely to come up. If we now want to generate the success of a clinical trial with success rate *P*, we need a random variable that has a value of 1 (success) with probability *P* and a value of 0 (failure) with probability (1-*P*). Using the following formula, we precisely get such a variable.

$$= if\left(rand() < P, 1, 0\right) \tag{4.16}$$

The cell with this formula takes the value 1 if the randomly generated number *rand()* is less than *P*. In the other cases, the cell takes the value 0. The formula also ensures that the simulations on average comply with the success rate for the phases. The more simulations we run the closer they approach the success rates.

The simulation of peak sales estimates is more complicated. While clinical success is an instantaneous random variable, the peak sales estimate underlies a dynamic stochastic process; it can increase or decrease, as modeled in the binomial tree. Therefore, the simulation of a peak sales estimate at time of launch does not only depend on the uncertainty, i.e. the volatility σ, but also on the time until launch *T-t*. The following formula gives the value for a simulated peak sales estimate at time *T*, *S(T)*, given the current estimate *S(t)* (with the growth rate μ).

$$S(T)=S(t)*exp((\mu-\sigma\text{^}2/2)*(T-t)+\sigma*(T-t)\text{^}(0.5)*normsinv(rand())) \tag{4.17}$$

Using these two methods to generate clinical success and peak sales estimates at launch we can set up an Excel sheet calculating the project value. Instead of calculating the probability of the cash flows, we simulate whether the project is still alive (1) at the time of the cash flow or not (0). If the project is alive, the cash flow occurs in this specific scenario, if not, it does not. By multiplying the cash flow with the cell that indicates whether the project is still alive (value 1 or 0) we get the cash flow we have to consider in this scenario. We then discount the cash flows and calculate the net present value.

We now set up an NPV calculation using randomly generated numbers determining clinical success and peak sales as described. Automating the calculation we can generate a large number of scenarios and retrieve each time the NPV for that scenario.

Implementation in Excel

Valuation of one generic scenario. The table below illustrates how to set up an Excel sheet that values a scenario according to the simulated result.

Table 4.8. Excel sheet with formulae for simulation

	A	B	C
1	Year	1	2
2	Phase	Approval	Market
3	Success rate	85%	100%
4	Success	=if(rand()<B3,1,0)	=if(rand()<C3,1,0)
5	Project alive?	1	=B5*B4
6	Peak sales	350	=B6*exp((μ+σ^2/2)*(C1-B1) +σ*sqrt(C1-B1)*normsinv(rand()))
7	Sales Curve		10%
8	Revenues		=C7*C6
9	Operating Expenses		=(1-margin)*C8
10	Investments	2	150
11	CF	=-B10	=C8-C9-C10
12	Real CF	=B11*B5	=C11*C5
13	Discount	1	=B13/(1+discount)^(C1-B1)
14	NpCF	=B12*B13	=C12*C13
15	NPV	=sum(B14:T14)	

We assume a project that is submitted for regulatory approval. We only display the first two years, the numbers for the other years being similarly calculated. In the row 4 we simulate the clinical success of the phases. For this we generate a random number and compare it with the success rate. In row 5 we then evaluate whether the project is still alive. This happens by multiplying the state of the previous year by the survival of the previous year. As soon as the project fails, all cells in row 5 left of that failure become zero. In cell C6 we simulate the peak sales for this scenario. As time step we used one year, the difference between the start of valuation and the time we want to know the peak sales for. The numbers μ and σ are supposed to be referenced in the Excel sheet. In the continuation we can assume the peak sales to be definite, i.e. they do not change any more. In row 8 and 9 we then use the simulated peak sales to deduce the revenues and the operating costs. All other cells are like in a standard DCF valuation. Note that we do not adjust the cash flows by their probability. A simulation is one possible version of reality, and in this version the cash flows actually happen. On average these cash flows occur with a percentage of all simulations that correspond to their probability. The simulations respect this way the probability (success rate) on average.

When pressing the button F9 (for Calc Now) the values of all cells get recalculated, above all the random numbers change. All values that are a result of these randomly generated numbers now adjust. Already using F9 we get an impression how the values can differ. But the real power of simulation lies in the number of recalculations. We will now see how we can calculate 10,000 values for this project.

Simulation of Scenarios

We now set up a work sheet that calculates the NPV for a randomly generated scenario. In order to automate the generation of scenarios and store the results we make use of the function "table". First, we must prepare a new worksheet that stores all simulation results. We reference cell B1 with the cell that returned the NPV for the generic scenario in the previous sheet. Second, we numerate the column A from 1 to n, starting with cell A2. n stands for the number of simulations we want to run. Typically n=1,000 or n=10,000, the higher the better. In our example we use n=10 for illustration purposes.

Table 4.9. Worksheet "scenario"

	A	B
1		=scenario!B15
2	1	
3	2	
4	3	
5	4	
6	5	
7	6	
8	7	
9	8	
10	9	
11	10	

We now select the cell range A1:B11, or in more general terms A1:B(n+1). We then go into the menu Data and choose Table. In the prompted pop-up we reference the column input cell to A1 as displayed in the figure below.

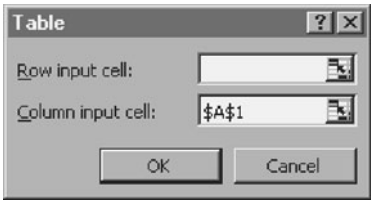

Fig. 4.13. Pop-up data-table

As a result, Excel automatically calculates scenarios for each row we have numbered before and stores the results in the cells B2:B11. The cells now contain the formula {=TABLE(,$A$1)}. We cannot fill in this formula directly; we always have to take the described way via the Table function in the Data menu.

Table 4.10. Worksheet "simulations"

	A	B
1		=scenario!B15
2	1	{=TABLE(,$A$1)}
3	2	{=TABLE(,$A$1)}
4	3	{=TABLE(,$A$1)}
5	4	{=TABLE(,$A$1)}
6	5	{=TABLE(,$A$1)}
7	6	{=TABLE(,$A$1)}
8	7	{=TABLE(,$A$1)}
9	8	{=TABLE(,$A$1)}
10	9	{=TABLE(,$A$1)}
11	10	{=TABLE(,$A$1)}

We have now managed to simulate *n* values of the project. Of course it is also possible to simulate the peak sales of a scenario, or the final phase, or simply all cash flows. For this we first need to calculate these values on the worksheet "scenario". Second, we must reference the cells in the first row next to B1 in the worksheet "simulations" with the cells we want to simulate in the worksheet "scenario". Imagine that cell B1 is referenced to the NPV, C1 to the peak sales estimate at launch, and D1 indicates whether the project has actually reached commercialisation in that scenario. We then must select the cell range A1:D11 and use again the function Table out of the menu Data. The worksheet "simulations" now looks the following:

Table 4.11. Worksheet "simulations" when simulating NPV, peak sales at launch, and whether product received approval

	A	B	C	D
1		=scenario!B15	=scenario!C6	=scenario!C5
2	1	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
3	2	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
4	3	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
5	4	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
6	5	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
7	6	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
8	7	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
9	8	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
10	9	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}
11	10	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}	{=TABLE(,$A$1)}

Analysis of Simulations

We can extract various information out of simulations. First of all, we can calculate the mean, which should correspond to the value of the project. The mean of the simulations however will never exactly match the value of the project as calculated with DCF, because the simulations are still only a random set of scenarios that only converge to the actual DCF value on average if we run an infinity of simulations. Nevertheless, the more simulations we run, the more we can trust the result to be close to the actual value. By grouping the simulation results into bins, i.e. into ranges, we can also see what the most likely outcome is, or if a positive value has realistic chances. Excel offers some powerful functions to retrieve interesting information out of a large data set in the menu *Tools*, under *Analyse Data*. We do not enter into more detail here, but present some results obtained with simulations that have proven very useful when valuing companies.

Manual

1. Set up spreadsheet that calculates a generic scenario with random test results and peak sales.
2. Simulate n scenarios (usually n=1,000, or n= 10,000) with Data-Table.
3. Analyse data set

Simulations and Real Options

Up to now, we have described simulations in a DCF framework. In the simulations we abandon projects if they fail in a clinical phase, i.e. if the result is negative. We have not included economically motivated abandonment, the principal idea of real options valuation. Therefore, the mean value of the simulations converges with the DCF value. We now assume that in the simulation the project will also be abandoned if its value drops below zero. We consequently simulate the peak sales up to the first decision point, i.e. the end of the current phase. In order to know if we have to abandon the project, we must know its value. But we don't. We actually run the simulations to get the value of the project. We would therefore need to run another set of sub-simulations for the peak sales estimate we have reached at the first decision point, and this for each simulation. In the sub-simulations we then encounter the same problem when arriving at the second decision point. Clearly, finding the real option value by this way of simulation is not an option.

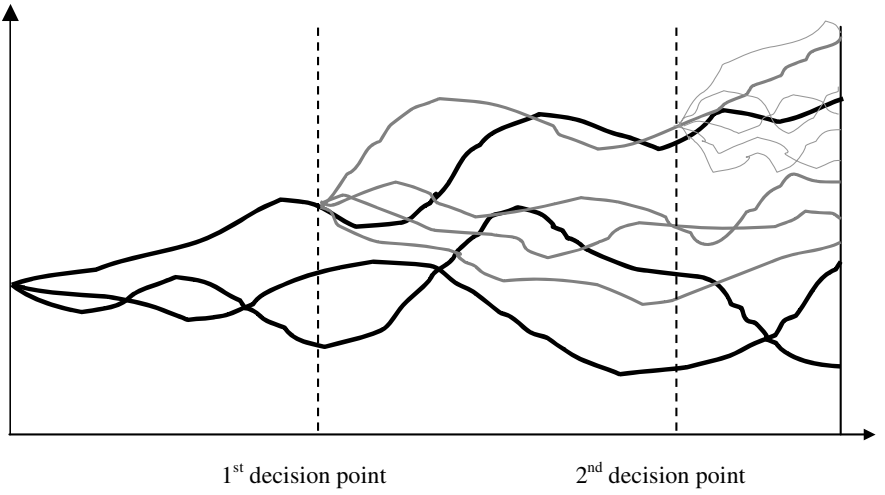

Fig. 4.14. Simulations with real options

We can elegantly solve this problem. Before starting the simulation, we must find out, what the minimum value of peak sales is for every decision point, such that the project still has a positive value. We call these values thresholds. They are calculated by putting oneself at the time of the decision point and then looking for the peak sales estimate that sets the project value to zero. The following graph displays how these thresholds influence

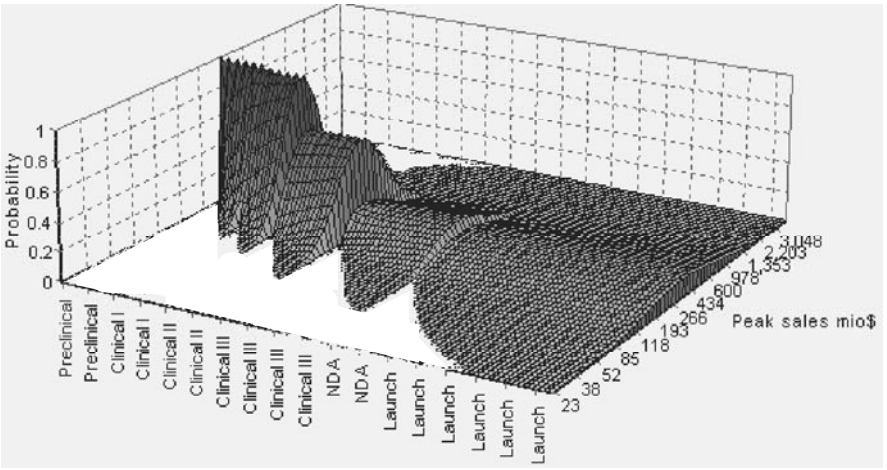

Fig. 4.15. Thresholds for a preclinical project (calculated with ri:val)

the simulations. The height of the graph displays the frequency of scenarios passing through that point (x-axis being the time, y-axis the peak sales estimate).

In the simulations we then have to implement the real options idea in the following way:

Table 4.12. Implementation of thresholds in worksheet "scenario"

	A	B	C	D
1	Year	1	2	3
2	Phase	Preclinical	Phase 1	Phase 2 (first year)
3	Success rate	70%	59%	100%
4	Success	=if(rand()<B3,1,0)	=if(rand()<C3,1,0)	=if(rand()<D3,1,0)
5	Peak sales	350	=B6*exp((μ+σ^2/2)*(C1-B1)+σ*sqrt(C1-D1)*normsinv(rand()))	=C6*exp((μ+σ^2/2)*(D1-C1)+σ*sqrt(D1-C1)*normsinv(rand()))
6	Threshold	0	214	198
7	Alive?	1	=B7*B4*if(C5>C6,1,0)	=C7*C4*if(D5>D6,1,0)

In row 5 we simulate for every year a new peak sales estimate. Just like in the tree, the peak sales estimate can change every year. Row 6 indicates the beforehand calculated thresholds. In row 7 we then decide, whether the project is continued. For this, the project must have been alive the previous year, the previous year must have been survived, and the current peak sales estimate must be higher than the threshold. Note that for years without decision the threshold is zero.

The rest of the simulation follows the same lines as in the DCF framework. But when simulating in the real options framework, the mean of the simulations approaches the real option value.

License Contract Valuation

In the following chapter we will learn how to value license contracts and how the value of different contract structures is captured. In the theoretical part and in the case studies we treat license contracts between two counterparties and then analyse sublicensing agreements involving three parties.

Structure of License Contracts

Most of the large players in life sciences owe their success to few products in the past. Revenues from these products have allowed them building large R&D centres to generate new innovative projects. This has often worked well. The best ideas however are not necessarily born in these laboratories, but all over the world. Nevertheless, once these ideas reach a mature stage, they need a machinery that first develops, later markets and sells them. The big players in the industry have these development and marketing machines. Licensing between innovators and big players gives new technologies and products better commercial prospects thanks to access to large development and marketing know-how. On the other hand, licensing fuels the marketing machines of the big players. In an innovation driven industry like life sciences, licensing is therefore a logical business model. Furthermore, some companies do not have the necessary financials to develop and launch a project, while others do have the money, but not the projects. Reasons for licensing and technology transfer are[2]:

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[2] "Licensing and Technology Transfer in the Pharmaceutical Industry". Philip Mendes, Partner, Innovation Law, Brisbane.

1. Forming alliances with partners that can progress the development of the technology to take it to market.
2. Forming alliances with partners with manufacturing capability.
3. Forming alliances with partners with marketing and distribution capability.
4. Exploitation in a different field of application.
5. No commercial capability.
6. Access to innovative projects

License contracts allow the licensor securitising at least a part of the project value. The licensor can bypass upcoming liquidity bottlenecks and reduce considerably the financial risk profile. The licensee on the other hand buys a new project, even if the payment modalities seem a little odd. License contracts need to distribute the risk to the license and the licensor and need to take into account the financial preferences of both sides. In order to take account of the different preferences, there is a multitude of possible license contract clauses and structures. Outlined below are some examples:

Upfront payment: An upfront payment takes place at the beginning of a license contract in form of cash or equity. The licensor profits from immediate cash and reduces or even eliminates its downside risk. The licensee on the other hand reduces its obligations (royalties) in case the product proves successful.

Milestones: A mailestone is a cash payment related to achieving certain milestones in research, development, or marketing, e.g. to successfully pass clinical phase 2 or reach the first $ 100 mn sales. Milestones incentive the licensor for good results. The licensee reduces the risk of spending a lot of money on a product that does not work by linking the payments to positive results. Due to information asymmetry the licensee prefers such staged payments to a one-time payment. .

R&D funding: The licensee takes over all or just a part of the licensor's costs for the development of the licensed product. Payments can be in form of FTE funding, lump sum payments or infrastructure financing. The licensor can build up further research capabilities and advance the company to a higher development stage. The licensee ensures that the project advances according to his plans and can reduce the overall price for the license.

Redemption: The licensee refunds sunk R&D costs to the licensor. Redemption is similar to R&D funding with the important difference, that redemption is usually linked to a milestone, e.g. positive results. Redemption is similar to milestone payments from a financial modelling perspective with the exception that the amount is not exactly known in advance.

Royalties: The licensor participates in the net revenues of the out-licensed product with a certain percentage. This percentage can be fixed or tied to the amount of sales revenues, i.e. have multiple levels. In practice, a licensor could receive 5% of the annual net sales <$ 100 mn, 6.5% for annual net sales between $ 100-250 mn and 7.5% for annual net sales > $ 250 mn. If the annual net sales amount to $ 300 mn, then the licensor receives 5% of the first $ 100 mn, 6.5% of the next $ 150 mn, and 7.5% of the remaining $ 50 mn. However, it has also been seen that the contract foresees in such a case the payment of 7.5% on all $ 350 mn. In the industry, this is denoted as royalty stacking. Some contracts fix the royalty rate until a certain amount of cumulative sales is achieved, e.g. 4% for the first $ 200 mn, no matter how long this takes. Royalty payments can have a fixed floor or ceiling. They can also depend on markets or indications. An important royalty structure for academia and research institutes is the reach-through royalty. These are paid not on the sales of the licensed product or technology but instead, on products, which derive from the licensed product or technology. Alternatively royalties can be paid on a per unit or per use basis, however, this is relatively uncommon in life sciences.

Royalties allow the licensor participating in the commercial success of the product. The licensee shares the commercial risk with the licensor and reduces upfront and milestone payments. Stacked royalties are an elegant way to account for the licensor's optimistic view of the project. Typically, the licensor claims that the product will have an extraordinary commercial success. The licensee rewards the licensor with attractive royalties if the product excels and limits payments if the product underperforms through a reduced royalty rate.

License fees: These are yearly payments, fixed or in relation to the development phase. License fees are common with academia, but do not play an important role in biotech-pharma contracts. These payments are suitable for the licensing of a technology, machinery, or instrumentation where the life of the license is not predefined. The licensor has a desire for safe fixed cash flows and wants to avoid any downside risk, while the licensee thinks there is an upside potential.

Guaranteed fixed minimum/maximum annual payments: Annual cash payments of a fixed maximum or minimum cash payment, mostly on a yearly basis. The licensee prevents this way that the licensor profits excessively from the upside potential.

Equity: The licensee compensates the licensor by giving equity instead of cash for the license. Alternatively, the licensee signs the obligation to buy equity from the licensor at a certain time during the contract. Equity can be in form of preferred stocks, common stocks, options, or convertible debt and might contain anti-dilution clauses. Traditionally, universities are paid by spin-off/start-up companies in form of equity because these lack cash. The university this way diversifies its license revenues that do not anymore solely depend on the success of the licensed product, but on the whole portfolio of the licensee. Equity investments of the licensor avoid fastidious fund raising of the licensee and tighten the partnership between the two counterparties. Equity investments are also a good instrument to bypass taxes. When receiving a large upfront payment, the licensor might have to pay taxes, because he suddenly made a profit. An equity investment at an overvalued price is a good way to incur an upfront payment, without having to account for it as income. Well understood, the overvalued price is intentionally a part of the agreement between the two parties.

Right of first look: The licensee buys the right to have the first look at the pipeline of the licensor. This way the licensee keeps the first mover advantage in a technology he believes in.

Call-back option: The licensor has the right to license back a product from the licensee at a later stage. A recent example of this is the licensing back of the rennin inhibitor Aliskiren, which was developed by Speedel and called back by Novartis after phase 2 trials (see box). Typically, the project initially does not fit into the licensor's pipeline, but wants to keep the back door open in case of success.

Sublicensing: Sublicensing occurs if an in-licensed product is out-licensed at a later time to a third party. This contract structure is common with projects biotech in-licenses from academia and out-licenses at a later development stage to pharma. The first licensor does not want to impede his licensee from sublicensing the project due to inflexible deal- terms. Therefore he participates directly in the sublicensing terms with a participation rate. This participation can be a percentage, with floor and ceiling, and maybe linked to either milestone payments or royalties.

Anti-stacking: Anti-stacking is a protection of the licensee against possible patent infringement claims from third parties. In case of such a claim, the license payments to the licensor reduce by the third party claim. Nevertheless, contracts often include a lower limit. Anti-stacking allows the licensee to insure potential damage that arises due to non-completeness of patents. The license contract was closed assuming that the underlying patents provide complete protection for the resulting product. If this is not the case, then it is only fair that the licensor does not receive the full amount of agreed license terms.

Co-development: licensor and licensee jointly develop a project sharing costs or the actual development work. The licensor wants to strengthen its marketing capabilities and the licensee wants to reduce its costs of introducing a new product.

Co-marketing: Both parties separately market the licensed product under different trademarks.

Co-promotion: Both parties jointly market a product under the same name.

The different clauses allow adjusting any license contracts in terms of:

1. Technical risk
2. Commercial risk
3. Liquidity preferences
4. Diverging sales assumptions

(…) Speedel partners with big pharma companies in early technical and clinical development. We in-license compounds at the point where data from animal models prove of interest, but before clinical trials in humans have begun. We then perform all the early technical and clinical development, through Phase II of development, where proof-of-concept in man is established. Speedel takes on all the financial risk itself throughout this development programme. The pharma company usually retains a "call back" option, so if Speedel is successful in establishing proof-of-concept in man, the pharma company may license the compound back and proceed to full development and commercialization, activities that big pharma companies perform exceptionally well. For example, in September 2002, Novartis exercised its call-back option from Speedel for Aliskiren (SPP100), an orally active renin inhibitor targeted for cardiovascular indications. In November 2003 Novartis announced that it was

moving Aliskiren into Phase III. Speedel had completed Phase I and the first ever successful Phase II development programme for this innovative class of molecule after in-licensing it from Novartis in 1999.

Speedel relieves the pharma company of the full burden of risk at this critical juncture in the development cycle, utilizing its own human, operational, and financial resources. The pharma company concomitantly avoids early stage risk and enjoys downstream opportunity; for its part, Speedel receives milestone and royalty payments. In cases where Speedel is successful, and for whatever reason, the big pharma partner (licensor) chooses not to call back the compound, Speedel is free to continue development and commercialization or to offer the asset to another third party licensee. In this scenario, Speedel represents a new source of late-stage compounds for the industry. For example, in May 2003 Speedel exercised its option to license from Roche all rights to an endothelin A antagonist (SPP 301) and Roche relinquished its call-back right, although it retains its rights to future royalty revenues. Having completed Phase I and IIa studies, (…)

Source: The Wallstreet Reporter Online

Academic institutions, medtech, pharma, and biotech have different motivations for licensing.

Universities: Universities are not in the position to enter into cost intensive R&D, e.g. clinical trials for medical device or new drugs. Academia is the premier source of innovative advances in the life sciences industry and has an interest in capitalising on this. Most large universities today have a technology transfer office, taking care of licensing the research findings. Licensing partners can either be pharma, biotech, or an academic spinout / start-up company. While biotech and pharma will agree to license contracts with remuneration in milestones, royalties and license fees, spinouts and start-up companies often cannot. Short in cash, these companies will provide the university with an equity stake in the company. As academia is licensing at a very early stage, it is well possible that the licensee will sublicense the project/technology at a later time. In this case, the university needs to define suitable sublicensing parameters ensuring adequate participation in the upside potential of the deal. The preference of academia is to generate a steady income stream of royalties, license fees and milestones while keeping the technical and commercial risk at a minimum.

Biotech: Biotech is acting on two fronts. First it in-licenses, often from academia, and second, it out-licenses to pharma or large biotech. There are numerous biotech companies solely built on in-licensed findings from academia, not only at the start but also later in order to fuel the pipeline along the growth of the company. Biotech, at any time in its life, is short of cash. Licensing is therefore an opportunity to fill the cash reserves. While the contracts usually have large upfront and milestone payments, they also contain royalties. So, biotech reduces its technical and commercial risk and at the same time keeps an upside by giving away its projects prior to the cost intensive final clinical and marketing phases.

Pharma: Pharma combines the expertise in clinical trials with a large marketing and commercial capability. To keep the machinery running, pharmaceutical companies need to replace existing products loosing patent protection with new innovative products. Thanks to the financing structure of the biotech industry, pharma has a wide field of innovative products to look at and license in. While liquidity is not an issue, pharma needs to reduce the technical risk, often due to imperfect information at in-licensing, by tying the payments to the achievement of certain milestones.

Medtech: In medtech the situation is similar to the one we have just described for the drug development industry. Due to shorter development times and cheaper trials sublicensing is more seldom. However, the motivations of academia, small, and big players remain the same.

Value Sharing

When negotiating a license contract, we have to judge what a fair license contract is. A common present approach is to define how to split the value of the project between the two parties depending on the phase. The numbers for drug development value sharing are[3]:

Table 4.13. Value share figures

	Licensor	Licensee
Preclinical	10%-20%	80%-90%
IND	20%-40%	60%-80%
Phase IIb/III	40%-60%	40%-60%
Approval	60%-80%	20%-40%

[3] Source: Pharmaventure, Recap, Burrill.

The more advanced the product is, the higher is the share the licensor gets, because he has borne more risk. We will discuss in a separate chapter how to approach licensing negotiations and the problem with the value sharing method. For illustrative purposes, we will use the method in the following examples on license contract valuation.

Valuation of License Contracts with Two Parties: DCF

Like with projects, to value a license contract we first define the cash flows, adjust them with their probability to occur, discount them with the discount rate of the licensor or the licensee, and sum them up.

Cash Flows

In addition to the cash flows related to R&D and marketing expenses, we now need to add upfront payments, license fees, milestones, and launch costs. We will value the license contract from both perspectives, the licensee's and the licensor's.

Time. We again have to define the timing of the different cash flows. License fees will be due on an annual basis, while milestones will be triggered at the beginning of new development stages after successful accomplishment of the antecedent phase.

Size. When we consider the size of the cash flows, we need to account for the perspective of valuation. For the licensee, all license payments to the licensor are expenses. Special care is needed when calculating the royalties. First, it needs to be defined on what basis the royalties are calculated; usually it is on net sales. Then we need to consider the case of stacked royalties, e.g., we have royalties of 5% on net sales up to $ 100 mn, and 7.5% if the net sales exceed $ 100 mn. In an example, we assume now net sales of $ 120 mn. Depending on the contract structure, we now either receive 5% * $ 100 mn +7.5% * $20 mn, or we apply the royalty rate of 7.5% on the entire amount of $ 120 mn. This difference is often neglected, even if it considerably influences the valuation. The peak sales need to be adjusted to the commercial potential of the licensee. We know that pharma has more marketing power than biotech and is more likely to reach higher sales. This especially matters for general care products. But not only will pharma better commericalise the drug, it usually also performs the clinical trials for a project in several indications at the same time, while biotech

cannot do that due to financial constraints. Pharma launches the different indications earlier than biotech and has a steeper sales ramp.

Probability to occur. The probabilities need to be chosen in accordance with the party being in charge of the relevant phase. If we know that pharma has other success rates than biotech, we need to use the corresponding success rates for all phases pharma is in charge of. If the license contract is split into various indications then the estimation of probabilities becomes delicate. Published success rates relate to compounds. As soon as one indication succeeds, the compound is counted as having passed the phase, no matter how many indications failed before. Success rates for indications are therefore lower. We will elaborate on this in more detail in the chapter about multi-indication projects.

Discount Rate

The value of a license to the in-licensing pharma company should be calculated with the discount rate corresponding to this company. Pharma conducts the trials, decides on continuing and abandoning, and markets the drug as if it were its own. However, pharma suffers from information asymmetry, i.e. it does not exactly know all the flaws of the project. This might justify a slight spread that comes on top of pharma's discount rate. From the out-licensing perspective the question of the discount rate is trickier. On the one hand, the project is now controlled by a more stable company not subject to risks that can typically break a small company's neck like liquidity, non-diversification, or lack of experience. This also justifies the use of pharma's discount rate even for the out-licensing biotech company. Nevertheless, biotech's shareholders will still ask for a higher cost of equity than for a pharmaceutical company. What really happens is that biotech's risk profile changes due to the license. The positive cash flows come much earlier and are more certain. On the other hand, biotech can only cash in a fraction of the sales by royalties. The prospect of less imminent losses and earlier profits reduces the discount rate of biotech.

When applying the value share principle, we should however use pharma's discount rate. Pharma's information asymmetry is already sufficiently compensated by the fact that they do not have to pay the full price, but only the mentioned share. Biotech on the other side has due to the lower discount rate access to more value in milestones. It is well possible that the upfront payment is already a large part of the project's value if valued with biotech's discount rate, leaving not much for the other milestones and

royalties. If calculated with pharma's discount rate, the value of biotech's share is much larger, allowing also reasonable milestone and royalty payments. The above-mentioned value share principle supposes a project value using pharma's discount rate. But in the end the counterparties' needs and negotiation skills decide on the license terms and the discount rate representing a reasonable value share.

In the case where pharma licenses a project to biotech because it does not really fit in its portfolio, or because it does not see too much value in it, or when an academic institution licenses a project to a biotech, then the above method is hard to justify. The discount rate would now be much higher than the company's standard discount rate. Biotech has a higher discount rate than pharma and academic institutions. When valuing the project with the licensee's, hence biotech's discount rate, and applying on top of that the value share principle, the upfront payment must be ridiculously small to allow some milestones and royalties. This happens simply because the project has already a much smaller value to biotech than to its counterparties because of its high discount rate. In reality, even academic institutions apply the value share principle assuming a pharma discount rate.

Valuation

Using the discounted cash flows method, we must perform the same steps as with project valuation twice, for the licensor, and for the licensee:

1. Adjust each cash flow by its probability to occur. This means that we multiply each cash flow with its probability *P*.
2. Discount each cash flow back to the present or to the date we want to know the value for.
3. Sum up all probability adjusted and discounted cash flows to the net present value.

As described above, only the cash flows change with respect to a normal project valuation. The licensee has additional expenses, namely the license payments. The licensor on the other hand is free from all further costs (assuming a full license without any co-development) and starts to earn money with the project immediately.

The following case illustrates how to value standard license contracts between two parties. The emphasis is put on learning how to modify different deal parameters without influencing the value of the contract.

Case Licensing with Two Parties

Mid-Sized Pharma has a new CEO, who has decided that the company needs to focus its R&D activities. After reviewing the pipeline, the CEO thinks that Mid-Size Pharma excels best by keeping and building up its cancer portfolio, and by out-licensing all projects in other indications. Therefore, Dr. Project Manager's project will be out-licensed, preferably to a global pharmaceutical company.

Mrs. License Officer is in charge of finding an attractive counterparty and closing the license deal. In order not to loose time she contacts the strategic alliances and licensing teams of several large pharmaceutical companies. While these are studying the technical dossier, Mrs. License Officer wants to prepare for the negotiations. For the calculation of the project value, she studies Dr. Project Manager's spreadsheet. Studying recent deals, she finds out that the average value share Mid-Sized Pharma should receive is 20-40% of the whole deal value. A crucial point she is not sure about is what discount rate to use in the valuation. She therefore has an initial talk with the licensing manager of the most promising buyer, BigPharma. BigPharma internally uses a discount rate of 9% to value the pipeline. Mrs. License Officer and her colleague from BigPharma agree that Mid-Sized Pharma reduces its risk associated with the project by outlicensing and BigPharma enters new risks through information asymmetry in the deal. They consider a value share of 40%-60% a good deal for both sides and agree to use a discount rate of 11% (40%-60% weighted average of 14% and 9%) to discount the license deal. Mrs. License Officer is now ready to define the different deal structures that give a value split of 40%-60% based on the following input parameters:

Table 4.14. Project parameters

	Clinical Phase 1	Clinical Phase 2	Clinical Phase 3	Approval Phase
Costs	$ 9 mn	$ 22 mn	$ 80 mn	$ 2.7 mn
Success Rate	63%	42%	75%	95%
Length	1 year	2 years	3 years	2 years
Launch Costs	$ 120 mn			
Peak Sales	$ 241 mn			
Discount Rate	11%			

After trying several deal terms, Mrs. License Officer comes up with the following three propositions.

Table 4.15. License parameters case study 2 parties

Emphasis on	Upfront	Milestones	Royalties
Upfront payment:	$ 3.78 mn	$ 1.5 mn	$ 1.5 mn
Milestone entry into clinical phase 2:	$ 1 mn	$ 2 mn	$ 1 mn
Milestone entry into clinical phase 3:	$ 1.5 mn	$ 4 mn	$ 1.5 mn
Milestone entry into approval phase:	$ 5.5 mn	$ 11 mn	$ 5.5 mn
Launch of the drug:	$ 10 mn	$ 18 mn	$ 10 mn
Royalty rate:	3%	3%	5.5%
Value share Midsize Pharma	40%	40%	40%
Value share BigPharma	60%	60%	60%

Solution of Case Study: DCF

The value of the project amounts to $ 22 mn. The value can also be calculated using the same spreadsheet as for case study 1 by setting the discount rate to 11%.

Determination of cash flows. For the in-licensing company – BigPharma – the license payments are additional expenses to the project. In the DCF calculation it is therefore sufficient, to add the license payments to the expenses of the project. The license payments include upfront, milestones, and royalties. While upfront and milestone payments have a fixed size, royalty payments are a percentage of the sales revenues. In year I the royalty payment amounts to:

$$Royalties(i)=SalesRevenues(i)*RoyaltyRate \tag{4.18}$$

Note that if the contract includes royalty stacking then the royalty rate depends on the level of the sales revenues. Technically, royalties correspond to a reduction of the licensee's margin.

Assuming a royalty rate of 5.5%, like in the license contract with emphasis on royalty, we receive for year 9:

$$Royalties(9)=SalesRevenues(9)*RoyaltyRate=12*5.5\%=\$\ 0.7\ mn$$

With this we perform the same DCF calculation as before by increasing the costs at the beginning of each phase by the upfront and milestone payments, and by reducing the margin by the royalty rate. However, beware that royalties are only due until expiry of patent protection. Afterwards BigPhara does not pay any further royalty to the licensor.

For Mid-Sized Pharma, the only relevant cash flows are the license payments from BigPharma. The DCF value to Mid-Sized Pharma does not depend anymore on the costs of the project, still assuming that all development and marketing costs are entirely paid by BigPharma.

In our example, we have only changed the discount rate. All other input parameters have remained the same. In practice when valuation a license, the licensor has to consider the increased capabilities of the licensee, e.g. better R&D or a strong marketing department. This would request to increase the peak sales or to adjust the launch costs. An in-depth discussion on this can be found in the section on negotiation.

Probabilities of cash flows. We must adjust all cash flows by their probability to occur. This gives us the formula for the risk adjusted net cash flows (rnCF) for the licensee:

$$rnCF(i)=Prob(i)*(SalesRev(i)-OpExp(i)-R\&DExp(i)-LicPay(i)) \quad (4.19)$$

In year 9 this corresponds to:

$$rnCF(9)=Prob(9)*(SalesRev(9)-OpExp(9)-R\&DExp(9)-LicPay(9))$$
$$=19\%*(12-4-40-11)=19\%*(-43)=-\$8\ mn$$

While for the licensee the license payments are expenses, they are revenues for the licensor. The licensor's risk adjusted net cash flows are therefore:

$$rnCF(i)=Prob(i)*LicPay(i) \quad (4.20)$$

In year 9 we have for the licensor:

$$rnCF(9)=Prob(9)*LicPay(9)=19\%*10.7=\$\ 2.0\ mn$$

Discounting of cash flows. Finally, we have to discount the risk adjusted net cash flows in order to get the risk adjusted net present cash flows. These summed up then give us the risk adjusted net present value (rNPV) for the licensee or the licensor.

The following table displays the cash flows for each year to BigPharma according to the contract that puts an emphasis on royalties. Note that Mid-Sized Pharma receives only royalties as long as patent protection last, i.e. until the year 23.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Pharma	**Phase 1**	**Phase 2**	**Phase 2**	**Phase 3**	**Phase 3**	**Phase 3**	**Approval**	**Approval**	**Market**	**Market**
Sales curve									5%	19%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues									**$ 12 mn**	**$ 46 mn**
Operating expenses									**($ 4 mn)**	**($ 16 mn)**
R&D Expenses	**($ 9 mn)**	**($ 11 mn)**	**($ 11 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 3 mn)**	**($ 40 mn)**	**($ 40 mn)**	**($ 40 mn)**
Licence Expenses	**($ 2 mn)**	**($ 1 mn)**		**($ 2 mn)**			**($ 6 mn)**		**($ 11 mn)**	**($ 3 mn)**
	Year 11	**Year 12**	**Year 13**	**Year 14**	**Year 15**	**Year 16**	**Year 17**	**Year 18**	**Year 19**	**Year 20**
	Market	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**
Sales curve	36%	51%	64%	75%	84%	91%	96%	99%	100%	100%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues	**$ 87 mn**	**$ 123 mn**	**$ 154 mn**	**$ 181 mn**	**$ 202 mn**	**$ 219 mn**	**$ 231 mn**	**$ 239 mn**	**$ 241 mn**	**$ 241 mn**
Operating expenses	**($ 30 mn)**	**($ 43 mn)**	**($ 54 mn)**	**($ 63 mn)**	**($ 71 mn)**	**($ 77 mn)**	**($ 81 mn)**	**($ 84 mn)**	**($ 84 mn)**	**($ 84 mn)**
R&D Expenses										
Licence Expenses	**($ 5 mn)**	**($ 7 mn)**	**($ 8 mn)**	**($ 10 mn)**	**($ 11 mn)**	**($ 12 mn)**	**($ 13 mn)**	**($ 13 mn)**	**($ 13 mn)**	**($ 13 mn)**
	Year 21	**Year 22**	**Year 23**	**Year 24**	**Year 25**	**Year 26**	**Year 27**	**Year 28**	**Year 29**	**Year 30**
	Market	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**	**Market**
Sales curve	99%	97%	95%	72%	53%	37%	24%	13%	6%	1%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues	**$ 239 mn**	**$ 234 mn**	**$ 229 mn**	**$ 174 mn**	**$ 128 mn**	**$ 89 mn**	**$ 58 mn**	**$ 31 mn**	**$ 14 mn**	**$ 2 mn**
Operating expenses	**($ 84 mn)**	**($ 82 mn)**	**($ 80 mn)**	**($ 61 mn)**	**($ 45 mn)**	**($ 31 mn)**	**($ 20 mn)**	**($ 11 mn)**	**($ 5 mn)**	**($ 1 mn)**
R&D Expenses										
Licence Expenses	**($ 13 mn)**	**($ 13 mn)**								

Fig. 4.16. DCF calculation for licensor

The following table shows the DCF calculation for BigPharma. The value of the in-licensed project to BigPharma, using a discount rate of 11%, amounts to $ 13.2 mn. Comparing this with the value without licensing payments, $ 22.0 mn, we see that BigPharma receives exactly 60% of the project value.

	Length (y)	Costs	Suc. Rate
Phase 1	1	$ 9 mn	63%
Phase 2	2	$ 22 mn	42%
Phase 3	3	$ 80 mn	75%
Approval	2	$ 3 mn	95%

Deal Terms	
Upfront	$ 2 mn
Phase 2	$ 1 mn
Phase 3	$ 2 mn
NDA	$ 6 mn
Approval	$ 10 mn
Royalties	5,5%

Launch costs	$ 120 mn
Peak Sales	$ 241 mn
Growth Rate	0%
Operating Margin	65%

	Pharma	Mid-Sized Pharma
Discount Rate	11%	14%

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Pharma	**Phase 1**	**Phase 2**	**Phase 2**	**Phase 3**	**Phase 3**	**Phase 3**	**Approval**	**Approval**	**Market**	**Market**
Sales curve									5%	19%
Peak Sales	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn	$ 241 mn
Sales revenues									**$ 12 mn**	**$ 46 mn**
Operating expenses									**($ 4 mn)**	**($ 16 mn)**
R&D Expenses	**($ 9 mn)**	**($ 11 mn)**	**($ 11 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 27 mn)**	**($ 3 mn)**	**($ 40 mn)**	**($ 40 mn)**	**($ 40 mn)**
Licence Expenses	**($ 2 mn)**	**($ 1 mn)**		**($ 2 mn)**			**($ 6 mn)**		**($ 11 mn)**	**($ 3 mn)**
Success Rate	63%	100%	42%	100%	100%	75%	100%	95%	100%	100%
Probability	100%	63%	63%	26%	26%	26%	20%	20%	19%	19%
Risk adjusted net CF	**($ 11 mn)**	**($ 8 mn)**	**($ 7 mn)**	**($ 7 mn)**	**($ 7 mn)**	**($ 7 mn)**	**($ 2 mn)**	**($ 8 mn)**	**($ 8 mn)**	**($ 2 mn)**
Discount	100%	90%	81%	73%	66%	59%	53%	48%	43%	39%
Net present CF	**($ 11 mn)**	**($ 7 mn)**	**($ 6 mn)**	**($ 5 mn)**	**($ 5 mn)**	**($ 4 mn)**	**($ 1 mn)**	**($ 4 mn)**	**($ 4 mn)**	**($ 1 mn)**
rNPV	**$ 13,2 mn**									
IRR	**13,1%**									
Mid-Sized Pharma										
Own Discount	100%	88%	77%	67%	59%	52%	46%	40%	35%	31%
Net present CF	**$ 2 mn**	**$ 1 mn**	**$ 0 mn**	**$ 0 mn**	**$ 0 mn**	**$ 0 mn**	**$ 0 mn**	**$ 0 mn**	**$ 1 mn**	**$ 0 mn**
Pharma Discount	100%	90%	81%	73%	66%	59%	53%	48%	43%	39%
Net present CF	**$ 2 mn**	**$ 1 mn**	**$ 0 mn**	**$ 0 mn**	**$ 0 mn**	**$ 0 mn**	**$ 1 mn**	**$ 0 mn**	**$ 1 mn**	**$ 0 mn**
Value 1	**$ 7 mn**									
Value 2	**$ 9 mn**									

Fig. 4.17 rNPV calculation for BigPharma

Using the same discount rate, the licensor's value must be exactly the difference, because the following equation holds:

$$CF(licensee)=CF(project)-CF(licensor) \tag{4.21}$$

This means that the cash flows for BigPharma are exactly the cash flows that belong to the project, and in addition BigPharma has to transfer the license payments to Mid-Sized Pharma, which are exactly all the cash flows Mid-Sized Pharma receives. And since all other parameters remain the same as in the normal project valuation without the license contract, especially the probabilities of the cash flows, we can deduce that in the DCF framework the value of the project can be split up in the licensee's part and the licensor's part, if all are calculated with the same discount rate.

$$rNPV(project)=rNPV(licensee)+rNPV(licensor) \tag{4.22}$$

This means that the rNPV value of a project that is not licensed corresponds to the sum of value shares of the licensor and the licensee if the same input parameter is applied (success rates, duration, peak sales, discount rate). Modifying the deal terms, i.e. upfront payments, milestone payments and royalty rates, we can find several deal structures that fit into the 60%-40% value split. This is exactly, what Mrs. License Officer has done.

The valuation of a license with DCF is the same as the valuation of a project. If the cash flows are carefully considered in the calculations, rNPV is a simple and straightforward way to value a license.

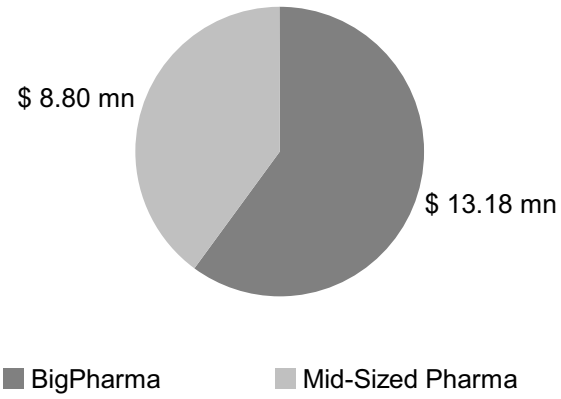


Fig. 4.18. Value share licensee-licensor

Valuation of License Contracts with Two Parties: Real Options

We have learned in the previous section how to value license contracts with DCF. The differences between project and license contract valuation are the adjustment of the input parameters to the licensee's capabilities, and the implementation of contract related cash flows. The adjustment of parameters concerns mainly the peak sales estimate, the development costs, and the discount rate. The contract related cash flows encompass upfront payment, milestones payments, and royalties. The remaining valuation part stays exactly the same: adjusting the cash flows with probabilities, discounting them back, and summing them up to the rNPV.

As in project valuation, ROV models the uncertainty of the project's economic success. According to its profitability, the project is continued or abandoned. But in a license contract we have two parties. And the project must be profitable for both. For the licensor this reasoning is quickly concluded: Instead of facing large investments with the perspective of uncertain income, the licensor securitised its project value and thereafter receives only positive cash flows. Since no investment is due anymore, the project will always be profitable for the licensor, no matter what happens. For the licensee however, the situation is more similar to the one discussed in project valuation. At the start of each phase, he must balance expenses and potential income to decide whether he still wants to pursue the project. Therefore it is possible that the licensee abandons a project, although this is against the interests of the licensor. While the consideration of the option to abandon adds value to the licensee, it deprives the licensor of safe earnings. In the case of abandonment, all rights on the project fall back to the licensor. Obviously, he can try to license the project to another partner, but this will probably have the same reasons not to continue the project as the first licensee. The flexibility of management to react to changes of the project's market potential creates normally value. In the case of licensing this is only true for the licensee. The option approach yields lower values for the licensor, because some scenarios with positive cash flows are wiped out against the interest of the licensor. The reason for this interesting circumstance is the control over the project that is transferred from the licensor to the licensee with the contract. This control enables management to enforce decisions. The licensor is now short in control.

For the valuation itself, the change of control has a significant impact. In order to know the value for the licensor we must know whether the licensee continues the project or not. We therefore must value the project also for the licensee.

Real Options Valuation of License Contracts

1. Span a binomial tree for the peak sales estimate
2. Value the project in each leaf of the tree for the licensee
3. Work back the tree to the root for the licensee. For each time step
   1. Take expectation of up- and down-step
   2. Apply success rate if necessary
   3. Discount for the elapsed time step
   4. Add cash flows
   5. Decide if it is a decision point
4. Value the project in each leaf of the tree for the licensor
5. Put value to zero if licensee abandons project in that state
6. Work back the tree to the root for the licensor. For each time step
   1. Take expectation of up- and down-step
   2. Apply success rate if necessary
   3. Discount for the elapsed time step
   4. Add cash flows
   5. Put value to zero if licensee abandons project in that state

$$V_t^{licencee} = \underbrace{\max\left\{\underbrace{\underbrace{(1+r)^{-dt}}_{3}\underbrace{P_t}_{2}\underbrace{\left(pV_{up}^{t+dt} + (1-p)V_{down}^{t+dt}\right)}_{1} + \underbrace{CF_t}_{4}}, 0\right\}}_{5} \tag{4.24}$$

$$V_t^{licencor} = \left(\underbrace{(1+r)^{-dt}}_{3}\underbrace{P_t}_{2}\underbrace{\left(pV_{up}^{t+dt} + (1-p)V_{down}^{t+dt}\right)}_{1} + \underbrace{CF_t}_{4}\right) \cdot \underbrace{I_{V_t^{licencee} \neq 0}}_{5} \tag{4.25}$$

With $I_{V_t^{licencee} \neq 0} = \begin{cases} 1 \ if \ V_t^{licencee} \neq 0 \\ 0 \ else \end{cases}$

Usually, DCF yields higher values for the licensor than real options valuation. This must not always be the case. If the license deal includes royalty stacking, it is possible that the real option value is higher than the DCF value. Assume for this an easy example. A project is clearly in the money and will not be abandoned. Peak sales estimates are at $ 400 mn with no growth, and the royalty structure envisions 10% for all sales under $ 500 mn

and 20% for sales exceeding this barrier. If we value this deal with DCF we will earn exactly 10% royalties. With real options valuation on the other hand, the tree might also display scenarios with peak sales that are higher than $ 500 mn. On average, we will therefore earn more than 10% royalties with under real options valuation.

Value for the licensee. At the beginning of each phase we must account for the upfront and later for the milestone payments, during commercialisation until patent expiry we must reduce the operating profit by the royalty payments. Using this set of cash flows, we can apply the same procedure to value an in-licensed project as for a self-conducted project. Actually, the license payments just increase the costs and later derogate revenues.

Value for the licensor. Once we have worked back the tree for the licensee we know exactly in which states the licensee abandons the project. We can now work back the tree also for the licensor, but considering that in these states the value is truncated to zero.

Solution Case Study: ROV

As in case study 1, we first span the tree. Second, we calculate the value of the project in all end nodes for the licensee. Third, we work back the tree for the licensee. In addition, we then value the project in the end nodes for the licensor, and finally fifth, work back the tree for the licensor.

	Year 7 Approval	Year 8 Approval	Year 9 Market	Year 10 Market	Year 11 Market	Year 12 Market	Year 13 Market	Year 14 Market	Year 15 Market	Year 16 Market
Sales curve			5%	19%	36%	51%	64%	75%	84%	91%
Peak Sales	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn
Sales revenues			**$ 2 mn**	**$ 8 mn**	**$ 14 mn**	**$ 20 mn**	**$ 25 mn**	**$ 30 mn**	**$ 33 mn**	**$ 36 mn**
Operating expenses			**($ 1 mn)**	**($ 3 mn)**	**($ 5 mn)**	**($ 7 mn)**	**($ 9 mn)**	**($ 10 mn)**	**($ 12 mn)**	**($ 13 mn)**
R&D Expenses	**($ 3 mn)**	**($ 40 mn)**	**($ 40 mn)**	**($ 40 mn)**						
Licence Expenses	**($ 6 mn)**		**($ 10 mn)**	**($ 0 mn)**	**($ 1 mn)**	**($ 1 mn)**	**($ 1 mn)**	**($ 2 mn)**	**($ 2 mn)**	**($ 2 mn)**
Success Rate	100%	95%	100%	100%	100%	100%	100%	100%	100%	100%
Probability	100%	100%	95%	95%	95%	95%	95%	95%	95%	95%
Risk adjusted net CF	**($ 8 mn)**	**($ 40 mn)**	**($ 46 mn)**	**($ 34 mn)**	**$ 8 mn**	**$ 11 mn**	**$ 14 mn**	**$ 17 mn**	**$ 19 mn**	**$ 20 mn**
Discount	100%	90%	81%	73%	66%	59%	53%	48%	43%	39%
Net present CF	**($ 8 mn)**	**($ 36 mn)**	**($ 38 mn)**	**($ 25 mn)**	**$ 5 mn**	**$ 7 mn**	**$ 8 mn**	**$ 8 mn**	**$ 8 mn**	**$ 8 mn**

	Year 19 Market	Year 20 Market	Year 21 Market	Year 22 Market	Year 23 Market	Year 24 Market	Year 25 Market	Year 26 Market	Year 27 Market	Year 28 Market
Sales curve	100%	100%	99%	97%	95%	72%	53%	37%	24%	13%
Peak Sales	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn	$ 40 mn
Sales revenues	**$ 40 mn**	**$ 40 mn**	**$ 39 mn**	**$ 39 mn**	**$ 38 mn**	**$ 29 mn**	**$ 21 mn**	**$ 15 mn**	**$ 10 mn**	**$ 5 mn**
Operating expenses	**($ 14 mn)**	**($ 14 mn)**	**($ 14 mn)**	**($ 14 mn)**	**($ 13 mn)**	**($ 10 mn)**	**($ 7 mn)**	**($ 5 mn)**	**($ 3 mn)**	**($ 2 mn)**
R&D Expenses										
Licence Expenses	**($ 2 mn)**	**($ 2 mn)**	**($ 2 mn)**	**($ 2 mn)**						
Success Rate	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Probability	95%	95%	95%	95%	95%	95%	95%	95%	95%	95%
Risk adjusted net CF	**$ 23 mn**	**$ 23 mn**	**$ 22 mn**	**$ 22 mn**	**$ 23 mn**	**$ 18 mn**	**$ 13 mn**	**$ 9 mn**	**$ 6 mn**	**$ 3 mn**
Discount	29%	26%	23%	21%	19%	17%	15%	14%	12%	11%
Net present CF	**$ 6 mn**	**$ 6 mn**	**$ 5 mn**	**$ 5 mn**	**$ 4 mn**	**$ 3 mn**	**$ 2 mn**	**$ 1 mn**	**$ 1 mn**	**$ 0 mn**

rNPV	**($ 13.7 mn)**

Fig. 4.19. Value of the lowest end node

Construction of the binomial tree: The binomial tree is constructed in exactly the same way as in the case study on project valuation.

Valuation of end nodes for licensee: We now value the project with DCF for every end node as if it were at the beginning of approval phase, using the peak sales estimate of the end node. The table below displays the calculation for the lowest end node. The final value of the project, if it reaches the approval phase with peak sales of $ 40 mn using the royalty weighted license contract amounts to $ (13.7) mn. The licensee would therefore decide to abandon the project.

Calculating the values for all end nodes we get:

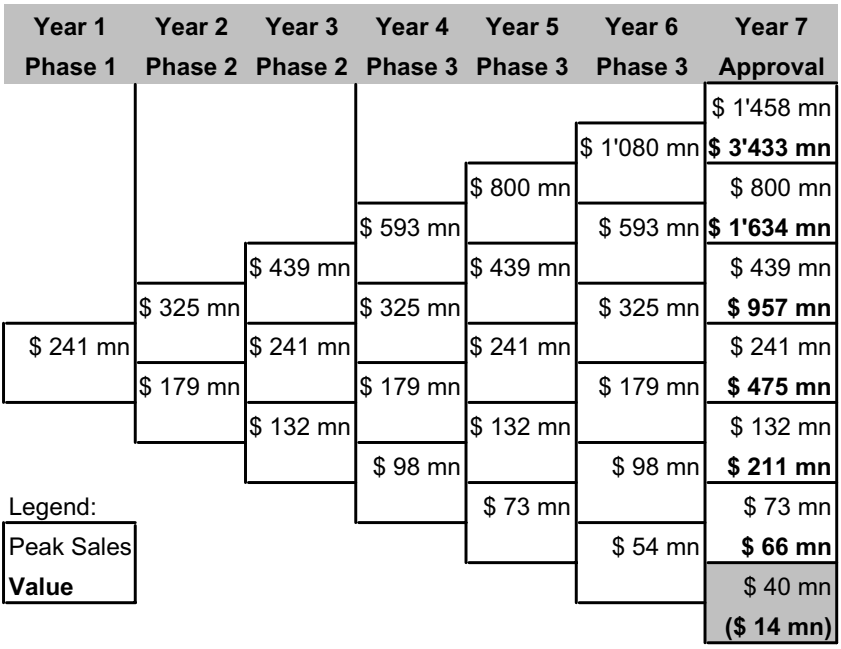


Fig. 4.20. Licensee's value of the end states

In the continuation we set the value of the lowest node to zero, representing the halt of the project in that state.

Working back the tree as licensee: There is no difference in the procedure to get back to the root node compared to common project valuation, with the exception that we must now also consider the milestone payments and at the root node the upfront payment. The final values are:

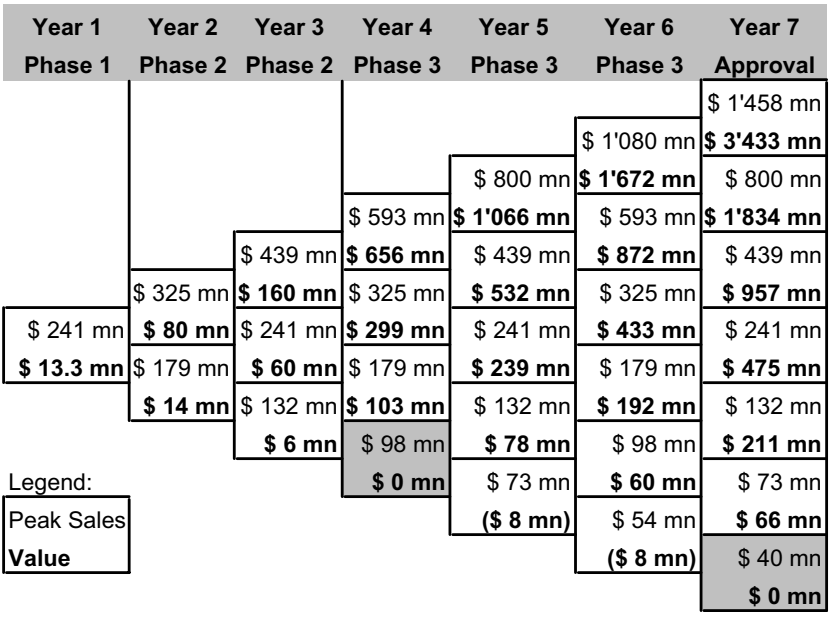


Fig. 4.21. Licensee's value of the root node

We see that the licensee would abandon the project in two nodes, in the one we have already discussed at the start of approval phase, and in the lowest at phase 3. We can retrieve the value of the license contract to the licensee from the root node, $ 13.3 mn. This compares to $ 13.2 mn with DCF (actual difference amounts to $ 0.16 mn). We see that real options valuation makes only a small difference. This is due to the lower discount rate than in case study 1. The project is with a discount rate of 11% clearer in the money than with 14%.

Valuation of end nodes for licensor: With DCF we value the project for the licensor in each end node, i.e. as if the project is at the beginning of the approval phase, with peak sales corresponding to the end node. This yields the situation shown in Fig. 4.22.

Note that in the lowest node BigPharma abandons the project. This means that Mid-Sized Pharma does not receive any milestone payments and royalties, although they would be worth $ 21 mn. The value must be reduced to $ 0 mn.

Working back the tree as licensor: We now work back the tree using the cash flows of the licensor, i.e. milestone payments. At a node of a decision point we then must check, whether the licensee would continue the project

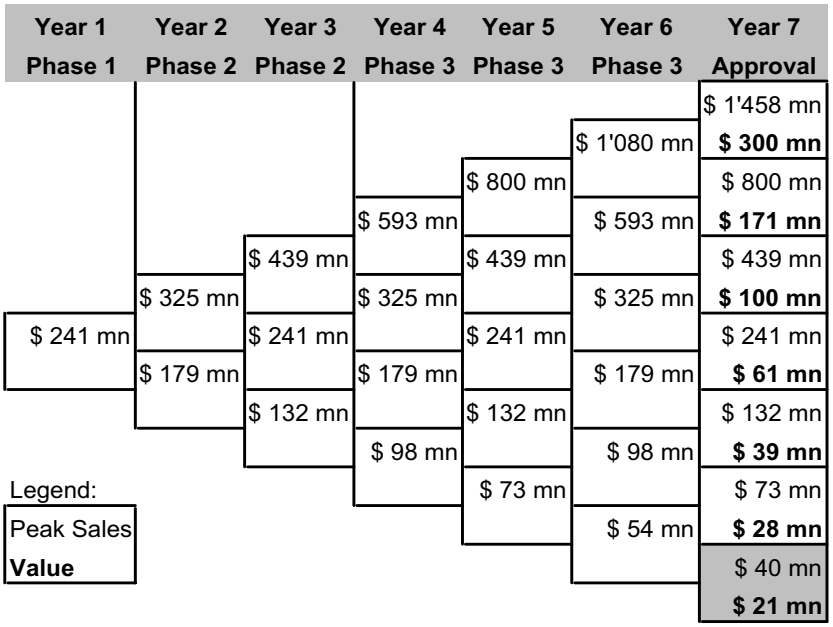


Fig. 4.22. Value of the end nodes for the licensor

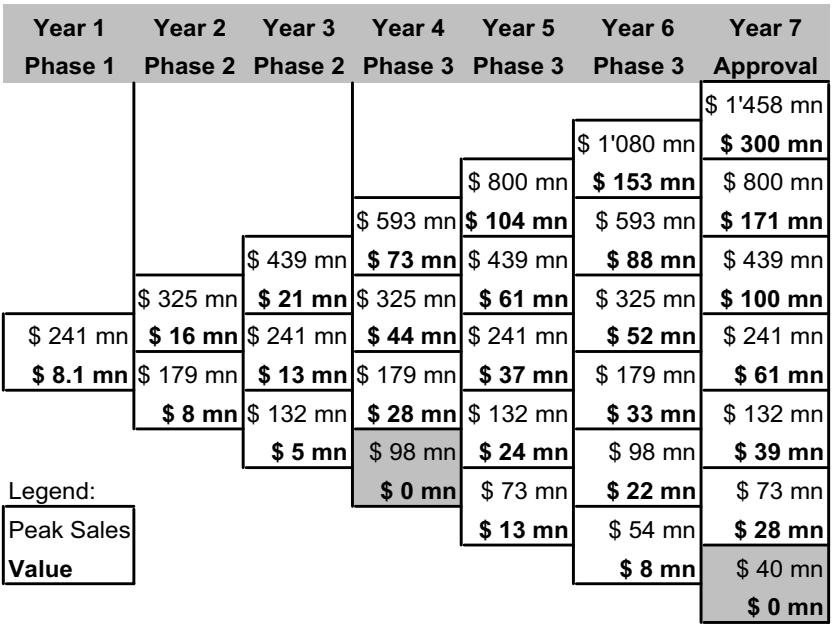


Fig. 4.23. Licensor's value of the root node

in that state, otherwise we must set the licensor's value to zero. This procedure explains, why real options valuation yields a lower value for the licensor than DCF.

The same nodes are put to zero as in the tree for the licensee. The final value for the licensor amounts to $ 8.1 mn compared to $ 8.8 mn. While with DCF we had an exact value share of 40%-60%, the same deal, calculated with real options valuation, corresponds now to a value share of 37.7%-62.3%.

Mrs. License Officer notices that the same deals, once calculated with DCF, once with real options valuation, do not have the same value share. Under the real option perspective Mid-Sized Pharma does not get what BigPharma promised, namely a 40% share in the project. Mrs. License Officer therefore modifies the deal terms such that the value share fits again.

Table 4.16. Adjusted ROV deal terms

Emphasis on	Upfront	Milestones	Royalties
Value share Mid-Sized Pharma DCF	39.9%	37%	37.7%
Value share BigPharma DCF	60.1%	63%	62.3%
Upfront payment:	$ 3.8 mn	$ 1.5 mn	$ 1.5 mn
Milestone entry into clinical phase 2	$ 1 mn	$ 2 mn	$ 1 mn
Milestone entry into clinical phase 3	$ 1.5 mn	$ 4 mn	$ 1.5 mn
Milestone entry into approval phase	$ 5.5 mn	$ 11 mn	$ 5.5 mn
Launch of the drug	$ 10 mn	$ 27.5 mn	$ 10 mn
Royalty rate	3%	3%	6.1%
Value share Midsize Pharma	40%	40%	40%
Value share BigPharma	60%	60%	60%
Difference to DCF	$ 0.02 mn	$ 9.5 mn	0.6%

While the upfront deal makes barely any difference, the changes for the milestones and royalty deals look attractive. In order to receive again 40% of the project, the two parties need to raise the approval milestone by $ 9.5 mn in the milestone deal, or lift the royalty rate to 6.1%. While a $ 20,000 increase of the upfront payment is hardly recognizable, the changes in milestones and royalties could easily fund an early phase of a future project. Mrs. License Officer, after considering the different license contract structures, decides to aim at a deal with emphasis on the milestones valued with real options.

Discussion

The case illustrates the important points when preparing a license contract valuation. The choice of the input parameters, especially the peak sales and the discount rate, is not trivial. All input parameters should reflect the characteristics of the licensing partner once the project is in his hands. Big pharma has the capabilities to get the maximum out of a project, while early-stage companies often have to start from scratch, i.e. building-up drug development and marketing expertise. This should be considered in the cost, duration, and success of the project. We might even assume that pharma has higher success rates in clinical trials, but there is no sound data set to adjust the drug development parameters to the license partner. Therefore, we use standard data as outlined in the chapter on fundamentals in life science.

When valuing a license contract we need to consider the risk profile of the licensee. It is evident that if big pharma acquires a license, the default risk is minimal and the financial strength of big pharma ensures that the project will not be hindered due to lack of cash. On the other hand, big pharma is stringent in stopping projects that do not pass the hurdle rate, i.e. are not profitable enough. One third of all clinical stage projects will be terminated due to this reason. This of course is not in the interest of the licensor, who after licensing has only positive cash flows. It is therefore a trade-off to enter a license with a large partner. It adds development and marketing power to the project, thereby pushing its success; on the other hand it adds the risk that if certain criteria are not met the project is halted even if it there are no concerns related to efficacy or safety. This would never happen in a small biotech company, because without the project the company would lose its right of being.

To split up the project value between the two parties, it is necessary to value both the licensee's and the licensor's part with the same discount rate. This discount rate lies somewhere in-between the two usually applied discount rates. A weighted average of the two discount rates according to the value split is a reasonable rate to agree on. The value split method will be discussed in further detail in the section about negotiation further down.

Not only the choice of the right input parameters is critical, but also the choice of the valuation method. DCF and real options valuation yield different valuation outcomes in our case. Even if at first sight it seems to be negligible, it makes a major difference in late stage license payments. While a $ 20'000 upfront payment increase is marginal, a $ 9.5 mn milestone increase at launch makes a difference. DCF can well be used to value license contracts, but does not consider the aspect that the licensee might

give up a project. Real options are closer to reality. The only additional input parameter is the volatility. While negotiating a license, it is advisable to value the contract with both methods. A difference can be used to negotiate better license terms for the licensor.

Diatos SA, a Paris-based privately held biopharmaceutical company, and Medarex, Inc. (Nasdaq: MEDX) have announced that Diatos has licensed from Medarex the exclusive European rights to develop and commercialize Super-Leu-Dox, a potential new cancer treatment.

Under the terms of the agreement, Diatos expects to develop and commercialize Super-Leu-Dox, which is currently in late pre-clinical development, in Europe. In return, Medarex has an option, exercisable before Super-Leu-Dox reaches Phase III development, to co-develop and co-commercialize the product with Diatos in Europe. If Medarex exercises its option, the parties will share equally all development and commercialization costs and future potential revenues from sales and sublicensing of Super-Leu-Dox in Europe. If Medarex elects not to co-develop and co-commercialize the product in Europe, Diatos will have the right to develop and commercialize Super-Leu-Dox in Europe and will be responsible for all development activities and costs. In that event, Medarex will receive royalties on any commercial sales of the product. Under the terms of the agreement, Medarex retains all rights to Super-Leu-Dox in non-European countries. Each party has the right to use pre-clinical and clinical data generated by the other party for developing Super-Leu-Dox in their respective territories. (…)

Source: World Biotech Online

Simulation of License Contracts

The simulation of license contracts allows accounting for stacked royalties. Contrary to a standard DCF calculation, in the simulations the peak sales can also take higher values than expected. This may lead to higher royalty payments than anticipated because of royalty stacking in the license contract. Imagine estimated peak sales of $ 400 mn and a royalty structure of 5% if annual sales are lower than $ 500 mn and 8% for the part exceeding $ 500 mn. In a DCF valuation we would always have to calculate with 5%, while in a simulation some scenarios are likely to have peak sales higher than $ 500 mn; in these scenarios the higher royalty rate of 8% applies.

Simulations also give a good idea about the likelihood of cash flows as displayed in the figure below.

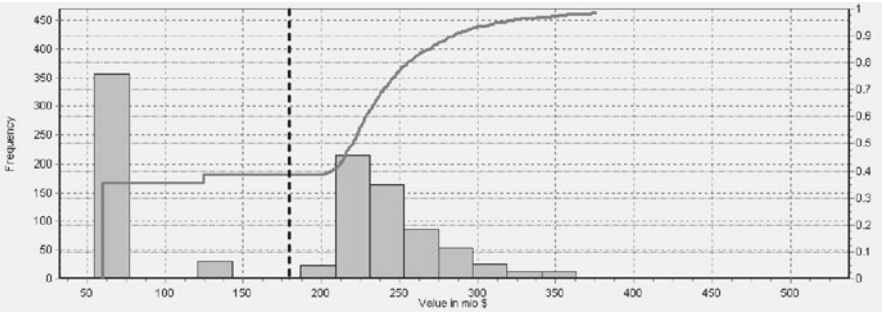


Fig. 4.24. Simulation of a phase 3 license contract (1,000 simulations calculated with ri:val)

We have simulated a phase 3 license contract. We see that in 35% we have to content ourselves with the upfront payment of $ 60 mn, this is in line with a phase 3 success rate of 65%. In very few cases we get in addition to the upfront payment also an NDA milestone before the project fails. This scenario corresponds to the second pillar in the figure. The other pillars then correspond to the scenarios when the project reaches commercialisation. According to the market potential of the compound the company earns more or less royalties.

Early-Stage Licensing with Possible Sublicensing

Research institutions and academia license their projects already at early stages, even before preclinical testing. Their licensees are often biotech companies that take the projects from research into preclinical and early clinical development. These companies mostly lack the possibilities to conduct expensive large-scale clinical trials. Therefore, they hand the project over to pharmaceutical companies, which then take the project through clinical phase 3 to the market. The biotech companies find themselves between academia and pharma and are linked with both via license contracts. Once both license contracts are in place, biotech just earns the differential of the two contracts. This means that it receives milestone payments or royalties from pharma and has to pass a part of it on to academia. For academia, this business model has two important implications: First, in early

stage the potential of a project is very uncertain. Large deal parameters are hard to justify, especially if the potential licensees are chronically short of cash. Second, as soon as biotech enters into negotiations with pharma, the license contract between academia and biotech serves as a lower barrier. If by that time research revealed that the compound could only be used in a an indication with limited market potential, the original contract between academia and biotech might already be too high, impeding the sublicensing to a potent partner.

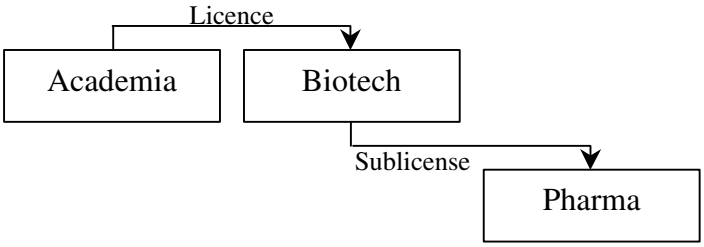


Fig. 4.25. Licensing and sublicensing

The industry came up with a solution for structuring early stage license contracts such that first, academia has an upside potential even though their licensees are normally financially weak biotechs, and second, biotech is not encumbered by high deal terms in their sublicensing negotiations: As soon as the project is sublicensed to a third party, academia takes a share in the new license terms. Typically, the license contract includes a clause that says that the licensor is entitled to the sublicense deal terms by a certain percentage, depending on the stage the sublicense contract was concluded. Until that moment, the biotech company must redeem academia according to the base scenario of the contract. The base scenario is a normal license contract between the two parties, assuming that the licensee himself takes the product to the market.

These sublicensing parameters allow academia offering relatively cheap license contracts, as it has an upside potential when its licensee sublicenses the project at better terms. On the other hand, it also bears the risk to be worse off if the project turns out to be not as attractive as anticipated. Academia accepts to share parts of the financial risk in exchange of a considerable upside potential.

Table 4.17. Sublicensing parameters

Sublicensed in	**Precl.**	**CP1**	**CP2**	**CP3**	**Appr.**	**Comm.**
Preclinical phase	50% share					
Clinical phase 1	Base sc.	40% share				
Clinical phase 2	Base scenario		30% share			
Clinical phase 3	Base scenario			20% share		
Approval phase	Base scenario				15% share	
Commercialisation	Base scenario					10% share

Biotech on the other hand is free of any constraints when negotiating with a potential partner. If the original contract between academia and biotech envisioned 4% royalties, but pharma is only ready to pay 3.5%, this would normally be a deadlock. Biotech could not even cover the royalties it has to pay to academia. However, since academia now does not insist on the original terms but agrees to just participate in the new deal terms by, let's say 50%, 3.5% royalties is still acceptable for biotech. Academia then receives 1.75% of the royalties paid by pharma to biotech and profits from their commercial capability. Academia is then still better off by accepting smaller deal terms compared to obstructing a deal with inflexible terms and not receiving any further payments at all. Note, that this contract structure implicitly admits that the value of the project or the sublicense contract is not known yet. It can turn out well, in this case academia profits from the upside, but it can also go bad, in this case it is important to save what can be saved and not to obstruct sublicensing negotiations with an unrealistic base scenario.

Some institutions add special features to these contracts. With a view to forcing the biotech company not to give too much way on the royalty side, they insist for instance on the original royalty rate. In the above example, the institution could maintain its claim of 4% royalties. The biotech must therefore negotiate higher royalties to the expense of lower upfront and milestone payments. Fixed royalties are typical for large, diversified institutions. They rely mostly on royalty payments, while milestone payments account only for a small fraction of their license income. Others take a percentage of the sublicensing terms, but fix a minimum. This reduces the downside.

In order to define fair sublicensing parameters, we must value the contract. We have a set of different possible scenarios, namely that the biotech company launches the product itself (base scenario), or that it out-licenses the project in one of the specified stages. Each of these scenarios has a

value. The base scenario corresponds to a normal license contract between academia and biotech and is therefore straightforward to value. As soon as the sublicensing terms become active, i.e. as soon as we have to assume that biotech further sublicenses the project, we must suppose a hypothetical license contract. We put ourselves at the time of sublicensing and figure out the structure of a fair license contract between biotech and pharma for each of the scenarios. This each time corresponds to the situation where Mrs. License Officer has found herself in the previous case; e.g. if biotech sublicenses the product at the end of phase 2, we design a hypothetical contract between pharma and biotech at the entry of phase 3. Having defined all cash flows between pharma and biotech, i.e. the upfront and milestone payments, and the royalties, we can now deduce the cash flows for academia stemming from this sublicensing based on the participation rate for sublicensing in phase 3. Having done this, we have now defined the cash flows for all three parties for the single scenario that biotech sublicenses after phase 2.

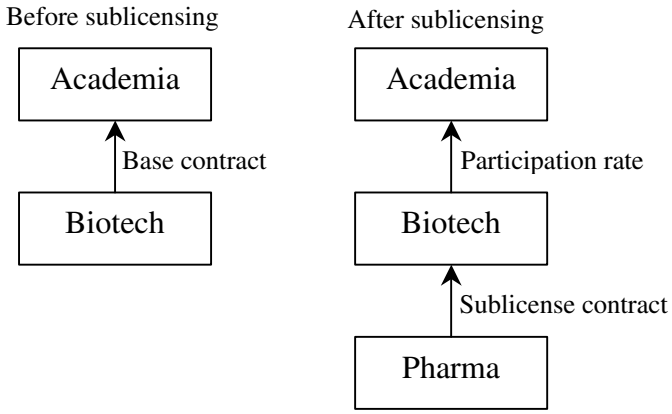


Fig. 4.26. Participation rate in sublicensing

We repeat that procedure for all possible moments of sublicensing. Having the value for all scenarios does not mean that we know the value of the contract. Finally, we do not know which scenario will happen. The actual value is the probability weighted average of all scenarios.

$$V_{contract} = \sum_i P(i) V_i \tag{4.26}$$

With P(i) being the probability of scenario i. If we determine the value of a given contract, then we apply the above probability weighing formula.

In this case the worst valued scenario already indicates a lower bound for the value of the license contract (all weight on the worst scenario), and the best valued scenario an upper bound (all weight on the best scenario). Either the strategy of the licensee already displays a clear preference for one scenario, in which case we can assume the value of this specific scenario, or we really must chose a value in the indicated range. However, it is factually impossible to quantify the probabilities of the scenarios. These depend on the financial strength of the biotech company, its strategic focus, its investors' moods, and potential sublicensee's appetite. Either we endeavour despite of that to quantify the probabilities, or, if still in negotiation, we can use an elegant solution for this problem: academia chooses a contract structure that is independent of these probabilities. This is typically the case if all scenarios have the same value, i.e. if biotech conducts and launches the product on its own, or licenses it at any stage. It makes sense that academia chooses the sublicensing terms in a way that the value of the contract does not depend on the biotech company's strategy or fate. This method then corresponds to negotiating the value of the base contract and then to determine all sublicensing terms such that the corresponding scenarios all give the same value. This technique should be applied by technology transfer managers of universities and research institutions.

Theory DCF

Valuation of a license contract with participation in sublicensing terms requires the valuation of each sublicensing scenario. To quantify these scenarios we assume license contracts at each possible stage of sublicensing. Knowing these license contracts, we can deduce the cash flows of all parties and value the contract scenarios. According to the purpose of the valuation we then either can set the sublicense participations such that all scenarios have the same value, or we can weigh the scenarios in order to get the value of the contract.

Sublicensing Case: DCF

Mr. Tech Transfer is in charge of licensing a molecule from its research institute to the industry. The molecule has just passed the lead validation phase and should now be taken to lead optimisation. There is a strong rationale for the compound being used as a CNS drug. A young biotech company that wants to broaden its pipeline is interested in the molecule. Mr. Tech Transfer therefore prepares for the negotiations. In a first step, he values the project with standard industry parameters as outlined in the table below.

Table 4.18. Project characteristics

	Lead Opt.	Preclinical	Phase 1	Phase 2	Phase 3	Approv.
Costs	$ 0.8 mn	$ 2 mn	$ 4 mn	$ 15 mn	$ 60 mn	$ 2 mn
Success Rate	70%	70%	66%	46%	62%	78%
Length	1 year	2 years	1 year	2 years	3 years	2 years
Launch costs	$ 300 mn					
	Market					
Peak Sales	$ 650 mn					
Margin	65%					
Discount Rate	15%					

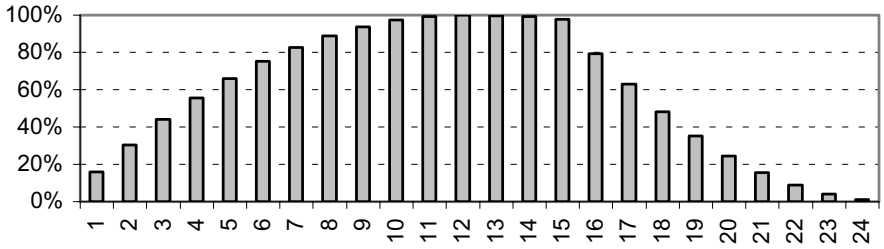


Fig. 4.27. Sales curve

Using a standard sales curve as displayed and a discount rate of 15%, Mr. Tech Transfer comes up with a net present value of $ 1.4 mn. Mr. Tech Transfer aims at a value split of 12%-14% and designs a contract that corresponds to these figures.

Table 4.19. Licensing parameters

	Upfront payment	Milestone Payments	Royalties
Lead Opt.	$ 0.1 mn		
Preclinical		$ 0.2 mn	
Phase 1		$ 0.3 mn	
Phase 2		$ 0.8 mn	
Phase 3		$ 1.5 mn	
Approval Phase		$ 3 mn	
Launch		$ 4 mn	3%

This license contract has a value of $ 1.9 mn, or 14% of the project value. The final contract that Mr. Tech Transfer has in mind uses these terms as base scenario and then specifies for each possible stage of sublicensing a participation rate.

Mr. Tech Transfer now has defined the base contract, i.e. the contract with biotech assuming no sublicensing, and tries to calibrate the sublicense participation rates in a way corresponding to a value of $ 1.9 mn for each possible sublicensing scenario. The final contract should include potential sublicensing at the beginning of preclinical phase, clinical phase 1, 2, and 3, and approval phase. Mr. Tech Transfer now calculates for each scenario based, on the value share figures we have outlined earlier, the sublicense terms. For the sublicense contract where biotech out-licenses to pharma in preclinical phase for instance he needs to know upfront, milestone payments, and royalties that would correspond to a value share of 20%-80% for the same project, assuming that it is already in preclinical phase. Mr. Tech Transfer designs the sublicense contracts on the basis of a discount rate of 12%, assuming that the sublicensee will be a mid-sized pharmaceutical company. He then comes up with the following terms for the different phases of sublicensing:

Table 4.20. Sublicense contracts biotech-pharma

In $ mn	Upfront	Milestone Payments					Royalties
Moment of Sublicense		Phase 1	Phase 2	Phase 3	NDA	Launch	
Preclinical	1.3	2.5	3.8	5.0	6.3	7.5	4.7%
Phase 1	3.4		6.8	10.1	13.5	16.9	6.1%
Phase 2	11.2			22.4	33.5	44.7	8.8%
Phase 3	46.0				92.0	137.9	13.8%
Approval Phase	134.0					268.1	28.5%

Mr. Tech Transfer now values each sublicensing scenario as if it were a contract on its own. Instead of using the milestones and royalties of the base scenario, he assumes a given participation rate in the sublicensing terms once the project is sublicensed. The table below represents the numbers he must use for the valuation. The light grey fields correspond to the base contract, the dark grey fields to the sublicensing participation. We see that the payments from the sublicense deals are linked with the participation rate.

Table 4.21. Base contract and sublicensing participation

	Lead	Precl.	CP 1	CP 2	CP 3	NDA	Launch	Royalties
Precl.	0.1	x_p*1.3	x_p*2.5	x_p*3.8	x_p*5.0	x_p*6.3	x_p*7.5	x_p*4.7%
Phase 1	0.1	0.2	x_1*3.4	x_1*6.8	x_1*10.1	x_1*13.5	x_1*16.9	x_1*6.1%
Phase 2	0.1	0.2	0.3	x_2*11.2	x_2*22.4	x_2*33.5	x_2*44.7	x_2*8.8%
Phase 3	0.1	0.2	0.3	0.8	x_3*46.0	x_3*92.0	x_3*137.9	x_3*13.8%
Approval	0.1	0.2	0.3	0.8	1.5	x_A*134.0	x_A*268.1	x_A*28.5%

Assuming a dummy participation rate, Mr. Tech Transfer can value each scenario. He then modifies the participation rate for each scenario in a way that the scenario value equals exactly the claimed $ 1.9 mn of the base contract. This he can do either by playing around with the participation rates, or by using the goal seek method in Excel (see exercises). He comes up with the following participation rates:

Table 4.22. Participation rates

Moment of Sublicense	Participation rate
Preclinical	38%
Phase 1	28%
Phase 2	19%
Phase 3	11%
Approval Phase	7%

*These participation rates mean that, for instance if the licensee decides to sublicense in phase 3, Mr. Tech Transfer's institute would receive 11% of all sublicense terms, i.e. milestones of 11%*46.0=$ 5.1 mn for phase 3, 11%*92.0 =$ 10.1 mn for approval phase, 11%*137.9=$ 15.2 mn at launch, and 11%*13.8%=1.5% royalties.*

Discussion

Once the project is sublicensed, the license revenues for academia change according to the sublicense terms and the participation rate. This can lead to substantially higher payments if biotech manages to reach a good deal, but can also result in a reduction of future revenues due to a poor sublicense

deal. As seen in the previous case, even average deals can change the size of specific payments considerably, e.g. 3% royalties compared to 1.5% if the project is sublicensed in phase 3. It is possible, to gear these changes with specific clauses in the contract. A research institute for instance can insist on its royalty claim and only apply the participation rate to upfront and milestone payments. This however means that biotech must at least negotiate this royalty rate in the sublicense contract, otherwise it would have to pay more royalties to academia than it receives from pharma. This narrows biotech's leeway in the negotiation and might lead to no deal at all. The participation rate has been introduced precisely to avoid such deadlocks in negotiations. Ultimately, a poor license contract is still better than none. Remember that for academia all cash flows stemming from the license deals are positive. If biotech must halt the project because it cannot sublicense it to a third party, then academia does not receive any license payments anymore. An attenuated version of the fix royalty claim is the introduction of a minimum royalty rate. Academia participates in the sublicense deal at the agreed rate, but receives at least the minimum royalty rate. With this, the possibility of a deadlock in sublicense negotiations still exists, but it is less likely, because biotech is given a bit more leeway now. Of course, the same clauses can also apply to milestone payments.

How does this translate into the valuation? If academia insists on its royalty claim from the base scenario, then the participation rate refers just to the milestone payments, and only the cash flows related to sublicense milestones are linked with the participation rate. The light grey fields in the table are the licence, the dark grey the sublicense parameters.

Table 4.23. License and sublicense parameters

	Lead.	Precl	CP 1	CP 2	CP 3	NDA	Launch	Royalties
Precl.	0.1	x_p*1.3	x_p*2.5	x_p*3.8	x_p*5.0	x_p*6.3	x_p*7.5	3%
Phase 1	0.1	0.2	x_1*3.4	x_1*6.8	x_1*10.1	x_1*13.5	x_1*16.9	3%
Phase 2	0.1	0.2	0.3	x_2*11.2	x_2*22.4	x_2*33.5	x_2*44.7	3%
Phase 3	0.1	0.2	0.3	0.8	x_3*46.0	x_3*92.0	x_3*137.9	3%
Approval	0.1	0.2	0.3	0.8	1.5	x_A*134.0	x_A*268.1	3%

If we use a minimum royalty rate, then the actual royalty rate would be whichever is higher, either the minimum royalty rate or the participation rate times the royalty rate of the sublicense contract.

For all these different contract forms, the DCF calculation works with fixed cash flows. Either the cash flows are really predefined, as is the case in the base scenario, where the milestones and royalty rate are clearly specified. Or we apply a participation rate to the license terms of the sublicense contracts. These however are assumed to be predefined as well. In the valuation it makes no difference whether we value a contract scenario with participation rates, or a contract scenario with predefined terms that equal the sublicense terms times the participation rate. The cash flows are equal. In reality these two contract structures are not the same. The participation rates have explicitly been introduced to make a difference, that is to say to offer biotech more chances to sublicense the compound and to have at the same time also an upside in case the sublicense deal turns out to be better than anticipated. Both motives are value enhancing, but not considered in the DCF calculation. Both motives deal with the uncertainty about future sublicensing scenarios. We do not know yet how well biotech manages to sublicense the project. Nevertheless, the rigidity of DCF forces us to assume hypothetical sublicense contracts, contrary to the very concept of participation rates and neglects that the predicted deal scenario is highly uncertain On these grounds, DCF has severe shortcomings when applied to the valuation of license contracts with sublicensing. We will elucidate how real options cope with this problem in the next section.

Theory Real Options

In the previous discussion about DCF valuation of contracts including sublicense participation rates we have noticed two important drawbacks of the DCF method:

1. DCF does not account for the possibility of deadlocks, i.e. the possibility that no viable sublicense contract can be closed.
2. DCF uses predefined sublicense contracts and consequently cannot quantify the upside academia has due to proportional participation also in above average sublicense deals.

The first point deals with the option of the sublicensee not to enter a deal. The second point addresses the uncertainty of the future sublicense contracts; its terms might be better or worse than anticipated. Both points call for the use of real options valuation. First, the option to decline a deal lies at the heart of the real options concept. Second, the trigger of the decision to enter a deal or not depends on the conditions, i.e. the sublicense contract

terms, and these depend on the quality of the project. This is exactly what we allow to fluctuate in real options valuation and more precisely in the binomial tree; the quality of the project, measured in monetary units.

In order to value such a license contract with real options, we must therefore first, model the sublicense contract in function of the quality of the project, i.e. in function of the peak sales, and second, model the decisions of the sublicensee.

*Generic license contracts***.** As we have seen before in the section about license contracts, these contracts can be defined by the discount rate and the value share each party gets. Upfront payment, milestone payments, and royalties can however be arranged in many ways to reach the same value share. Hence, if we want to value a sublicensing scenario, we must assume a generic license contract. This can be defined by the following parameters:

1. Applied discount rate
2. Value share licensor-licensee
3. Value split upfront-milestones-royalties
4. Relative weights between milestones

The discount rate is necessary to define the project value that is to be shared between the two parties. With the value share we get the licensor's piece. A value repartition between upfront payments, milestone payments, and royalties allows the determination of how much each term contributes to the value and allows to adjust the risk profile of the contract. This then directly determines the upfront payment, and the royalty rate can be deduced. For the milestones, we further need the relative weights between them. The calculation of a generic contract is shown in the example below. Assume the following generic license contract in clinical phase 3:

Table 4.24. Generic contract

Discount rate	12%
Licensor-licensee value share	50%-50%
Upfront-Milestones-Royalties	30%-30%-40%
Milestone weights (approval, launch)	1:2

Assume that the project valued with 12% yields a value of $ 600 mn. The licensor captures 50% of this, i.e. $ 300 mn. 30% of this value stem from the upfront payment, 30% form the outstanding milestone payments, and

the remaining 40% from the royalties. This means that the upfront payment equals $ 90 mn. The sum of the risk adjusted and discounted milestones equals $ 90 mn as well, while the risk adjusted and discounted royalty streams equal $ 120 mn. From this we can deduce the milestones using the following development:

$$V_{milestones} = p_3(1+r)^{-t_3} n + p_3 p_{approval}(1+r)^{-t_3 - t_{approval}} 2n \tag{4.27}$$

This formula indicates the rNPV of all milestone payments, i.e. the part of the license contract value that can be attributed to the milestone payments.

$$n = \frac{V_{milestones}}{p_3(1+r)^{-t_3} + 2p_3 p_{approval}(1+r)^{-t_3 - t_{approval}}} \tag{4.28}$$

Using the $ 90 mn as $V_{milestones}$, 12% for the discount r, and the corresponding success rates (60% for phase 3 and 90% for approval phase) and durations (three years for phase 3 and one year for approval phase), we can deduce x, the milestone unit. In this specific case we get:

$$n = \frac{\$\,90\ mn}{60\%(1+12\%)^{-3} + 2 \cdot 60\%90\%(1+12\%)^{-5}}$$

$$n = \underline{\underline{\$\,80.8\ mn}}$$

The relative milestone weights tell us that the approval phase milestone equals $ 81 mn and the launch milestone $ 162 mn, two times the unit. If now academia receives 20% of all cash flows stemming from a sublicensing deal in phase 3, it receives 20% of the upfront payment at the beginning of phase 3, i.e. $ 18 mn, 20% of $ 81 mn at the beginning of approval phase, i.e. $ 16 mn, and 20% of $ 162 mn at launch of the compound, i.e. $ 32 mn. For the royalties we use a similar development:

$$V_{royalties} = p_3 p_{approval} \sum_i (1+r)^{-t_3 - t_{approval} - i} roy \cdot sales_i \tag{4.29}$$

This formula shows how the rNPV of all royalty streams depends on the royalty rate *roy*. To deduce this rate we must isolate *roy*:

$$roy = \frac{V_{royalties}}{p_3 p_{approval} \sum_i (1+r)^{-t_3 - t_{approval} - i} sales_i} \tag{4.30}$$

The above formula yields the royalty rate that corresponds to a rNPV of all royalty streams of $V_{royalties}$, in our case $ 120 mn.

We can deduce the license contract terms from the above given generic structure. Assuming a generic structure for each stage, i.e. from preclinical through to commercialisation, we are able to deduce all required cash flows we for the valuation.

Let us assume Mr. Tech Transfer's project at the beginning of phase 3. The targeted generic license structure looks as follows:

Table 4.25. Generic contract for phase 3

Moment of Sublicense	Value Share	Milestones-Royalties	Phase 3	NDA	Launch
Phase 3	50%-50%	50%-50%	1	2	3

The project should be split into two equal parts (we assume a joint discount rate of 12%), half of its value should be contributed by milestone payments (assuming the upfront payment as the phase 3 milestone payment), and the relationship between the milestone payments of phase 3, NDA, and Launch is 1:2:3.

The value of the entire project amounts to $ 497.7 mn. The licensee should get 50% thereof, i.e. $ 248.8 mn. Milestones make up 50%; the other 50% are contributed by royalty payments. Assuming *n* to be the milestone for phase 3, the milestone at NDA would amount to *2n*, and the launch milestone to *3n*. The rNPV of the milestone payments can be written as:

$$n = \frac{V_{milestones}}{1 + 2p_3(1+r)^{-t_3} + 3p_3 p_{approval}(1+r)^{-t_3 - t_{approval}}} \tag{4.31}$$

Using the actual numbers this gives the following solution:

$$n = \frac{50\%\ \$\ 248.8\ mn}{1 + 2 \cdot 62\%(1+12\%)^{-3} + 3 \cdot 62\% \cdot 78\%(1+12\%)^{-5}}$$

$$n = \underline{\underline{\$\ 46.0\ mn}}$$

With this we can deduct the size of the milestones for phase 3 ($ 46.0 mn), NDA ($ 92.0), and launch ($ 137.9 mn). For the royalty rate we have to proceed in a similar way:

$$roy = \frac{V_{royalties}}{p_3 p_{approval} \sum_i (1+r)^{-t_3 - t_{approval} - i} sales_i} \tag{4.32}$$

$$roy = \frac{50\% \$\ 248.8\ mn}{62\%78\% \$\ 1{,}864\ mn} = 13.8\%$$

Note that the deduction of the license terms as described corresponds to a DCF calculation. Of course, this could also be done by using a real options approach, but the calculation would be much more complex. For this exercise, that is to say to know approximately the terms of the sublicense contract, this approach is more illustrative.

As a second remark, we must add that the above-mentioned method is only one possibility to define a generic contract structure. As we will see in the chapter about negotiations, the contract terms do not necessarily have to be defined by a value share method, but can also be determined by some other rationale.

Valuation of scenarios. As with DCF, we must first value each possible sublicensing scenario. The valuation of a specific sublicensing scenario comprises however some special features that have to be addressed. First, we cannot simply span a tree up to approval phase and then work back to the root node as we have done for project and license valuation. Place yourself in an end node at approval phase like in the figure. In order to value the project in that node, we must know the terms of the sublicense contract that is valid in this node, i.e. the milestone payments and royalties, otherwise we cannot determine the cash flows necessary for the valuation.

The sublicense contract is determined at the time of sublicensing (e.g. start of phase 1 for the scenario with sublicensing in phase 1), in the "sublicense nodes". The figure displays that an end node is accessible from various sublicense nodes. Hence, the sublicense terms in the end node depend not only on the end node, but also on the path that lead to this end node, or better on the sublicense node that has been passed on that path. It is therefore not possible to value the tree from the end nodes, because we do not know the sublicense terms. However, we do know how to value license contracts from the previous section, and a sublicense is not any different from a license contract with respect to valuation. According to this, we can value the sublicense contract at the sublicense nodes as displayed in the figure. We can therefore attribute a value to each sublicense node with the algorithm outlined in the previous section on license contracts. As a consequence, we only need to span the tree from the date of valuation up

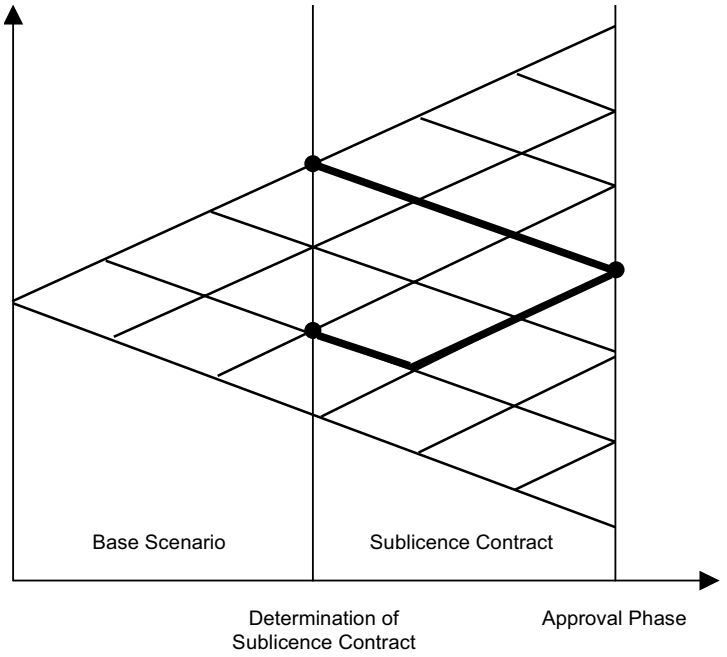


Fig. 4.28. Various paths leading to the same end node

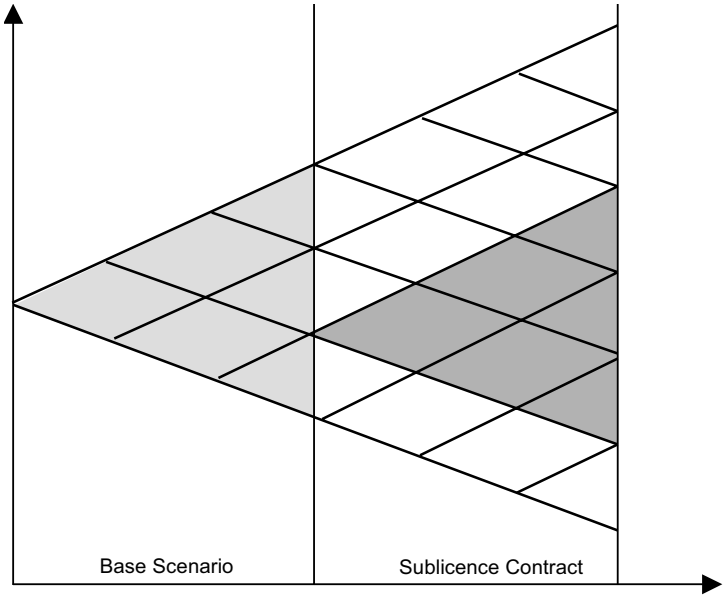


Fig. 4.29. Nodes that can have the same sublicense contract

to the time of sublicensing. We can then determine, due to the assumed generic structure of the sublicense contract, the upfront and milestone payments and royalties for the valuation of the sublicense contract in each sublicense node. For the valuation of the sublicense contract we then need to span a tree from the time of sublicensing to approval phase in each sublicense node. This obviously increases the complexity of the valuation considerably.

As a second particularity, license contracts with sublicensing involve not only two, but three parties, namely academia, biotech, and pharma. We therefore have to value the project for three parties. Although we might only be interested in the value to academia, we must value the project from the view of biotech and pharma as well, because they are in control of the project from some time and consequently decide whether to continue or abandon the project. For the valuation of the sublicense contract in the sublicense nodes, we must value the project for pharma in order to know whether the project is still alive or abandoned because of economic reasons. While valuing the project for pharma, we must use the sublicense payments paid to biotech and the academias participation thereof to value the sublicense contract for biotech and academia. As a result, the sublicense

Manual for Valuation of License Contracts with Sublicensing

1. Define license contract as if biotech commercialises the project (base scenario)
2. Define possible points of sublicensing (sublicensing scenarios)
3. Value each sublicensing scenario
   a. Span tree until moment of sublicensing
   b. Generate for each end node a possible sublicense contract
   c. Value the sublicense contract for each pharma, biotech, and academia using ROV for license contracts
   d. Set the project values at the end nodes to the values of the sublicense contract for academia and biotech respectively
   e. Work back the tree to the root node using ROV for license contracts, assuming the license terms of the base scenario
   f. Choose participation rates such that sublicensing scenarios and base scenario have the same values

If we value an already signed contract, then we just have to value all scenarios (point 3) and probability-weigh them.

valuation provides three values, one for pharma, one for biotech, and one for academia. Then we can work back the tree from the sublicense nodes back to the root node using the known algorithm for real options valuation of license contracts. In this part of the tree, the license payments correspond to the ones of the base scenario.

Valuation of the contract. With the algorithm described above we manage to value each scenario of the license contract between academia and biotech. As with DCF, we should now aim at calibrating the participation rates in a way that all scenarios have the same value like the base scenario. If the contract is already signed and the participation rates therefore are fixed, we deal again with the same problem as in DCF, we must quantify the probabilities of each scenario. One possibility to bypass the somehow arbitrary weighing of scenarios is the following: Biotech chooses the scenario that represents the greatest value to it. This argument uses the same logic real options are based on, maximisation of value. Although this reasoning is correct, we should consider that these scenarios have very different risk profiles. While early sublicensing offers biotech revenues in the near future, it also limits considerably the upside. The more risk biotech is ready to bear, i.e. the further it takes the compound on its own, the higher the upside. In reality value maximisation is just one criterion in strategic planning, aspects like risk minimisation, focus on core business, or avoidance of dilution might indicate other strategic options.

Sublicensing Case: ROV

Mr. Tech Transfer feels a bit disturbed that his DCF valuation does not make a difference between a standard license contract with predefined terms and a license contract with participation rates. He is convinced, that his institute as well as the partnering biotech company profits from the introduction of participation rates by facilitating sublicensing negotiations. But his DCF calculation does not visualise this effect. He therefore decides to value the same project with real options.

Using exactly the same input parameters like in the DCF calculation and a volatility of 30%, Mr. Tech Transfer first works out a base license contract between his institute and the biotech company. Again, he aims at a 14% value share, using a discount rate of 15%. The contract is calculated like any standard license contract between two parties. Details can be found in the first part of the licensing chapter. Mr. Tech Transfer comes up with the following base scenario:

Table 4.26. License parameters with real options

	Upfront payment	Milestone Payments	Royalties	Δ to DCF
Lead Opt.	$ 0.1 mn			$ 0 mn
Preclinical		$ 0.25 mn		$ 0.05 mn
Phase 1		$ 0.45 mn		$ 0.15 mn
Phase 2		$ 1 mn		$ 0.2 mn
Phase 3		$ 1.5 mn		$ 0 mn
Approval Phase		$ 3 mn		$ 0 mn
Launch		$ 4 mn	3.25%	0.25%

The value of this license deal amounts to $ 2.0 mn for academia, and $ 12.2 mn for biotech, corresponding to a value split of 14%-86%. Mr. Tech Transfer notes satisfied that the use of real options valuation helps him justifying higher deal terms in the base contract. He then goes on and defines the points of sublicensing. As in the DCF case these points are start of preclinical development, start of clinical phases 1-3, approval phase and at commercialisation of the product. He now defines what the generic sublicense contracts should look like at the respective points of sublicensing. For consistency, he chooses generic contracts that correspond to the contracts he has used in the DCF calculation. The numbers in the phase rows represent the weights of the milestones relative to one another:

Table 4.27. Generic sublicense contracts with real options

Moment of Sublicense	Value Share	Milestones-Royalties	Precl.	Phase 1	Phase 2	Phase 3	NDA	Launch
Preclinical	20%-80%	50%-50%	1	2	3	4	5	6
Phase 1	25%-75%	50%-50%		1	2	3	4	5
Phase 2	35%-65%	50%-50%			1	2	3	4
Phase 3	50%-50%	50%-50%				1	2	3
Approval Phase	70%-30%	34%-66%					1	2

Using a peak sales estimate of $ 650 mn and a joint discount rate of 12%, these generic license contracts provide exactly the sublicense terms as used in the DCF case. In the next step, Mr. Tech Transfer undertakes the valuation of the first scenario, i.e. the scenario where the biotech company sublicenses the project already at the beginning of preclinical phase. Therefore, he first spans the tree until the start of preclinical phase, i.e. over a time period of one year. Using a time step of one year in the tree, this corresponds to one time step.

For each sublicense node Mr. Tech Transfer now calculates a license contract corresponding to the generic structure he has previously defined. He uses the same formulae as described above.

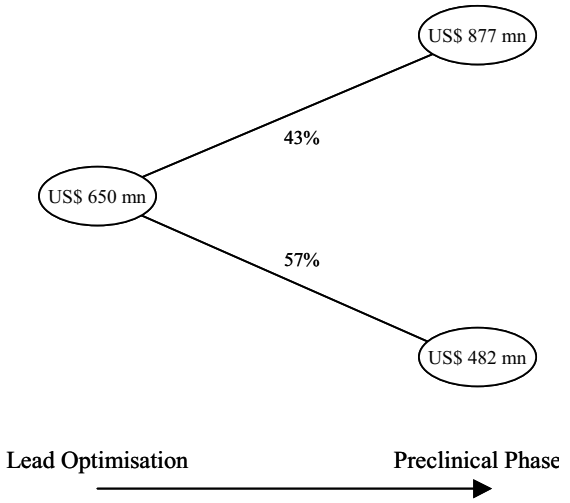


Fig. 4.30. Going one time step forward

He must therefore first calculate the value of the project at the corresponding nodes using the DCF method. The value of the project, assuming peak sales of $ 877 mn, a discount rate of 12% and that lead optimisation is successfully passed, amounts to $ 77.9 mn, and to $ 30.9 mn assuming peak sales of $ 482 mn in the lower node. From this value biotech is expected to capture 20%, i.e. $ 15.6 mn or $ 6.2 mn. 50% thereof are allocated to royalties, and 50% to milestones. This corresponds to a royalty rate for biotech of 5.3% or 3.8%, respectively. Mr. Tech Transfer then calculates the upfront and milestone payments in the way as explained above in the section about generic license contracts. He receives the following results:

Table 4.28. Upfront milestone and royalty payments

Sublicense Node	Royalties	Precl.	Phase 1	Phase 2	Phase 3	NDA	Launch
$ 877 mn	5.3%	1.9	3.8	5.8	7.7	9.6	11.5
$ 482 mn	3.8%	0.8	1.5	2.3	3.0	3.8	4.6

Mr. Tech Transfer notices that without the use of a participation rate, the biotech company would not be able to enter a license contract if the peak sales estimate deteriorates, i.e. if the project is at the lower sublicense node. The offered sublicense terms are all below the base scenario and consequently, the biotech company would have to pay more to Mr. Tech Transfer's institute than it would receive from the pharmaceutical company, resulting in a net loss. The biotech company would therefore prefer not to sublicense the project, i.e. to let the project die. Mr. Tech Transfer's institute wouldn't earn any further license payments at all that way, despite the project having passed all previous phases. Using a participation fee, the institute and the biotech company would split the sublicense revenues between each other, leaving both a profit. So, how should this participation rate be chosen such that the scenario of sublicensing in preclinical phase equals the base scenario in terms of value? For this Mr. Tech Transfer performs a real options valuation of the sublicense contract for the sublicensor (the biotech company) and the sublicensee (the pharmaceutical company). Although he is not interested in the value of the sublicense contract to the pharmaceutical company, he needs to know in which states it abandons the project, as in these states the biotech company does not receive and further sublicense payments. Mr. Tech Transfer receives the following value for the share biotech receives in the sublicense contract with pharma:

Table 4.29. Biotech's share in the sublicense contract

Sublicense Node		Value
$ 877 mn	Sublicensor @ 15%	$ 12.1 mn
$ 482 mn	Sublicensor @ 15%	$ 4.5 mn

The value of the sublicense contract at the time of sublicensing will then be split between the institute and the biotech company according to the agreed participation rate x_{precl}. This means that in the upper sublicense node the project would have a value of x_{precl} $ 12.1 mn for Mr. Tech Transfer's institute, and x_{precl}*$ 4.5 mn in the lower sublicense node. For*

the biotech company the values amount to (1- x_{precl})$ 12.1 mn and (1-x_{precl})*$ 12.1 mn respectively. To simplify Mr. Tech Transfer has assumed that both, the biotech company and the institute, use a discount rate of 15%. Otherwise we would have to calculate the value of the sublicense contract for the sublicensor with the discount rate of the institute, and the institute would get x_{precl} thereof, and once with the discount rate of the biotech company, and the biotech company would get (1-x_{precl}) thereof.*

Table 4.30. Value distribution in sublicense nodes

Sublicense Nodes		Value
$ 877 mn	Biotech	$(1-x_{precl})\cdot 12.1$
	Institute	$x_{precl}\cdot 12.1$
$ 482 mn	Biotech	$(1-x_{precl})\cdot 4.5$
	Institute	$x_{precl}\cdot 4.5$

Mr. Tech Transfer knows now the values for biotech and the institute in all sublicense nodes. He now works back the tree to the root node, which in this case is just one time step. For the biotech company the value is defined by the following calculation:

$$\underbrace{\left[p(1-x_{precl})\cdot 12.1+(1-p)(1-x_{precl})\cdot 4.5\right]}_{1}\underbrace{P_{precl}}_{2}\underbrace{\frac{1}{1+r}}_{3}\underbrace{-0.8}_{4}\underbrace{-0.1}_{5} \tag{4.33}$$

The numbers in the equation correspond to

1. Expectation of future values at the end of the time step
2. Success rate for current phase
3. Discounting for one time step
4. Costs for current phase
5. License payments due to the institute

In a similar way Mr. Tech Transfer calculates the value for the institute:

$$\underbrace{\left[px_{precl}12.1+(1-p)x_{precl}4.5\right]}_{1}\underbrace{P_{precl}}_{2}\underbrace{\frac{1}{1+r}}_{3}\underbrace{+0.1}_{5} \tag{4.34}$$

Trying several values for x_{precl} Mr. Tech Transfer comes up with the following table:

Table 4.31. Participation rates and corresponding values

Participation Rate	Value for Institute	Value for Biotech
36%	$ 1.79 mn	$ 2.11 mn
38%	$ 1.89 mn	$ 2.02 mn
40%	$ 1.98 mn	$ 1.92 mn
42%	$ 2.08 mn	$ 1.83 mn
44%	$ 2.17 mn	$ 1.74 mn

A participation rate of 40% would yield about the targeted $ 2.0 mn from the base scenario, corresponding to a 49%-51% value split. Clearly, the scenario of sublicensing in preclinical phase does not provide biotech the original 86%-14% value split, but only a 49%-51% value split. However, since biotech contributes only the conduct of lead optimisation in this scenario, a far lower participation in the value is justified.

Mr. Tech Transfer now undertakes the valuation of all other scenarios. For each possible sublicense node he designs a contract that complies with generic structure.

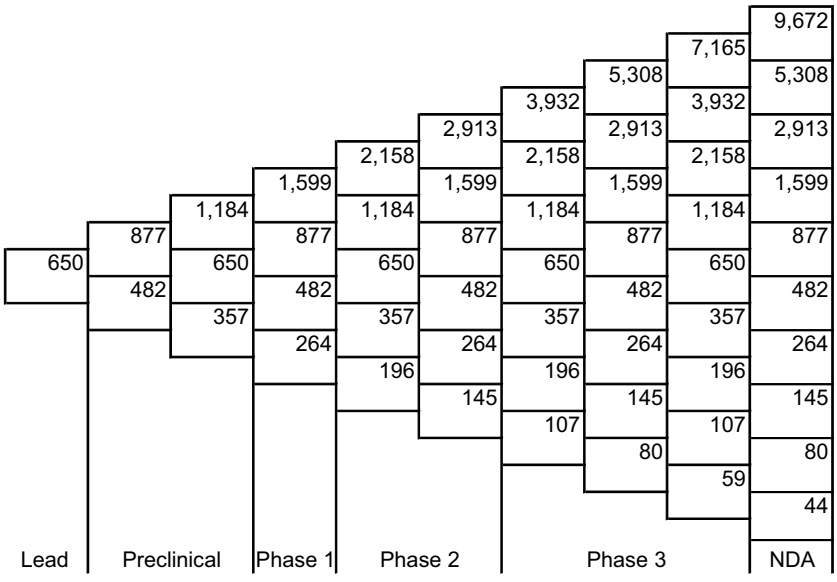


Fig. 4.31. Binomial tree

He receives the following intermediary results:

Table 4.32. Sublicense contracts for each sublicense node

Scenario	Sublicense node	P1	P2	P3	NDA	Launch	Roy. rate	Value @ 15%
Phase 1	265	0.5	0.9	1.4	1.8	2.3	2.0%	2.0
Phase 1	482	2.1	4.2	6.3	8.4	10.5	5.1%	11.4
Phase 1	877	5.1	10.2	15.3	20.4	25.5	6.8%	28.4
Phase 1	1599	10.6	21.2	31.8	42.4	52.9	7.7%	59.1
Phase 2	196	-	0.2	0.4	0.7	0.9	0.6%	0.7
Phase 2	357	-	4.1	8.2	12.3	16.4	5.9%	15.4
Phase 2	650	-	11.2	22.4	33.5	44.7	8.8%	45.8
Phase 2	1184	-	24.1	48.1	72.2	96.3	10.5%	100.4
Phase 2	2158	-	47.6	95.2	142.7	190.3	11.3%	198.3
Phase 3	107	-	-	0	0	0	0%	0
Phase 3	196	-	-	4.6	9.2	13.9	4.6%	17.6
Phase 3	357	-	-	19.3	38.6	57.9	10.5%	78.8
Phase 3	650	-	-	46.0	92.0	137.9	13.8%	194.7
Phase 3	1184	-	-	94.6	189.2	283.9	15.6%	403.9
Phase 3	2158	-	-	183.3	366.7	550.0	16.5%	787.7
Phase 3	3932	-	-	344.9	689.9	1034.8	17.1%	1485.3
NDA	44	-	-	-	0	0	0%	0
NDA	80	-	-	-	0	0	0%	0
NDA	145	-	-	-	14.4	28.7	13.7%	49.7
NDA	265	-	-	-	42.8	85.6	22.3%	172.1
NDA	482	-	-	-	94.2	188.4	27.0%	446.4
NDA	877	-	-	-	187.8	375.7	29.6%	919.9
NDA	1599	-	-	-	358.9	717.8	31.0%	1783.6
NDA	2913	-	-	-	670.3	1340.6	31.8%	3332.4
NDA	5308	-	-	-	1237.9	2475.7	32.3%	6197.5
NDA	9672	-	-	-	2272.0	4544.1	32.5%	11368.2

Using the values of the sublicense contracts to the sublicensor, Mr. Tech Transfer can now fill the values for his institute and the biotech company at the sublicense nodes for each scenario. Working back the tree as if it were a standard license contract using the base scenario terms, he calculates the value of the contract for the root node. The only task that remains is to adjust the participation rate in a way, that the institute's value equals $ 2.0 mn. Finally, Mr. Tech Transfer finds the following participation rates:

Table 4.33. Comparison of DCF and ROV participation rates

Moment of Sublicense	Participation Rate (ROV)	Participation Rate (DCF)
Preclinical	40%	38%
Phase 1	29%	28%
Phase 2	20%	19%
Phase 3	12%	11%
Approval Phase	9%	7%

Mr. Tech Transfer is happy that this long exercise pays off. In the license negotiations the real options valuation does not only provide him with arguments for better base scenario terms, but also suggests higher participation rates.

Discussion

The valuation of early stage licensing contracts with participation fees certainly belongs to the most difficult tasks in financial life sciences. The example with Mr. Tech Transfer shows important advantages over the common DCF method. First, the use of real options allows the licensor (the institute) to negotiate higher license terms, maintaining the agreed value split. The base contract in the example is considerably more favourable for the institute if negotiated with real options. Second, we note that real options completely capture the idea of the participation rate. As seen in the example, in each sublicense node the milestones and royalties change, while DCF just calculates with one set of license parameters as if these were agreed on from the beginning. In addition, it is not a big deal to implement in the model a clause saying that the licensee, i.e. the institute, receives a minimum royalty rate. This might occur following a licensee (biotech) asking for smaller participation rates. In order to compensate the value loss due to a decrease of the participation rate, the institute might insist on a minimum royalty rate. While in the real option model this clause becomes immediately visible, it might have no effect in the DCF model. Imagine the discussed scenario when sublicensing at the start of preclinical phase. The hypothetical license contract in the DCF model assumes a sublicense royalty rate of 4.7%. In the real options model we have received in the upper sublicense node a royalty rate of 5.3% and in the lower sublicense node a royalty rate of 3.8%. Assuming a participation rate of 40%

this would result in an effective royalty rate of 1.88% in the DCF model and 2.12% and 1.52% in the real options model. The biotech company offers you a minimum royalty rate of 1.8% and asks you how much you could accommodate with the participation rate. In the DCF model a minimum rate of 1.8% has absolutely no effect, because it is still lower than the assumed scenario of 1.88%. Consequently, the valuation does not indicate any leeway in return of the offered minimum royalty rate. This clearly doesn't make sense. In the real options model on the other hand, the institute profits from the minimum royalty rate in the lower sublicense node. It would raise the royalty form 1.52% to 1.8%. In return, Mr. Tech Transfer can cede a little of the participation rate. In this particular example the minimum royalty rate of 1.8% offsets a lowering of the participation rate by 2% to 38%.

For the valuation of these complicated contract structures, real options valuation is useful in many ways, not mainly because it includes the option to abandon the project at some point. The main argument for real options is the very nature of the contracts that explicitly assumes that at time of signing the fate of the economic potential of the project and the ability of the biotech company to sublicense it is not known yet. Real options valuation makes use of generic sublicense contracts allowing us to adjust the participation rate to the time and potential of sublicensing. DCF on the other hand has to use hypothetical license contracts ignoring any possible change of economic potential and its influence on the sublicensing contracts. Exactly this contradicts the idea of the participation rate. Real options valuation reflects precisely this idea, that we do not know yet what sublicense contract can be achieved. All contract features that consider the uncertainty with respect to product performance or sublicense deal terms can be quantified. This does not only refer to various possible sublicense contracts, but also stacked royalties, or as seen above to minimum royalties.

The large set of future scenarios requires an exact and extensive financial model. The two license partners have a lot of options to design the contract according to their preferences. Some might prefer larger milestone payments to the cost of lower royalties, while others want to put more weight on the royalty side. A flexible financial model is the perfect tool to check the influence of any change in the terms. As we have seen in the example of Mr. Tech Transfer however, this is a challenging task. But considering the ease during negotiation, the flexibility to quickly evaluate the counterparty's propositions, the gained confidence, and the potential to negotiate higher license terms more than justify a sound model, even if it costs a considerable amount of work. When valuing early-stage license

contracts with real options we reach the limits of the usability of spreadsheets. Nevertheless, the valuation can be elegantly programmed in Excel using VBA.

Negotiating License Deals

Licensing is an integral part of the life sciences industry. Universities do not have the potential to take their inventions through late stage preclinical tests and early stage clinical trials. Biotech companies in-license many of these products and conduct the early stage clinical research. Finally, they most often too lack the financial strength and expertise to bring an invention to market and out-license the product to large multinational pharmaceutical companies. With their financials, they conduct late stage trials and ensure the best commercialisation of the product based on their strong marketing departments. Furthermore, the big pharmaceuticals are not only answering to the financial need of biotech and universities, they themselves are forced to fill their pipeline with new innovative projects. They are dependent on licensing to do so, as the in-house research does not meet that need.

Most license contracts take place between two parties, the in- and the out-licensing company. Signing a license deal, the parties first need to evaluate if the license terms are fair and meet their preferences in terms of financials and risk. Both parties need to value the contract in order to position themselves in the negotiation process. The results of the negotiation must benefit both parties. The in-licensing company wants to learn what the maximum price is they can afford for the license, the out-licensing company what the minimal price for the disposition is. These upper and lower boundaries are the leeway of the negotiation.

To get the upper boundary of the negotiation, i.e. the highest price big pharma is willing to pay, we have to calculate the project value as if pharma is conducting the project as a self originated project based on its in-house capabilities and capacities. We use the costs, duration, peak sales for pharma and discount at a pharma discount rate between 8% and 12%. We have now calculated the value of the project as if it was pharma's own project.

In the next step, we calculate the lower boundary of the license contract. This corresponds to the project value as if the biotech company conducts the project on its own. We therefore choose the input parameters according to the capabilities of biotech. The peak sales are lower, as biotech does not dispose of a marketing department comparable to big pharma. Further-

more, biotech often takes a risk reducing approach to the clinical trials. It first conducts one single indication to get the proof of concept, and then in case of success sequentially launches the trials for further indications. Therefore, we assume that the sales revenues grow slower than pharma's. The project is discounted at the biotech's discount rate, typically above 14%. We could also adjust the success rates of the clinical trials if we can quantify the difference reasonably.

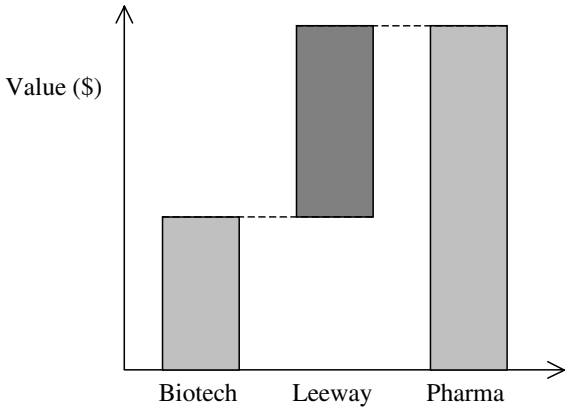


Fig. 4.32. Leeway in license negotiations

If the terms of the license contract render a value for biotech below the lower boundary, the company is better off conducting the project on its own. On the other hand, if the value is above the upper boundary, pharma should not sign the contract, as it would buy a project at a price exceeding its value.

Of course, both parties need to value independently the project's upper and lower boundary to know the acceptable range for the negotiation. The final contract value should be between the upper and the lower boundary. Nevertheless, pharma is sometimes willing to pay more than the upper boundary due to strategic considerations, and biotech sometimes wants to get rid of a project it could not finance, to avoid new fundraising rounds.

If there are several bidders for the project, e.g. due to a new and innovative technology, biotech can try to get more than the lower boundary price. Biotech should also be allowed to profit from the capabilities of the pharmaceutical partner. Pharma can try to argue to pay less than the upper boundary as it brings all its expertise into the project and leverages the value and because it suffers from information asymmetry. Pharma never knows all facts

about the project it licenses. If biotech wants to reduce the discount due to this information risk, it can agree to set more weight on royalty payments and therefore shares more risk with pharma. The final terms should ultimately reflect the parties' need for cash and risk preferences.

As we have seen in the section on licensing, there is an alternative way to negotiate license contracts based on the value share principle. The in- and out-licensing companies agree to share the value of the project. The share of the out-licensing company increases the more advanced the development. The argument goes that the licensee takes large risks, due to high investments and attrition rates. The licensee wants to be rewarded for this risk. Nevertheless, if we value the project based on risk adjusted NPV or real options, we account for the risk with the success rates and the discount rate, and for the investments with the cash flows. We would therefore reward the pharma company twice to take the risk. The value share method has its strength when used to compare different deals with each other. This can even be applied to deals of different values, as we look at a relative figure with the value share method.

Negotiation Case (First Part)

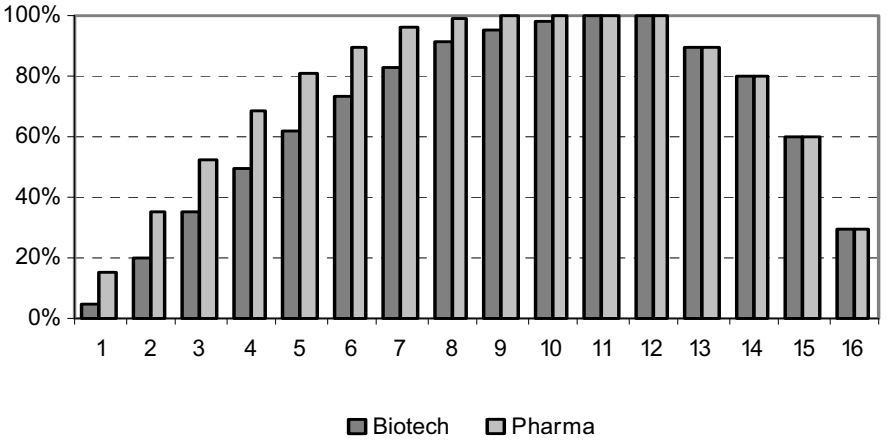


Fig. 4.33. Sales curves for biotech and pharma

A biotech company has just successfully reached proof-of-concept in man, i.e. finished clinical phase IIa testing, and considers to out-license the compound or to conduct all development and to market it on its own. It wants to take this strategic decision based on a clear number. It calculates

Table 4.34. Input parameters for biotech and pharma

	Biotech	Pharma
Phase 3		
Duration	3 years	3 years
Cost	$50 Mio	$60 Mio
Success Rate	65%	65%
NDA		
Duration	1 year	1 year
Cost	$3 Mio	$3 Mio
Success Rate	88%	88%
Market		
Launch costs	$120 Mio	$120 Mio
Peak Sales	$250 Mio	$250 Mio
Discount rate	17%	11%
rNPV	53 Mio	203 Mio

the value of the project if it does everything in-house. The inputs respect the characteristics of the company in terms of financial strength and marketing expertise. The company then also calculates the value of the project if the main candidate for the licensing conducts the project on its own. The drug development costs and the sales ramp is higher if pharma conducts the project. The discount rate for biotech is 17%, for pharma 11%. The calculation, based on the parameters from the table below gives us the upper and the lower boundary of the negotiation. Biotech should keep the project and continue developing it on its own if the value of the deal drops below $ 52 mn. Conversely, if the value of the license mounts above $ 203 mn, big pharma should walk away. At the upper boundary, the return on investment for pharma corresponds to its discount rate.

We now consider a license contract where biotech receives the following payments from pharma:

Table 4.35. Negotiation case contract

Upfront	$ 20 mn
Milestone clinical phase 3 completion	$ 40 mn
Milestone NDA approval	$ 80 mn
Royalty rate	17%

The license contract has a value of $ 105 for biotech, and -$ 150 mn for pharma. The project therefore increases in value for biotech by $ 53 mn, and for pharma by $ 53 mn as well, once they enter into the licensing agreement. The difference of value of the license contract arises out of the different discount rates for biotech and for pharma. The figure below pictures these numbers: (1) is the original value for biotech and the lower boundary, (2) is the value increase for biotech trough licensing, (3) the difference arising out of the discount rates, and (4) the value increase for pharma.

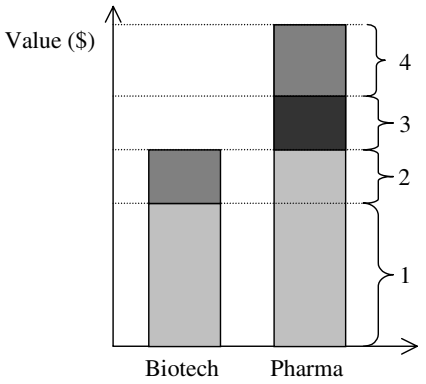


Fig. 4.34. Decomposition of value

As biotech and pharma do not use the same discount rate, we cannot properly distribute the value between them a portion of the value (3) is not attributable. This also explains why license contracts are not communicated in terms of NPV, but rather in terms of cash flows, e.g. $ 20 mn upfront, further $ 120 mn in milestones, and undisclosed royalties. If biotech prefers to have higher upfront payments, the difference in discount reduces. If biotech does not urgently need cash it wants to receive delayed payments in form of milestones and royalties, leveraging the value of the project in case of success.

We can refine the valuation approach by incorporating the value of the biotech's option to self-conduct the project. We can argue that once biotech brings its first compound through late stage clinical trials and builds up an own marketing department, all subsequent projects are more valuable due to the increased expertise and capabilities of biotech and moreover due to a decreased discount rate. Even if the real option to become a

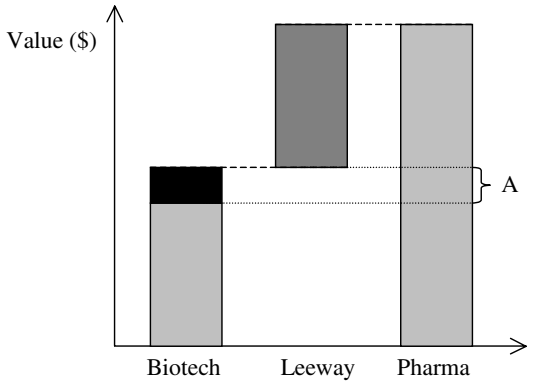


Fig. 4.35. Increased lower limit for biotech due to strategic value (A)

fully integrated biopharmaceutical company is not evident in the value of the lead project (the value of the license contract might be higher than if biotech conducts the project on its own), it can pay off for the following projects. These benefit from the new properties of the biotech company, i.e. expertise, already established distribution network and steeper sales ramp, and lower discount rate. The lower boundary for the negotiation then increases and in some cases, biotech might even be better advised to conduct the project on its own.

We can also argue that biotech profits from the cash it receives from the license deal and from the reduced risk. This might as well be factored in a reduced discount rate, and a consequent value increase.

We should also not forget to mention the aspect of control. Once biotech out-licenses the project it has lost the control over it. Pharma could delay development and thus reduce the value of the project. Also, we should keep in mind that milestones are non-dilutive cash.

Case (Second Part)

We now want to put a number on the biotech's strategic option to conduct the development on its own and to become a fully integrated drug development company. We will contrast the value of the biotech pipeline as it is now, with a discount rate corresponding to the company's maturity, with the value of the pipeline if the company becomes as well a drug selling company. We assume that if the drug is marketed, we can reduce the biotech's discount rate from 17% to 15%. The value for the other projects in the pipeline, Project-B, Project-C, and Project-D, changes due to the in-

creased expertise of the company. This increase only takes place if the biotech company is able to launch the first project, the probability being 65%*88%=57.2% The strategic value for the subsequent project then amounts to 57.2%*(9.1+12.6+7.8)=$ 16.9 mn. The lower boundary therefore rises from $ 53 mn to $ 70 mn. If the biotech would have been offered a license contract worth less than $ 70 mn it might have opted to develop the compound on its own.

Table 4.36. Value and value increase

Project	Project-B	Project-C	Project-D
Phase	Phase 1	Phase 1	Preclinical
Value @ 17%	$ 7.9 mn	$ 16.8 mn	$ 8.1 mn
Value @ 15%	$ 17.0 mn	$ 29.4 mn	$ 15.9 mn
Value Increase	$ 9.1 mn	$ 12.6 mn	$ 7.8 mn

We can conclude that the above discussed negotiation paradigm gives a sound basis for fair negotiations, both, for the licensee and the licensor. To be successful in negotiations, you have to know your leeway and your options. The discussed approach requires some work, but provides security on fixing the deal terms.

A further application of the method, namely strategic decision making, should be considered when evaluation the option to license. The ultimate goal for any company is to increase its risk adjusted value. The method therefore is much more than a simple negotiation framework.

Valuing Projects with Multiple Indications

Background

It is not uncommon that one compound has several possible indications, as is the case with most cancer drugs. The developing company usually has to conduct separate trials for every indication it wants to market. Before phase 2, i.e. in the lab or in phase 1 trials, the indication is not yet an issue and the results of the compound can be used for any indication. However, in phase 2 and phase 3 trials the company must prove that the drug is an efficacious treatment for the proposed indication. A drug development project that is still in an earlier stage than phase 2 has therefore the following structure:

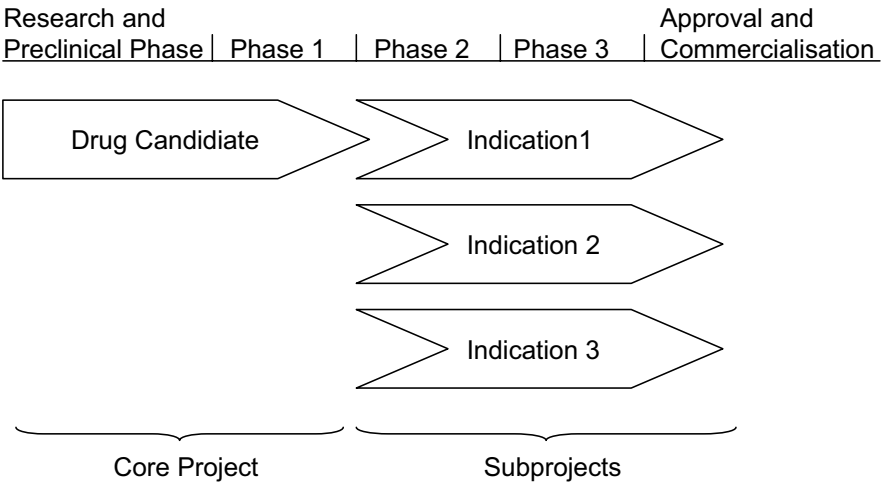


Fig. 4.36. Subdivision of a project into core and subprojects

Once the trials are conducted for specific indications, each indication of the compound represents a project on its own, we call these indication specific projects subprojects. The joint preceding part up to phase 1 is called the core project.

This splitting up into several subprojects has important implications for the valuation. First, the project with just one indication might not be profitable enough to justify its continuation. Expanding the drug into other indications can increase its value such that it is worthwhile to develop it further. Second, we need to know the success rates not only of the project, but also of the subprojects. Published success rates for phase 2 and 3 refer to compounds and not to indications. A compound counts as having successfully passed the phase if at least one indication has successfully passed phase, no matter whether others fail. This implies that the success rate of indications is lower than the success rate of compounds. Common sense suggests that if one indication passes, the second is more likely to pass, than if the first has failed. This is a concept called correlation. In the following we will treat these two major points – consequences on valuation and success rates – more in detail.

Consequences on Valuation

DCF. It makes sense that any additional indication adds value to the project, as long as the indication itself has a positive NPV. From a DCF point of view the value of the project is simply the sum of the values of the core

project and all subprojects. The core project, being composed of exclusively investments, has necessarily a negative NPV (sum of its risk adjusted cash flows). No revenues can be generated in these phases, at least not if it is self-conducted. Nevertheless, these expenses are necessary to enable the subprojects. The core project can be seen like an investment that gives access to the subprojects. Clearly, we have to adjust the subprojects by their probability. The subprojects are only reached with the probability that all phases up to phase 1 are successfully passed, i.e. that the core project succeeds. From then onwards the subprojects use their own success rates that we discuss further below.

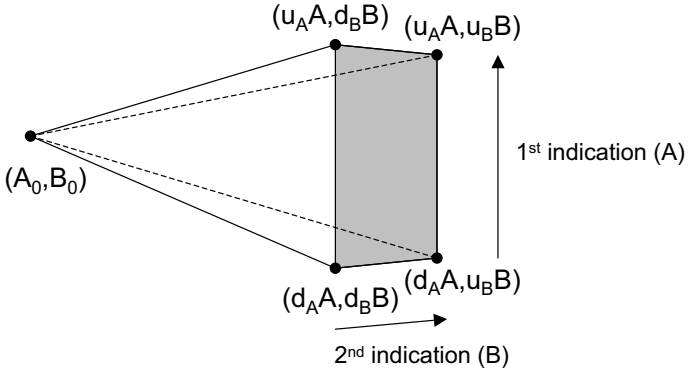


Fig. 4.37. 2-dimensional binomial tree, one time step

Real Options. In real options valuation the inclusion of different indications requires a new concept of tree. We now do not only have one underlying of the option as in the previous models. We now have to assume peak sales for every indication. These fluctuate as usual, but they do not necessarily fluctuate in the same way. If the sales potential for one indication deteriorates, this does not have to mean a decrease of the second indication's sales potential. We can imagine a competitor launching a drug in the first indication, while the second remains unaffected. Or, the compound performs better in one indication than in the other. However, usually the drug acts in similar ways in the various indications and some changes in sales potential occur simultaneously. This joint behaviour resumes in a positive correlation between the two peak sales estimates (or sales potentials). A common binomial tree cannot deal with two non-identical underlyings, i.e. peak sales estimates. We therefore have to superimpose two trees as displayed in the figure. We use a two-dimensional tree

(when visualizing, this becomes three-dimensional, since we have not counted the time axis as a dimension). While moving forward in the tree (in time) the sales potential of the first indication can go up (increase) or down (decrease), and the sales potential of the second indication can go left (increase) or right (decrease). We now have to correctly define the tree parameters, i.e. the step size up, down, right, and left, and the corresponding probabilities. Assume that the two indications are perfectly correlated. Then they should either go jointly up and left, or down and right. On the other hand, if they are independent of each other they should go up and down, left or right, independently on the other indication. This corresponds to the following scenarios:

Table 4.37. Joint probabilities

Perfectly correlated	left	right	Independent	left	right
up	p_{ul}	0	up	p_u*p_l	p_u*p_r
down	0	p_{dr}	down	p_d*p_l	p_d*p_r

In order to model a joint movement of two correlated underlyings we can use the following set of tree parameters.

Table 4.38. Joint probabilities for correlated indications

u (u_A)	$e^{\mu_A \Delta t + \sigma_A \sqrt{\Delta t}}$	l (u_B)	$e^{\mu_B \Delta t + \sigma_B \sqrt{\Delta t}}$
d (d_A)	$e^{\mu_A \Delta t - \sigma_A \sqrt{\Delta t}}$	r (d_B)	$e^{\mu_B \Delta t - \sigma_B \sqrt{\Delta t}}$
p_u	$\frac{1-d}{u-d}$	p_l	$\frac{1-r}{l-r}$
p_d	$1-p_u$	p_r	$1-p_l$
p_{ul}	$\rho\frac{p_u+p_l}{2}+(1-\rho)p_u p_l$	p_{ur}	$(1-\rho)p_u p_r$
p_{dl}	$(1-\rho)p_d p_l$	p_{dr}	$\rho\frac{p_d+p_r}{2}+(1-\rho)p_d p_r$

This set of parameters is a good approximation as long as the two volatilities do not differ too much ($0.5*\sigma_A<\sigma_B<2*\sigma_A$).

We can now model the tree until the end of phase 3. This then corresponds to a construct as displayed in the figure.

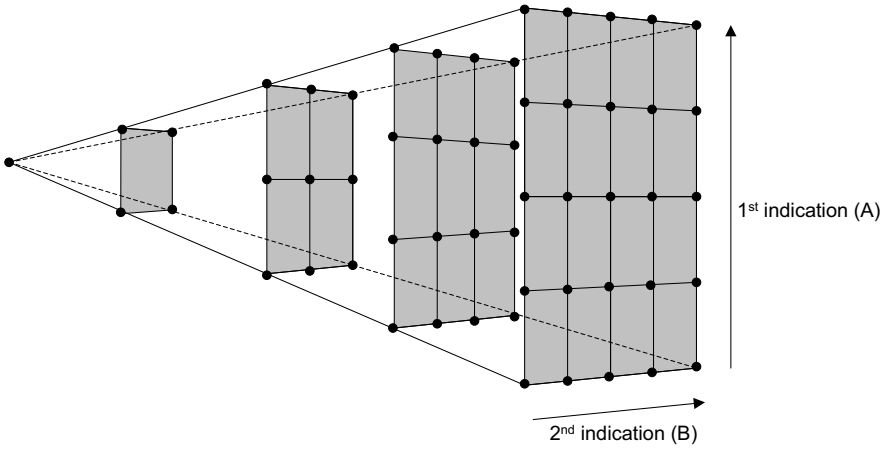


Fig. 4.38. 2-dimensional binomial tree over several time steps

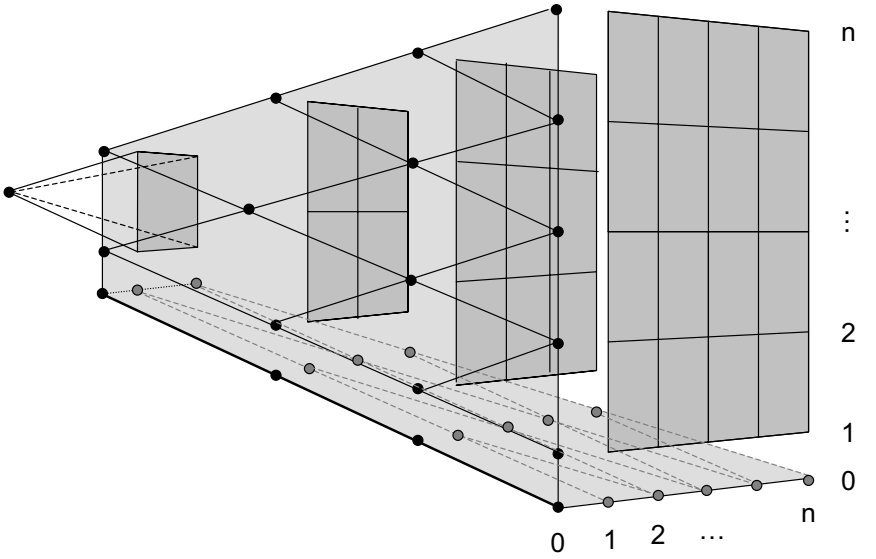


Fig. 4.39. 2-dimensional binomial tree with zero-layers

When placing ourselves in the end nodes, we know in each node the peak sales estimate for both indications. We can therefore value the project assuming that both indications passed all phases. However, it is also possible that only one indication reaches commercialisation. We must therefore add a column (1st indication) and a row (2nd indication) where only one indication is still alive. In the figure the additional columns are displayed by the

wall next to the tree, the additional rows by the floor under the tree. We numerate for each time t step the nodes for the two dimensions $s^t_{i,j}$. The nodes $s^t_{i,0}$ correspond to the states where the second indication already failed, in the nodes $s^t_{0,j}$ the first indication failed, and in $s^t_{0,0}$ both failed. We call these states building the wall and floor to the multi-dimensional tree "zero-layers". Valuing a multi-indication project with real options follows the same lines like standard real options valuation of a project, with some nuances:

1. Span the tree, including the "zero-layers" for each dimension until the last decision point.
2. Attribute a value to all end nodes according the respective peak sales estimates of the indications.
3. Work-back the tree to the root node $s^0_{1,1}$.

Spanning the tree. While the concept of spanning the tree has been outlined above, the technical implementation is somewhat tricky. A spreadsheet offers just two dimensions, columns and rows. We can either design the spreadsheet in a way that we put the various time steps of the tree under each other, or we put them on different worksheets. Both methods are too cumbersome. An elegant way is to program the tree in VBA, the programming language that comes along with Excel. We give here a short piece of code explaining how the tree can be programmed. It first calculates all tree parameters, i.e. the steps up, down, left and right. Then it calculates the joint probabilities of the joint steps within the tree. Finally the tree is spanned, i.e. each node is attributed a peak sales estimate for each indication. The zero layers have to be spanned separately.

```
ReDim tree(0 To n, 0 To n + 1, 0 To n + 1, 1 To 2) As Double
‘arguments: time, indication A, indication B, peak sales for A and B
‘n being the number of time increments

Dim i As Integer ‘counter
Dim j As Integer ‘counter
Dim t As Integer ‘counter of time

Dim up As Double ‘step up
Dim down As Double ‘step down
Dim left As Double ‘step left
Dim right As Double ‘step right
Dim Prob_u As Double ‘probability up
```

```
Dim Prob_d As Double ‘probability down
Dim Prob_l As Double ‘probability left
Dim Prob_r As Double ‘probability right

Dim Prob_ul As Double ‘probability up and left
Dim Prob_ur As Double ‘probability up and right
Dim Prob_dl As Double ‘probability down and left
Dim Prob_dr As Double ‘probability down and right

‘calculation of tree parameters
up = Exp(mu_A * dt + sigma_A * dt)
down = Exp(mu_A * dt – sigma_A * dt)
left = Exp(mu_B * dt + sigma_B * dt)
right = Exp(mu_B * dt – sigma_B * dt)
‘mu_A and mu_B are the continuously compounded growth rates
‘sigma_A and sigma_B are the volatilities

‘calculation of single probabilities as intermediary step
Prob_u = (1 – down) / (up – down)
Prob_d = 1 – Prob_u
Prob_l = (1 – left) / (left – right)
Prob_r = 1 – Prob_l

‘calculation of joint probabilities, rho being the correlation
Prob_ul = rho * (Prob_u + Prob_l) / 2 + (1 – rho) * pu * pl
Prob_ur = (1 – rho) * pu * pr
Prob_dl = (1 – rho) * pd * pl
Prob_dr = rho * (Prob_d + Prob_r) / 2 + (1 – rho) * pd * pr

‘initialisation of root node tree(0,1,1,.)
tree(0, 1, 1, 1) = peak_sales_A
tree(0, 1, 1, 2) = peak_sales_B

For t = 1 To n
 ‘node tree(t,1,1,.)
 tree(t, 1, 1, 1) = tree(t – 1, 1, 1, 1) * down
 tree(t, 1, 1, 2) = tree(t – 1, 1, 1, 2) * right
     For i = 2 To t + 1
     ‘nodes tree(t,i,1,.) and tree(t,1,i,.)
     tree(t, i, 1, 1) = tree(t – 1, i – 1, 1, 1) * up
     tree(t, i, 1, 2) = tree(t, 1, 1, 2)
     tree(t, 1, i, 2) = tree(t – 1, 1, i – 1, 2) * left
     tree(t, 1, i, 1) = tree(t, 1, 1, 1)
    For j = 2 To t + 1
     ‘nodes tree(t,i,j,.)
     tree(t, i, j, 1) = tree(t – 1, i – 1, j – 1, 1) * up
     tree(t, i, j, 2) = tree(t – 1, i – 1, j – 1, 2) * left
```

```
Next j
Next i
For i = 1 To t + 1
'zero layer
tree(t, i, 0, 1) = tree(t, i, 1, 1)
tree(t, i, 0, 2) = 0
tree(t, 0, i, 2) = tree(t, 1, i, 2)
tree(t, 0, i, 1) = 0
Next i
Next t
```

Attributing values to the end nodes. At the end nodes we can perform a standard DCF calculation of the project according to the peak sales for each indication. If it is a licensed project, the royalties are taken from the joint sales of all indications.

Working back the tree. This step is slightly more complicated than in a one-dimensional tree. First, we have to take the expectation not only of two, but of four subsequent scenarios. Second, the success rates and decision points relate sometimes only to one indication while the other is not affected by a success rate or a decision. Third, the decisions are not about continuing the project, but about continuing indications. The application of the success rates and the decision points have to be treated in more detail.

Assume you are in the last node of a phase of the first indication. In the next time step, the results reveal whether the indication passes or fails. It passes with the assumed success rate for this phase and indication. In this case we will move to one of the four subsequent nodes of the next time point in the tree. If the trial results are negative, the project is not automatically abandoned, because other indications might still be in testing. The project therefore only moves to a state without the first indication, i.e. to a state of the zero layer. The following formula displays how to calculate the project value when a success rate P^1 for the first indication applies.

$$V_{i,j}^{t} = \underbrace{\frac{1}{(1+r)^{\Delta t}}}_{1}\left(\underbrace{P^1\left(p_{ul}V_{i+1,j+1}^{t+1} + p_{ur}V_{i+1,j}^{t+1} + p_{dl}V_{i,j+1}^{t+1} + p_{dr}V_{i,j}^{t+1}\right)}_{2} + \underbrace{\left(1-P^1\right)\left(p_l V_{0,j+1}^{t+1} + p_r V_{0,j}^{t+1}\right)}_{3}\right) \underbrace{+ CF_t^1 + CF_t^2}_{4} \tag{4.35}$$

1. Discount for the time step
2. Expectation if trial successful
3. Expectation if trial not successful
4. Cash flows occurring between t and Δt

The same procedure has already been applied in previous tree calculations with only one indication, but there we could simplify the formula, because the zero layer, i.e. the states of the project where the indication failed, has only zero values. Consequently, step 3 drops out.

If trials of both indications end in the same time step, then we even have to further expand the above formula, taking account of cases where both, only the first, or only the second succeeds, or both fail. We will see in the paragraph about success rates how to assess these joint probabilities.

The decisions in a multi-indication project are not solely about continuing the project, but even more importantly about selecting the right indications and then continuing the indications. After phase 1 a company has the choice to start trials for several indications. While it could prepare trials for any thinkable indication, it reasonably only selects the indications that add value to the project. This depends on the characteristics of the compound that must be translated into judicious peak sales estimates. After a successful phase 2 trial, the company then does not need to decide on the continuation of the project, but only on the continuation of the indication. In our multi-dimensional tree such a decision becomes to a choice of the maximum value of the project with the indication, $V_{i,j}^t$, and without the indication, $V_{0,j}^t$.

The above displayed method can be extended to more than two dimensions. For the adjusting of the joint probabilities of the tree the reader is referred to the literature from quantitative finance (Kaushik 1991,1995).

The real options method is especially suited for the calculation of license contracts. Often license contracts for cancer compounds include milestones for different indications, but royalties, most often stacked, on a project basis. Milestones are specified for phases and can vary whether it is the first, second or third indication. Some contracts also make a difference between minor (e.g. haematological cancer) and major (colorectal cancer) indications. The royalties on the other hand are taken from the sales of all indications of the drug. When the royalties are fix, then one can calculate the subprojects separately, using the right probabilities. However, if royalties are stacked, i.e. the royalty rate depends on the sales revenues, then we must know how much is sold in order to determine the royalty rate. Assume two indications, both with sales of $ 200 mn. If the license contract

specifies that the licensor receives 15% for sales lower than $ 300 mn and 20% for sales higher than $ 300 mn we have the following problem: The licensor actually receives 20% royalties on $ 400 mn. When valuing the indications separately we do not know whether at that time the indication will be the only one or complemented by another one, possible lifting the joint sales above the $ 300 mn barrier. When valuing the project with a multi-dimensional tree it is each time clear, how large the sales are and how many indications are still alive.

Success Rates

Published success rates refer to compounds and not to indications. For valuation purposes we nevertheless need to know the success rates per indication, and even the joint probabilities, i.e. the probability that none, the first, the second, or both indications are successful. In what follows we offer a simple method to solve the success rate problem. The main challenge is to maintain the project's overall success rates by calibrating the indications' success rates.

A straightforward approach is to assume that the indication that passes first, passes at the success rate P_2. A second indication obviously only passes if another indication has already passed. This second indication is often assumed more likely to pass, because the compound proved viable in the first indication. The conditional success rate for the second indication P_2^{2nd} to pass, given another indication already passed, is therefore higher than the success rate P_2. This means that the overall success rate for the second indication amounts to $P_2 \cdot P_2^{2nd}$. If the success rate is 36% and the probability that a second indication passes, given another has already passed, amounts to 70%, then we have the following scenarios for the project: in 36%*70%=25.2% of all cases two indications pass, in 36%*(100%-70%)=10.8% only one, and in 100%-36%=64% no indication passes. The assumption of the conditional success rate P_2^{2nd} for the second indication to pass corresponds to the success rates by indication and correlation ρ:

$$P_{phase2}^{indication} = P_{phase2} \frac{P_2^{2nd} + 1}{2} \tag{4.36}$$

$$P_2\left(A \text{ and } B\right) = P_{phase2} P_2^{2nd} \tag{4.37}$$

$$P_2(only\ A) = P_2(only\ B) = \frac{P_{phase2} - P_{phase2}P_2^{2^{nd}}}{2} \tag{4.38}$$

$$\rho = \frac{2P_{phase2}P_2^{2^{nd}}}{P_{phase2} + P_{phase2}P_2^{2^{nd}}} - P_{phase2} + (1 - P_{phase2})\frac{P_{phase2} + P_{phase2}P_2^{2^{nd}}}{2 - \left(P_{phase2} + P_{phase2}P_2^{2^{nd}}\right)} \tag{4.39}$$

For phase 3 the resulting joint probabilities are:

$$P_3(A\ and\ B, given\ A\ and\ B\ enter\ phase) = P_3P_3^{2^{nd}} \tag{4.40}$$

$$P_3(only\ A, given\ A\ and\ B\ enter\ phase) = \frac{P_3 - P_3P_3^{2^{nd}}}{2} \tag{4.41}$$

$$P_3(only\ B, given\ A\ and\ B\ enter\ phase) = \frac{P_3 - P_3P_3^{2^{nd}}}{2} \tag{4.42}$$

$$\begin{aligned} P_3(A, given\ only\ A\ enters\ phase) &= P_3 \\ P_3(B, given\ only\ B\ enters\ phase) &= P_3 \end{aligned} \tag{4.43}$$

With this we can also calculate the probability that both indications survive, only one, or none.

$$P_{2+3}(A\ and\ B) = P_2P_2^{2^{nd}}\ P_3P_3^{2^{nd}} \tag{4.44}$$

$$\begin{aligned} P_{2+3}(only\ A) &= P_2P_2^{2^{nd}}\ \frac{P_3 - P_3P_3^{2^{nd}}}{2} + \frac{P_2 - P_2P_2^{2^{nd}}}{2}P_3 \\ P_{2+3}(only\ B) &= P_2P_2^{2^{nd}}\ \frac{P_3 - P_3P_3^{2^{nd}}}{2} + \frac{P_2 - P_2P_2^{2^{nd}}}{2}P_3 \end{aligned} \tag{4.45}$$

If the formulae are correct, then the probability that at least one indication passes phases 2 and 3 should equal P_2*P_3, which is effectively the case.

We can now value the project either with DCF or with real options valuation. In DCF we have to correctly probability adjust each cash flow of each indication. The royalties can now be calculated by considering every scenario with its probability, i.e. no, one, or two indications reach the market.

Using the multi-dimensional tree approach with two indications, this method can be implemented in the following way: We place ourselves in a node right before the end of a phase of indication A, hence the trial results of A are revealed in this time step. If we are in a node of the regular tree (with i≥1 and j≥1), this obviously means that both projects are alive. If indication B has already previously passed the same phase and is now in the next, then indication A would be the second indication to pass that phase. We must use P^{2nd} as success rate of indication A. If indication B finishes the same phase only later, then indication A would be the first indication to pass this phase and we must use P as success rate. For nodes in the zero layer (j=0) indication B failed already earlier and indication A would be the first indication to pass this phase anyway.

Again, this method can be extended to more than two indications.

The estimation of the correlation or the conditional probabilities P_2^{2nd} and P_3^{2nd} is a difficult task. Data for projects with various indications are scarce and not published in way it is useful for our purposes. We propose to choose the conditional probabilities in a way that the average expected peak sales correspond to sales figures of comparable projects.

Valuing Projects with Multiple Markets

It is frequent that drug development companies only maintain a sales force in their home market, American companies in the United States, European companies in Europe. These companies then out-license the commercialization rights for the rest of the world to a global or several local partners. The payoff structure stemming from the market abroad is therefore different. In some cases, the partners already start to jointly develop the compound. In this case, the company that originated the project receives R&D funding and only pays a part of the development costs, or receives upfront and milestone payments. Usually once the companies must apply for approval, the geographic separation starts. As a consequence, the originator receives milestones and royalties. Different geographic markets behave slightly differently, sometimes it even happens that a drug is approved in one country but disapproved in another. Also the commercial potential can change independently due to political or demographic reasons.

In DCF we assume peak sales for every market and consider the cash flows from all markets in the calculation. It is possible to assume different success rates for the approval phase. When valuing the project with real

options, we have the choice between modeling the markets differently, which is done by multi-dimensional trees, or we can assume the sales potentials in each market to move jointly. This means, if we have an increase in expected peak sales in the European market by 10%, the sales potential in the rest of the world increases by 10% as well. The tree then models the worldwide peak sales of the drug. This can be split into different markets, e.g. 40% USA, 40% Europe, 10% Japan, 10% rest of the world. We can then calculate the value of the project in the end nodes for each market with the corresponding share of global revenues, some commercialized by the company itself, others licensed. We then have to sum up the values and work back the tree as usual.

Technology Valuation and Feed Rate

We can classify technology in two categories, first, technology serving as a tool, and second, technology generating projects. The two classes are valued differently.

Technology serving as a tool, e.g. for RNAi synthesis, can be used in the own laboratory for research, to provide it to customers on a service basis, or to license it out. The valuation relies mostly on the prediction of the future cash flows derived from service or licensing. These must then be discounted back to valuation date and summed up with using standard DCF valuation. Commercial success, competition, legal protection, reinvestment and amplification are to be considered when predicting the future cash flows.

The valuation of a *technology that generates new projects* is challenging. Imagine an apple tree. Each year the apple tree grows apples that can be sold on the market. For this the tree must be watered, dung, cut, and harvested. The apples can be seen as revenues, the labour as costs. A valuation of an apple tree would then include the apple sales and the invested labour of each year. First, the value depends on the kind of apple tree, Granny Smith apples are differently priced than Belle de Boskoop apples. Second, it matters whether the apples are sold directly to customers or to a vendor; again the prices are different. Third, the tree's yield determines the quantity of apples that can be picked each year. Forth, we must account for the labour required to finally sell the apples. A project generating technology is similar to an apple tree. Its value lies in the projects resulting from it. Like with the apple tree, the nature of the projects is important. Is it a technology generating leads in oncology or does it offer validated

targets for cardiovascular diseases? The company's strategy matters as well. Are the projects taken to market by the company itself or out-licensed at some stage? We must also know the yield of the technology, the *feed rate*. How many projects does the technology generate each year? Finally, what are the costs to run the technology? The main components of a project generating technology are therefore:

1. Project characteristics (disease area, indications, stage etc.)
2. Strategy of company (self-conducted, licensed)
3. Feed rate
4. Costs

Using these four points we can quantify the value of the technology using the formula below.

$$V_{tech} = \underbrace{-Costs}_{First\ year} + \sum_{i=1} \underbrace{(1+r)^{-i}}_{discount} \left[\underbrace{f_i}_{feed\ rate} \underbrace{V_{project}(kind, strategy)}_{project\ value} - Costs \right] \tag{4.46}$$

Each year, we account for the generated value with the technology, i.e. the value of the generated projects. From this we subtract the costs to run the technology. Note that the costs for the first year are due immediately, while then the costs for each consecutive year coincide with the project output of the previous year. The value of the technology is then the sum of the discounted values of each year.

If the feed rate remains constant, the projects are assumed to have all the same value, and the costs are fix, we then can even apply the value for the terminal value.

$$V_{tech} = -Costs + \left[fV_{project} - Costs \right] \sum_{i=1} \underbrace{(1+r)^{-i}}_{discount} = \frac{\left[fV_{project} - (1+r)Costs \right]}{r} \tag{4.47}$$

IP Valuation

In life sciences it is important that inventions can be protected by patents. Particularly the development of drugs and medical devices requires a lot of investments and time, and is furthermore subject to a high degree of uncertainty. If the inventor cannot protect the resulting product, probably nobody

would endeavour to develop a drug or a medical device, because once it is proven to be viable, competitors could jump the train and profit from the work. Others would harvest the fruits of the inventor's work. It is therefore necessary to allow the inventor a certain timespan, where he can exploit his product on an exclusive basis. Hence, patents, or in more general terms intellectual property (IP), represent the major source of value in life sciences industry. In what follows we discuss how to value intellectual property.

Intellectual property comprises intangible assets (non-physical resources or rights to other assets) such as patents, trademarks, and copyrights, protected by law. In life sciences, IP refers mostly to patents, i.e. molecules, technologies, proteins, formulations, etc. A patent is defined as the exclusive right to commercially exploit an invention and the right to sue others for infringement. The invention and the claims tight to it in the patent are protected by IPR. Often there is no clear use of the terms IP and patents. For the purpose of the valuation we have to clearly define if we talk of a single patent or of a basked of patents or IPR allowing commercialisation of a project. Often it is impossible to distinct between a patent and the entire project to commercialise the invention. Some patents however do not offer sufficient protection if not linked to other patents. And if not the complete basket of required patents is in the same hands, the single patents may turn out to be worthless.

Projects in life sciences start with certain inventions and know-how that at one point will be patented or already are protected. In contrast to project, license contract, or technology valuation, IP valuation takes place at a very early stage. We often do not even know how the IP will be used. Additional uncertainties are involved; a patent may not be filed at the time of valuation and the granting of the application, as well as the comprising claims is uncertain. Furthermore, due to its early stage, the degree of commercial and technical success is much more volatile. The result of patent valuation is therefore subject to a high degree of uncertainty.

Since the life sciences industry makes its living out of exploiting intellectual property, IP/patent valuation naturally matters in a variety of situations:

- Fundraising
- M&A
- Licensing
- Lending
- Litigation
- Accounting

We either want to define how valuable is the IP as part of a company to invest in or to take over. Or we want to fix the price of a license, to use IP as security for lenders, or to calculate the damage inflicted on the holder of the IP. The different situations require that the IP is valued in their context.
Fundraising.. The value of a start-up company or young biotech company is mainly attributed to its IP. To represent the value of the company, the management has to value the IP in a way corresponding to how the raised funds will be used to exploit the IP.

M&A. In the case of an M&A the buyer and the seller will value the company with its IP assets. The two parties will attribute different values to the IP. The seller needs to know what is the value of the IP in his company prior to the M&A. He considers what profits the company could generate by exploiting the IP. The buyer on the other side needs to know what value the IP has once it is integrated in his company. It might be that it generates more value than in the seller's company by complementing existing IP, or by the buyer's better ability to exploit it.

Licensing. Universities often out-license IP at a stage where it has not yet generated a project but offers the possibility to do so. Often universities do not have the resources to develop the IP further and therefore want to sell it. As the university itself can't go ahead with the IP, buyers often get it at a very low price. In the case where a company wants to out-license a patent it can't exploit on its own to a company that has the complementary IP to use the patent, we have to value the patent in this context, i.e. we have to calculate the potential of the patent in the hands of the in-licensing company. As we will see later, this value is the upper limit for the negotiation. IP must always be valued in the right context. Valuing IP for licensing or M&A, we calculate the value of the IP for the buyer and seller in respect to his capabilities.

Lending. As with fundraising, lenders want to know where they put their money and what kind of security they have. IP can then be used to collateralise the debt.

Litigation. In the case of litigation, the valuation has to produce the value of the damage that was generated by the infringement of IP rights. The holder of the rights wants to be reimbursed for the incurred loss of profits and a possible damage to his brand.

Accounting. Valuation of IP is a part of the balance sheet represented in intangible assets and goodwill. Valuation for accounting purposes is per-

formed according to national or international accounting standards (US-GAAP, IFRS).

In order that IP can be valued it should be:

- A standalone asset
- Licensable in total or in parts
- Protected

A standalone asset is IP enabling a company to exploit it without requiring further patents. We should not value a patent that on its own cannot be used, i.e. where a concomitant technology is needed. Patents that on their own cannot be exploited do not represent any value to the company. It is of course possible to commercialise a project without it being protected by IPR. The value of the patent in this situation lies in the excess profits arising from protecting the invention. Imagine for instance a patent that protects a product in a certain geographic area, or a patent that covers an improvement of the original product. These patents allow avoiding competition in this geographic area. Or they might cover an improved version of the product and consequently increase and lengthen sales. In the valuation, we have to adjust the cash flows taking into consideration the influence of IPR.

The IP might offer different fields of applications, e.g. it might be a technology to be used for cancer drug research or a service technology used for other companies. Obviously, the more applications a patent offers, the more value it has. But for any application that we value, we have to account for the required resources to exploit it, i.e. capital, head count, laboratories. All these factors influence the risk and the cost of capital of the company and need to be considered when valuing IP in the context of the whole firm.

IP valuation techniques. There are three main methods used to value IP:

1. Income based (DCF, ROV)
2. Cost based
3. Market based (comparables)

Income based approach. The income based approach uses the methods we have outlined above, i.e. DCF or ROV. The value of the IP is composed by the various cash flows generated by it, either in form of projects, licenses, or services.

Cost based approach. The cost based approach works by defining the cost to replace the value of the IP. The disadvantage of this method is that is does not relate to any market value or future profits. This method is generally used in accounting statements.

Market based approach. The market based approach looks for comparable IP that has been traded and whose value is known. The approach is widely used and often very helpful when the determination of the input parameters is difficult due to a high degree of uncertainty. Despite being very simple and straightforward, we often encounter the problem that there is no comparable IP, or that the details of license contracts of comparable IP are not disclosed. IP might be acquired for strategic reasons and with a considerable premium. These transactions also cannot serve as comparable.

As mentioned above, IP valuation follows the same rules as project and license contract valuation. There are differences that need to be considered in addition to what we have already outlined in the previous chapters. As IP often covers different applications we need to know when we value which application. This is determined by the context of the valuation. If we value IP for fundraising, we will most likely try to value most applications to achieve a higher value. While in licensing, the IP rights are often split in different applications. The buyer will therefore only be ready to pay for the licensed application, not the entire IP entity. In this context, we have to decide in what direction the IP will be exploited and then value it according to the projects or licenses that are generated. However, often IP valuation takes place in a too early stage to know where its development will lead.

In life sciences, IP is the basis of drug or medical device development projects, or IP covers a technology that is used for service providing. IP therefore either leads to the generation of new projects, or as a means to provide a service to clients. We have discussed in the chapter on technology valuation that a technology producing projects can be valued using the feed rate. IP covering a technology for service can also be valued with DCF or ROV as we will outline below.

We will now discuss the theory of IP valuation using DCF and ROV followed by a case study.

The DCF valuation of IP follows the theory outlined above. We first define the applications we need to include into the valuation depending on the goal of the valuation and then go trough the same steps as for the previous DCF valuations.

Cash Flows

The cash flows for the valuation of IP are again defined by their time, their size, and their probability to occur. They are assessed in the same way as described in the previous chapters. Costs that have to be taken into account are the filing costs for national and international applications and the patent renewal costs. In many cases we will have to assume that the IP or the resulting projects will be out-licensed. We will then suppose a potential license contract based on industry figures.

Discount Rate

The discount rate depends on the company working on the IP and the anticipated scenario of the IP. If the IP is licensed, the discount rate must reflect the risk of the licensee.

Case Study IP Valuation

Dr. Postdoc has developed and patented a new technique generating new cytotoxic molecules to fight cancer. As he is not able to exploit the technology in its full potential, he considers licensing it to a large company developing cytotoxics. He now wants to find out how much value the technology might have in the hands of a company with adequate resources. He considers this value to be the upper limit in the negotiations with the buyer. In order to get a better understanding of the potential value of his invention, he first determines the following four points:

1. *Project characteristics (disease area, indications, stage etc.)*
2. *Strategy of company (self-conducted, licensed)*
3. *Feed rate*
4. *Costs*

The molecules will be for the treatment of cancer, mostly late stage advanced cancers. The exact indications at this point are completely in the dark. Dr. Postdoc assumes the following numbers for the typical project generated by the technology (cf. Table 4.39).

Dr. Postdoc estimates that the technology can be exploited as long as the patent protection is valid, hence for 16 years. The peak sales are the median sales for cancer drugs, in our case $ 344 mn. The launch costs are about half of a peak sale, for the prototype project $ 150 mn, and include building manufacturing and setting up a marketing campaign. Dr. Postdoc

Table 4.39. Project parameters

	Lead	Preclinical	Phase 1	Phase 2	Phase 3	NDA
Costs ($ mn)	2	3	5	15	50	2
Success Rate	70%	70%	64%	42%	65%	90%
Length (years)	1	1	1	2	3	1

calculates with a margin of 65%. The margin accounts for the cost of production and marketing. The sales curve follows the curve outlined in the previous chapters.

The technology allows generating new chemical entities that enter lead optimisiation. He assumes that the company will develop and launch the project on its own, i.e. not to license it. With the right capacities, the technology allows to bring one project into lead phase every year. The costs for running the technology consist of headcount, use of infrastructure, material etc. He estimates a feed rate of one project entering lead optimization can be achieved with allocating $ 1.5 mn each year, with the first project entering that phase after one year, with a prior investment of $ 1.5 mn.

Solution

We first value the prototype project generated by the technology. We calculate the project value with DCF and real options, assuming that in year one and year two we have $ 1.5 mn per year of expenses. Then we can start with the project. The project valuation, based on a volatility of 25%, yields the following result:

Table 4.40. Prototype Project Value

Discount	DCF	ROV
15%	$ 2.99 mn	$ 3.71 mn

The value for the prototype project is $ 3.0 mn with DCF, and $ 3.7 mn with real options. Assuming that the technology keeps generating one project each year until infinity at the predefined costs we have to apply the following formula:

$$V_{tech}^{\infty} = \frac{\left[fV_{project} - (1+r)Costs\right]}{r} \tag{4.48}$$

However, it is only assumed that the technology generates projects for *n* years; in this case *n* equals 16 years. We therefore have to subtract from the value above all projects generated after *n* years, the exceeding projects. Placing ourselves *n* years later in the future, the value of all exceeding projects would amount to exactly V_{tech}^{∞}, because the situation after *n* years would be the same as now: The technology generates each year two projects at the predefined costs until infinity. The value must therefore be the same. And since the value of all exceeding projects amounts to V_{tech}^{∞} in *n* years from now, the present value of the exceeding projects amounts to $V_{tech}^{\infty}(1+r)^{-n}$ today. The value of the technology over the next *n* years is therefore:

$$V_{tech} = \frac{\left[fV_{project} - (1+r)Costs\right]}{r}\left(1 - \frac{1}{(1+r)^{n}}\right) \tag{4.49}$$

Using Dr. Postdoc's numbers for the costs ($ 1.5 mn), the feed rate (1), the duration of the technology (16 years), and the prototype project we get:

Table 4.41. Technology value

Discount	DCF	ROV
15%	$ 7.53 mn	$ 11.82 mn

The technology has a value of $ 7.5 with DCF and $ 11.8 with real options. The difference stems from what we have discussed in earlier chapters, namely the option to abandon projects that are not profitable.

Discussion

We have learned how to value a technology that generates projects over a certain time span, or infinitely. The approach is very useful for the valuation of intellectual property and firms and is simple to handle, once the standard concepts of DCF and ROV are mastered. Technologies can even be valued assuming that the resulting projects are licensed out at one point using the valuation outlined previously.

A tricky part of the method is to properly allocate the costs the technology causes. This is not always evident. A further point to stress is the sensitivity of the method to the used discount rate. A high discount rate has a tremendous effect on the value of the technology, as the formula is comparable to a terminal value calculation. In cases where companies are expected to grow over time, as most young biotech companies do, the formula can be adapted

to a changing feed rate. We then have to introduce g for the growth rate (in percent) into the term, resulting in the following expression:

$$V_{tech} = \frac{\left[fV_{project} - (1 + r - g)Costs\right]}{r - g}\left(1 - \frac{1}{(1+r)^n}\right) \tag{4.50}$$

In the case where we cannot predict a feed rate, but rather the time when certain projects enter the respective phases, we create a timetable for all future projects and value them according to the standard methods. This is more time consuming but gives us more flexibility in our prediction.

Our example has shown that valuating with real options can make a sensible difference. The higher value in the case of real options valuation can be used to negotiate better terms in technology licensing.

Pipeline Valuation

A pipeline is a basket of projects. The value of a pipeline is therefore the sum of its projects. But the value is only one aspect we are interested in when valuing a pipeline. Other aspects are the risk profile, the distribution of cash flows and the associated liquidity needs, or the structure of the pipeline. A standard project valuation does not offer much insight into these aspects. Simulations however are the perfect tool to analyse a pipeline with respect to risk and development in time. A very important property of simulations is the ability to consider correlations. If we flip two coins and receive a dollar for heads, we expect to win one dollar on average, half a dollar on average by coin. If by some magic way, the second coin always shows the contrary of the first coin (perfect negative correlation between the coins), we would even end up with a safe dollar, because we either win with the first or with the second coin. Valuation just tells us that playing the game is worth 1 dollar, for each coin half a dollar on average. Simulations on the other hand tell us that the first game is risky; in 25% we end up with zero dollars. Since people usually are assumed to be risk averse, one would prefer playing the second game.

In a pipeline of a life sciences company we can also observe such correlations, although not as extreme as in the coin example. Two drugs that base on the same mechanism of action are partly affected by the same risks, e.g. COX-2 inhibitors. After the withdrawal of Vioxx by Merck, Pfizer had to withdraw its COX-2 inhibitor Bextra as well, and Novartis temporarily withdrew its COX-2 inhibitor Prexige in the EU.

Simulations allow us to include such correlations by simulating common risk factors. This is especially helpful for portfolio management purposes, where companies want to achieve a sound diversification. If several projects depend on the same risk factors, e.g. another company launching a product that competes with several own products at the same time, simulations will visualise this cluster risk.

The figures below display a diversified and an undiversified pipeline. The first pipeline is composed of projects in various disease areas, using different technologies and mechanisms of action; the second is composed of similar projects, all using the same mechanism of action. The average value remains the same, but we clearly see that the undiversified pipeline has much lower and higher extreme values. This is a consequence of the correlation between the projects. While an uncorrelated pipeline remains in almost all cases a mix of success and failure, a correlated pipeline is much more a black and white picture, either the mechanism of action is efficacious and safe and all projects pass, or it is not efficacious or safe and no project passes.

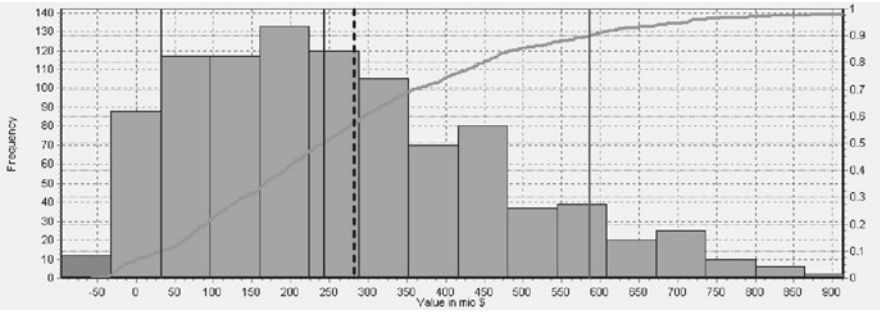


Fig. 4.40 Diversified pipeline (calculated with ri:val)

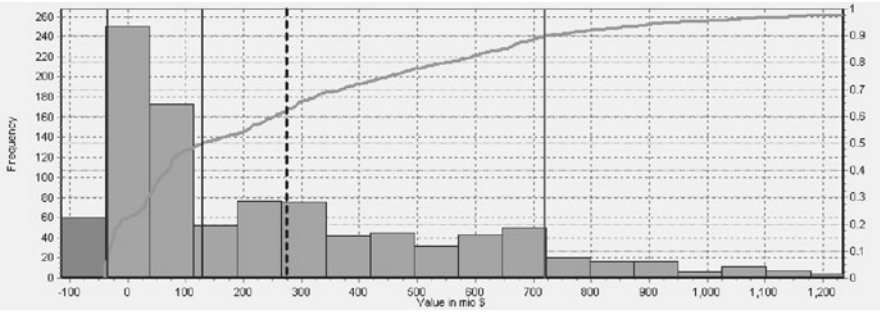


Fig. 4.41. Undiversified pipeline (calculated with ri:val)

Another very interesting aspect is the simulation of the pipeline structure, i.e. how many projects are in which phase. A portfolio manager can anticipate future gaps in the pipeline and can either advocate for larger resource allocation to in-house research or initiate further in-licensing activities. The figure below illustrates the median case of the pipeline, i.e. 50%-best case. In half of the cases the company can count with taking at least two compounds to the market. Nevertheless, within two years the current pipeline of 8 projects will have shrunk to just 4 projects. It should therefore take care of a sustainable pipeline feed.

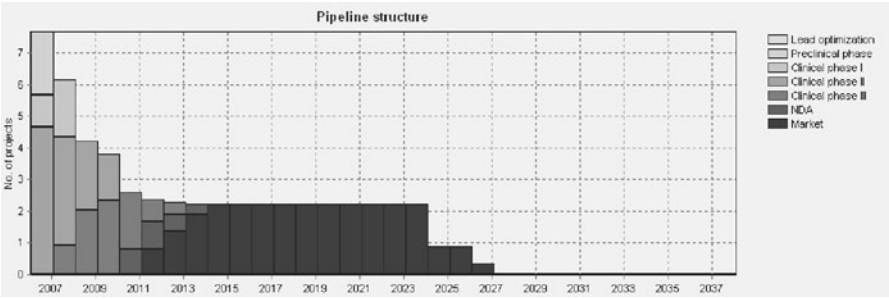


Fig. 4.42. Median company structure (corresponding to 50%-percentile, calculated with ri:val)

Portfolio Management

Introduction

A detailed discussion of portfolio management is beyond the scope of this book. The aim of the following section is to give some ideas on new directions in portfolio management.

Portfolio management is inseparably connected to management of biopharmaceutical companies. It forms a company's future success and position by defining how to use resources. Portfolio management is comparable to asset allocation in banks; it has the same goals:

- Investment in the best assets
- Alignment of risk and strategy
- Maximisation of profits
- Diversification of the portfolio

- Sustainable growth of revenues
- Management of liquidity

The task of portfolio management is to decide which projects to continue, which one to in- or out-license, and which ones to abandon.

The main difference between financial asset allocation and resource allocation in the life sciences industry are:

1. *Access to assets*. The assets being projects cannot be bought and sold on an exchange like shares, bonds, or commodities. Usually a company owning a project aims at commercialising it or licence it to a partner company. So at most two companies have access to one project. Compared to financial asset allocation the universe is at the same time considerably smaller.
2. *Unity of assets*: While in finance we can hold 0.1%, 1%, or 10% of a company, we can only invest in the full project. It is not possible to multiply a good asset. Licensing part of a project, however, is a possibility.
3. *Risks*. Life sciences assets underlie special forms of risk. Next to common market risk most assets are subject to large attrition rates.

Unfortunately, these differences do not allow the standard application of portfolio optimisation strategies known from finance. The elegant models of Markowitz and Sharpe (efficient frontier) are not applicable to assets sharing the above listed properties. It is therefore necessary to look for new ways to manage a life sciences portfolio. One central problem of portfolio management lies at its very root: What should be optimised? Generally, people tend to say that portfolio management is a multidimensional task. Several aspects matter:

1. Value
2. Sustainable revenues
3. Balance between projects in different phases
4. Balance between or focus on disease categories
5. Balance between high and low risk projects

All else being equal it is relatively easy to decide between two portfolios that differentiate in only one of the above aspects. Higher values dominate lower values, sustainable revenues dominate volatile revenues, balance is preferred to clustering. If already two aspect are different, it becomes much

less clear which project selection is preferable, e.g. the one with a higher value, or the one with less risks? Some companies specifically concentrate on one disease area or one mechanism of action, hoping for more efficiency, leading to a higher value at the expense of higher risk. Others prefer a balanced pipeline, sacrificing some of the upside potential.

Qualitative Approaches

It is impossible to optimise a portfolio if it is not clear, which aspect to optimise. Portfolio management therefore often remains a rather vague topic, focussing mainly on qualitative aspects like market attractiveness, positioning with respect to competitors, strategic alignment, technical feasibility, or legal and regulatory issues. Qualitative approaches assign a value to each of these aspects and then weigh them against each other in a scoring model. Portfolio management should be objective and not prone to political interests of departments, an often seen problem within larger companies. Therefore, the process of assessing data is of enormous importance. Opposing various properties like remaining patent protection, market potential, risk, competition, or investments allows comparing projects in diagrams like bubble graphs or radar plots. Such graphs are very popular and should further encourage the discussion about pros and cons of the projects. A lot of literature and congresses elaborate on qualitative approaches. As the focus of this book is the quantitative approach to valuation, we will not go into any further details of qualitative portfolio management. In what follows, we take a stand for quantitative approaches.

Quantitative Approaches

The fundamental idea of quantitative approaches is that any decision should be justifiable by a calculation. If one strategy is claimed to be better than another strategy, this should be reflected somewhere in the calculations. Strategy finding can be a very emotional process where most of the participants trust their gut feeling. Quantitative approaches try to get rid of these subjective gut feelings. Often soft factors or possible industry developments are held responsible for one strategy being superior to another. If these soft factors or industry developments are implemented in the calculation model, then the claimed strategy must yield better values; otherwise it simply is not superior. Building quantitative models on portfolio or company level is a challenging task and requires many assumptions with respect to future market developments, correlations, and resources. These assumptions

are the above-mentioned soft factors and it is the responsibility of the management board to define these assumptions. Once they are set, the portfolio management can start finding an optimal resource allocation that respect the assumptions from the management board.

Approach 1: Comply with Imposed Restrictions

The first approach corresponds to the situation usually the portfolio management department faces: the management board gives some premises on how much resources are provided for project funding, on the focus in disease areas or molecule types (e.g. biologicals vs. chemicals), or on the number of projects to reach market within the next five years. We denote this set of premises with γ. Portfolio management then must find a resource allocation that complies with γ. We denote a resource allocation with ζ. Portfolio management must decide, which projects get funding, which are scaled down, put on hold, licensed, or abandoned. It is possible that for some projects there are different project plans that require different funding and yield different revenues (Sharpe et al. 1997). Some compounds might only be developed for one indication, other indications might be considered once the first proves to be successful. Other projects might be considered for out-licensing to a partner.

A special challenge of portfolio management is to find a solution ζ that takes account of the dynamics of drug development. In the next budgeting period the selected projects require different funding because they have moved to another phase. The resource allocation ζ should avoid the creation of bottlenecks in subsequent budgeting periods. If on the other hand the management is willing to raise capital in the equity or debt market, then this condition can be relaxed. Obviously, some projects are likely to fail and do consequently not require further funding. Therefore, it might be advisable not to plan for the worst case, but maybe to avoid these bottlenecks for a certain percentage of scenarios (e.g. in 90% of all scenarios the selected portfolio can be financed throughout its life cycle). Portfolio management equally has to consider the entry of new projects thanks to feed rates for each type of project (disease area, biologics vs. chemical, licensed vs. self-originated).

The resource allocation problem requires the general market dynamics (feed rate of outside opportunities, market growth and development, competition), the company parameters (current projects, cash balance, feed rate of internally developed products) and the strategy (constraints) as input parameters. The solution can be approached using simulations framed by a

much larger concept called artificial evolution. This solution is a resource allocation ζ^* that complies with γ and optimises a function f. Possible options for the function f could be the value, the 10% value at risk of the pipeline, a value-risk ratio, or a measure of the sustainability of future revenues. Mathematically ζ^* becomes:

$$\zeta^* = \arg\max_{\zeta} \left\{ f\left(\zeta(\gamma)\right) \right\} \tag{4.51}$$

The equation states that ζ^* is the one resource allocation out of all resource allocations ζ complying with γ that maximises the function f. We see that the optimal resource allocation ζ^* is a function of the premises γ. Remember that the premises γ were imposed by the management board. In more common terms γ is the strategy defined by the management board, and the resource allocation ζ^* simply must be in line with the strategy. Assuming the outlined resource allocation problem as a function of the strategy we can then try to optimise the strategy of the company. Knowing what resource allocation $\zeta^*(\gamma)$ will result from which strategy γ, we can try to find the strategy γ^*, i.e. the restrictions for the resource allocation, such that the function f is optimised on a global level.

$$\gamma^* = \arg\max_{\gamma} \left\{ f\left(\zeta^*(\gamma)\right) \right\} \tag{4.52}$$

In the outlined approach we have interpreted the resource allocation problem as a Stackelberg game from game theory. Game theory is a mathematical discipline that has already provided excellent solutions in other areas of science and economy and has earned John Nash the Nobel Prize in 1994.

Approach 2: Value Maximisation

At first sight, value maximisation seems to be a straightforward problem: Simply select all projects with a positive value. Still, this approach neglects the portfolio effect. The diversification between projects leads to a reduced risk profile. This then translates into a lower discount rate, possibly justifying even the development of previously not considered project. Nevertheless, the inclusion of some projects might also lead to cluster risks, increasing the discount rate again. This approach requires a sound model for the discount rate, that correctly takes account of the degree of diversification of the portfolio. Using the proposed framework in the section about discount rates, the value of the pipeline directly depends on the dis-

count rate r, which is a function $r(\zeta)$ of the resource allocation ζ which is equivalent with the pipeline. The optimal resource allocation strategy ζ^* can then be written as:

$$\zeta^* = \arg\max_{\zeta} \left\{ value\left(r(\zeta), \zeta\right) \right\} \tag{4.53}$$

The basic idea is that the value eventually should also include the risk of a certain strategy. This way we achieve a single measure by which we can classify all possible portfolios and make a sharp selection.

This second approach is a special case of the first approach, the function f being the value function. As a special aspect, the discount rate depends on the resource allocation ζ as well.

Company and Stock Valuation

Introduction to Company Valuation

Company valuation – or better: valuation of a company's equity – is indispensable in different fields of the life sciences industry. We encounter it throughout the entire life cycle of the industry:

Fundraising. Any investor wants to know what he gets for his money. As most young companies are private, the company's share price is unknown. Seed investors, venture capitalists, and private equity investors need to value a company to know the right share they are entitled to when investing. Equally, the existing shareholders need to value the company; they want to limit the dilutive effect. In the negotiations the parties agree on a value and allocate the new issued shares accordingly. Consequently, each round corresponds to a valuation. Investors will have different goals during the negotiations, as illustrated by the minicase at the end of this section.

Licensing. Licensing payments often include the exchange of equity. As with fundraising, companies are often not listed. There is no official share price. The value of equity needs to be derived by the valuation of the company.

M&A. Mergers or acquisitions are common situations where the value of a company is essential. The valuation, in addition to fixing the fair value of equity, can provide information about the value of potential synergies and economies of scale. In the negotiations for the M&A, valuation delivers the lower boundary for the seller and the upper for the buyer.

IPO. The issuing price of the share at an initial public offering will obviously derive from the value of the company. As in private rounds, the investors set the price, but in an IPO these investors are the public market players.

Analysts. Analysts regularly value private, and mostly public companies. Based on the valuation they recommend buying or selling firms.

The following minicase illustrates the different views of investors during a round of financing.

Minicase Investors' Preferences

Mr. Venture, Dr. Capital, and Mr. PrivateEquity are investors in the private company BioComp. Today, Mr. Venture holds 70% of BioComp and Dr. Capital the remaining 30%. In the upcoming financing round, Dr. Capital and Mr. Private Equity are going to invest $ 20 mn each. All three have to perform a valuation, Mr. Venture in order to defend its right as shareholder, Dr. Capital as shareholder an investor, and Mr. Private Equity as new investor. After preliminary valuations they agree that BioComp's pre-money value lies between $ 40 mn and $ 60 mn. After the financing round, BioComp's post-money value will therefore be between $ 80 mn and $ 100 mn. Dr. Capital and Mr. Private Equity invest $ 40 mn; the new issued shares must correspond to 40% (if pre-money value $ 60 mn) to 50% (if pre-money value $ 40 mn) of the share capital. What are the respective interests of the three involved parties?

*Mr. Venture currently holds 70% of the shares, corresponding to a value between $ 28 mn (=0.7*40) and $ 42 mn (=0.7*60). After the financing round, his stake in the company therefore drops to 35% to 42%. Mr. Private Equity contributes $ 20 mn to the new company, corresponding to 20% to 25%. Finally, Dr. Capital already owns 30% of BioComp, corresponding to $ 12 mn to $ 18 mn. With the additional $ 20 mn he invests, this becomes $ 32 mn to $ 38 mn, corresponding to 38% to 40% of the company value.*

Table 4.42. Investor's share

In $ mn	Pre-Money		Contribution	Post-Money	
BioComp	40	60	40	80	100
Mr. Venture	28	42		35%	42%
Dr. Capital	12	18	20	40%	38%
Mr. Private Equity			20	25%	20%

As we can see in the table, Mr. Venture tries to negotiate a high valuation; the higher BioComp is valued, the less his shares are diluted. Mr. Private Equity clearly favours a low valuation, giving his contribution more weight. For Dr. Capital the situation is a little different; he acts both as existing and new shareholder. As an existing shareholder, he is interested in a high valuation as Mr. Venture. But in order to capitalise on his new investment he also wants a low valuation, like Mr. Private Equity. Since Dr. Capital contributes 50% of the new capital, contrasting his mere 30% of ownership, he prefers a low valuation. Not only that a post-money valuation of only $ 80 mn gives him 2% more ownership, he also becomes the main shareholder of BioComp, overtaking Mr. Venture. If Dr. Capital would contribute less than 30% of the new capital, then he is better off with a high valuation.

Theory

Methods and Fundamentals

We will now discuss how to value companies and stocks and show the difference in the valuation of public and private companies. For better understanding we will repeat several basics of finance.

The balance sheet of a company is formed by assets on the left hand side and equity and liabilities on the right hand side. The balance sheet is a snapshot of the firms accounting value; the value at a certain point in time.

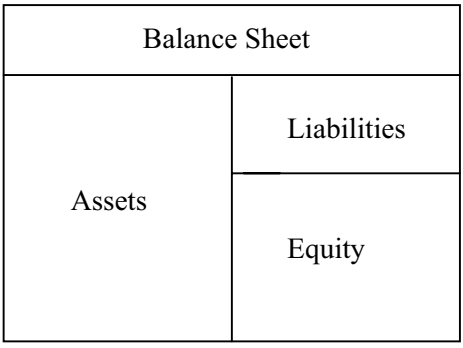


Fig. 4.43. Structure of a balance sheet

The balance sheet shows what the firm owns (left side) and how these assets are financed (right side). The value of the company is the value of its assets. The assets are financed on the one hand by equity, on the other hand by debt (liabilities).

In contrast to the balance sheet, the income statement and the statement of cash flows tell us about the firm's financial activities during a certain period, e.g. one year.

The different angles to look at a company, value, income and cash flows, are the source for different methods to value a company. The figure below summarises common approaches:

Firm valuation approaches	
Asset based	Adjusted book value
	Liquidation value
	Cost to create
Income based	Economic value added
	Excess earnings method
	Capitalisation of benefits
Cash flow based	Discounted cash flows
	Real options
Market based	EBIT multiples
	EBITDA multiples
	Revenue multiples

Fig. 4.44. Company valuation methods

Asset based firm valuation. The asset based valuation approaches mainly use the numbers as represented in the balance sheet. However, the balance sheet serves accounting purposes and does not correspond to a fair valuation of the assets mentioned therein. Asset based approaches are often not suitable for life sciences companies, where most of the value is captured by intellectual property, which is not appropriately represented on the balance sheet.

Income based firm valuation. These methods deduce the company value from the income statement. As only a fraction of life sciences companies makes profit, income based approaches play a marginal role in early stage life sciences valuation. They are better applicable to late stage companies.
Cash flow based valuation. The value of a company can be derived from its future discounted cash flows. We focus on cash flow based methods like DCF and real options, as this approach is the only accounting for the particularities of early stage life sciences companies.

Market based valuation. With these methods we can compare different companies. Like the asset and income based methods these approaches are

little useful for life sciences companies until these start generating earnings, because earnings and profitability are the main input parameters. Even for publicly traded companies many ratios and measures simply cannot be applied, as shown in the figure below.

Table 4.43. Osiris Therapeutics fundamentals (Source: NASDAQ)

Last Sale	$ 11.10
Change Net / %	0.32 2.8%
Best Bid / Ask	N/A / N/A
1y Target Est:	$ 20.00
Today's High / Low	$ 11.49 / $ 11.10
Share Volume	7,096
50 Day Avg. Daily Volume	N/A
Previous Close	$ 11.42
52 Wk High / Low	$ 12.30 / $ 9.84
Shares Outstanding	27,036,000
Market Value	$ 300,099,600
P/E Ratio	N/A
Forward P/E (1yr)	N/A
Earnings Per Share	N/A
Annualized Dividend	N/A
Ex Dividend Date	N/A
Dividend Payment Date	N/A
Current Yield	N/A
Beta	0

The table above summarises the publicly available financial figures for Osiris Therapeutics. As the company is not generating any remarkable earnings yet; we cannot use the standard multiples like the P/E ration or earnings per share. In the continuation, we will only treat the cash flow based approach, the best suited approach to value life sciences companies.

Building Blocks of Company Value

Life sciences companies depend on the fate of their projects. Their maturity depends on the state of their pipeline, success rates act on projects, and decisions are made on a project basis. This strong project orientation

makes it necessary to structure the valuation accordingly. The value of equity therefore is composed of:

1. Projects
2. Technology and IP
3. Cash
4. Other fixed assets
5. Unallocated costs
6. Debt
7. Taxes

Projects and technologies are intangible assets, but do not appear at a fair value in the balance sheet. For valuation purposes, we must use the NPV of their cash flows, either calculated with DCF or real options. The value for cash and other fixed assets, we can directly take from the balance sheet. Unallocated costs do not appear on the balance sheet, but are necessary to maintain operations; without these expenses the projects could not be realised. Debt and taxes are again NPV's of cash flows related to these items. The proposed method is a cash flow to equity approach, without accounting subtleties like depreciation or amortization. We therefore have to use the cost of equity as discount rate, even for the debt part. If we want to value the company as an entity, we would have to use the WACC, without deducing the debt. Unallocated costs, debt, and taxes are value diminishing.

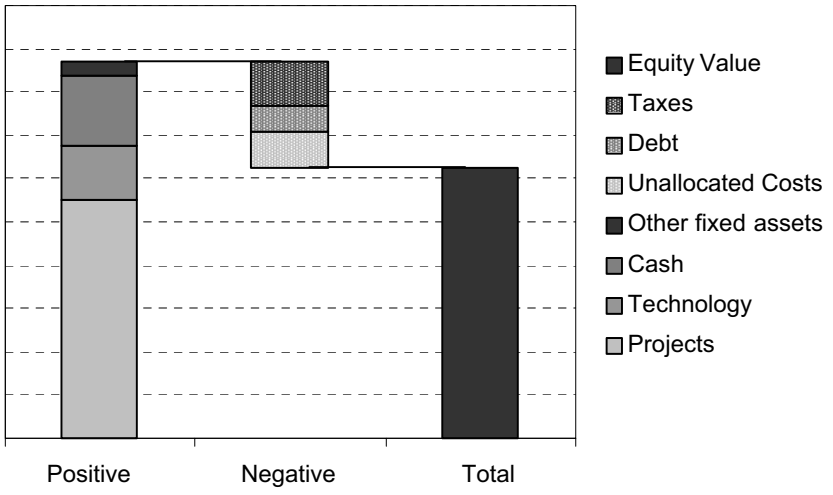


Fig. 4.45. Structure of equity value

Projects. Each project represents value. Since characteristics and decisions vary from project to project, it makes sense to value each project separately. Important is the overall analysis (due diligence) of the company's work, if is well protected by IPR and if does not face the risk of litigation. All assets are valued with respect to their legal security.

Technology and IP. The technology of a company is its ability to generate new projects from its IP. Assuming the company value built just by what actually exists, i.e. by the projects and technologies the company owns, the cash flows of the company vanish after the life cycle of the longest lasting project. This would mean that the company would stop existing after that project. Of course, this is not realistic. The company will generate new projects also in the future; after all that is the main task of the management. Hence, it is legitimate to assume that the company will also have cash flows after that. It is very uncertain to predict cash flows in life sciences; they are subject to a substantial attrition rate. It is much easier to assume that the research department of a company is able to generate a certain output deriving from the company's IP portfolio or that the licensing office is able to close a certain number of deals each year. This then corresponds to feed rates of projects and licenses as we have introduced them in the section about technologies.

While a small biotech company might own a technology enabling it to generate some leads each year for a certain disease group or using a certain mechanism of action, a large pharmaceutical company has the capacity to generate a multitude of new drug candidates in various disease areas and closes a many license contracts each year. For a large pharmaceutical company, we therefore have to assume feed rates for several prototype projects, self-originated or in-licensed. If the company does not provide the feed rate publicly, we can elaborate by comparing the state of the pipeline several years ago, and then track new projects entering a certain phase.

Cash: Of course, we must consider the company's cash and cash equivalents. This item does not require any valuation and can be taken directly from the balance sheet.

Other fixed assets. Other fixed assets include plants, property, and machines and are also part of the balance sheet.

Unallocated costs. A company has costs that cannot be allocated to a specific project or to a technology. Typically, the CEO's salary, or the office rent is a cost that has to be considered on a company basis.

Debt. All liabilities reduce the value of equity. We must account for all cash flows that serve paying back the debt, i.e. interest payments and payback of the debt's principal at the end of the maturity.

Taxes. On a company basis we also include taxes. Taxes must be paid on earnings after interest payments, in case the company has debt. Young biotech companies do not make profit and therefore do not have to pay taxes. But if we predict cash flows for the future, we must consider tax influence also for those companies. In most countries, the losses can be taken forward; only once the earnings offset the accumulated losses, the company starts to pay taxes. Some governments offer tax credits, i.e. the companies can reclaim parts of their losses, i.e. for R&D funding. This way the companies earn tax credits.

Financial Statements

As we have already treated in the previous sections the valuation of the components of a life sciences company, we now want to discuss some specific problems of company valuation. We start with financial statements

Table 4.44. Biotech Company income statement

Biotech Company Income Statement 2XX7 (in 000's)	
Total operating revenues	$0
Gross Profit	$0
Operating Expenses	
R&D	$28'000
Selling, General, and Administration	$8'000
Operating Income	$(36'000)
Additional Income/Expenses and Tax	$12'000
Earnings before Interest and Tax	$(24'000)
Interest Expense	$1'200
Earnings before Tax	$(25'200)
Minority Interest	$0
Net Income-Cont. Operations	$0
Disc. Operations	$0
Net Income	$(25'200)
Net Income to Common Shareholders	$(25'200)

used as data source. Unfortunately, standard financial statements do not allocate revenues and costs to projects and technologies; they summarise them over the entire firm. For the valuation however, we need to break down the cash flows into cash flows allocated to projects, technologies, and cash flows that are unallocated.

The table above displays the income statement for Biotech Corporation in the year 2XX7. The company has three projects in development, and an income generating technology. Project X3 is licensed out, triggering a milestone payment in 2XX7. We immediately see, that the table does not allocate any of the costs to the individual projects of the company. We can now crudely allocate income and expenses to the projects. Tax and SG&A belong to unallocated costs, costs that are not assigned to the projects.

Table 4.45. Biotech Corporation allocated and unallocted costs

Biotech Corporation 2XX7 (in '000s)						
	Technology	Pr. X3	Pr. B2	Pr. L4	Unallocated	Firm
Income	$1'000	$11'000	$0	$0	$0	$12'000
Expenses	$0	$0	$0	$0	$0	$0
SG&A	$0	$0	$0	$0	$8'000	$8'000
R&D	$9'000	$0	$11'000	$8'000	$0	$28'000
Interest	$0	$0	$0	$0	$1'200	$1'200
Tax	$0	$0	$0	$0	$0	$0
Net Income	$(8'000)	$11'000	$(11'000)	$(8'000)	$(9'200)	$(25'200)

As a second inconvenient, financial statements report either values in a way that serves accounting but not valuation, or they give cash flows only for one year. For the valuation of the company, we theoretically need the cash flows until infinity. In practice, we use the time of the life cycle of its current projects. The feed rates then take care of the remaining cash flows until infinity. Consequently, the financial statements are only little help for the valuation of a company. We have to use forecasts not only for the projects and technologies, but also for the unallocated costs. The financial statement can be used to see whether the forecasted R&D spending or unallocated costs are in line with the company's past expenditures.

Feed Rate and Terminal Value

The feed rate represents the ability of the company to generate or to license projects. The feed rates correspond in a way to the terminal value in standard valuation. Like terminal value, the feed rate is a very sensitive variable that can have a major impact on the value. A feed rate is however a more imaginable parameter than a constant cash flow in 20 years from now. Imagine a company that has one extraordinary product responsible for most of its revenues like in the figure below. If we apply the terminal value principle at a moment when this project still strongly contributes to the company's revenues (A), this implies that we assume that the company can replace this product by another of the same economic power. We can only use this assumption when there is an indicator that the company can indeed replace the product with a similar one. If on the other hand we apply the terminal value only once the project is off-market (B), then most other projects' life cycles might have ended as well and the terminal value becomes too low. The terminal value this way might misguide and give a much too high or low value. We therefore propose to use the feed rate approach.

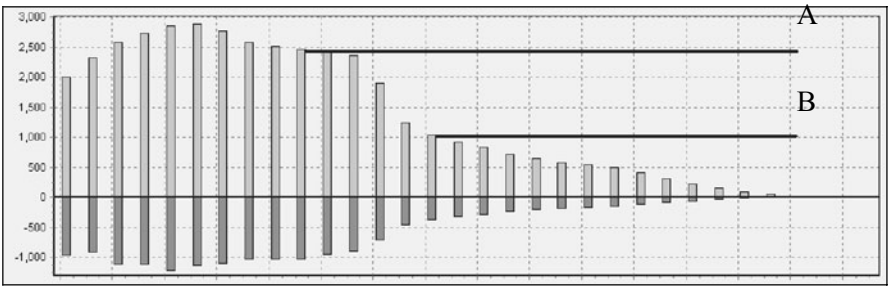


Fig. 4.46. Where to start assuming constant cash flows for the terminal value?

Taxes

The calculation of taxes first requires annual net cash flows. Second, we have to keep track of the accumulated losses; only once these are offset by earnings, the company starts to pay taxes. Applying the tax rate to project valuation is not a clean solution, because taxes are assessed on a company level. Earnings from one project can be used up by investments in another project. Calculating the tax value on a risk-adjusted basis is also not correct as displayed in the following example: Assume a one-project company. If one day it has to pay taxes, i.e. if its product reaches market, it can

first use up all accumulated losses, i.e. all investment necessary to take the project to market. In this case the investments have to be summed up in full. Now assume a second scenario where the company has two projects. When one project reaches commercialisation, either just its own investments are deductible if the other project has been abandoned immediately, or in addition also some investments for the second project, if it has been abandoned somewhere on its way to market, or even all investments of both projects, if both reach market as well. As a consequence it is not clear in what way we have to calculate the accumulated losses (risk adjusted, not adjusted, or something in between).

There are, however, ways to bypass this inconvenience. First, we can assume a dummy tax rate that applies simply to the overall company value, the idea being that all cash flows are finally subject to taxes. This approach is clearly wrong; it does neither consider that you can bring losses forward nor that you can apply for tax credits, but it yields quite fair results when applied to get a quick approximation of the tax value. Second, we can run simulations using the real options paradigm, i.e. abandoning projects if their peak sales estimates falls below the their thresholds. In simulations, we can easily calculate the net annual cash flow, the accumulated losses, and the resulting tax payments. We do it exactly the same way as in reality; after all, simulations are just different versions of a possible reality. Third, it is even possible to calculate the company value using a tree that is expanded into many dimensions so that all projects can be considered. This method however is limited by its complexity and cannot cope with a feed rate that goes until infinity (this would mean that we have to build a tree with infinite dimensions).

Discount Rate

It is not uncommon to use different discount rates to value project and companies. A company in-licensing a new compound might consider the project riskier due to information asymmetry than those developed in-house and set the hurdle rate higher. But once we value a company as an entity, the projects are part of the portfolio. We discount the portfolio consequently at the company's discount rate. As outlined in the section about discount rates economists have not yet agreed on what should be included, whether only non-diversifiable risks (CAPM), or also diversifiable risks (MCPM). The reality shows a picture that lies somewhere in between these two standpoints; the discount rate should reflect the risks that stem from the pipeline, the diversification the pipeline provides, and the maturity of

the company. If we value the company as an entity we should use the WACC; in case we only value equity – which is more of the case – we use the cost of equity. In case the company has no debt there is no difference between WACC and cost of equity.

Debt

Equity belongs to the company's shareholders, debt to its creditors. There are some very important differences between equity and debt. First, shareholders have a say in the company. A share gives them the right for one vote in the shareholder assemblies. Creditors cannot influence the company's strategy. Second, equity and debt have different payoff profiles. Debt is a fixed amount, that has to be paid back at maturity and earns interests until then. If the company is not able to pay back its debt, it goes bankrupt and the liquidation value belongs to the creditors. Debt has therefore a limited upside, i.e. the maximum when all interest and the full amount are paid to the creditors. This is the normal case. The payoff of the debt only worsens in case of bankruptcy of the company, when the debt value corresponds to what is left of the company. Equity is what shareholders receive, once all debt is paid back – the circumstance that creditors are served before shareholders is called seniority. The payoff profile of equity is symmetric. If the company performs well, then the shareholders fully profit from this upturn, while creditors only receive the fixed amount of the debt. However, if the value of the company drops dramatically, the creditors do not lower their claim, only the shareholder's equity drops simultaneously in value. And if the company is not able to meet this requirement, the shareholders lose all its rights on the company. These different payoff profiles are illustrated in the figure below.

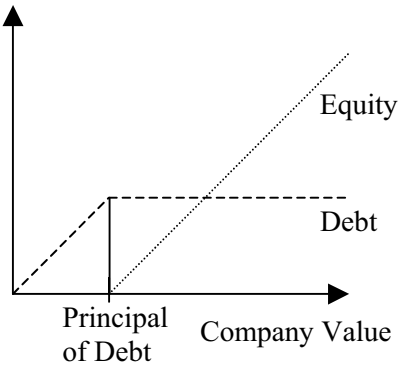


Fig. 4.47. Payoff profile of equity and debt

Only settled and stable companies are creditworthy and can raise debt. The cost of debt then depends on the amount of debt and the company's rating, i.e. its probability to meet the debt requirements.

Private companies often do not have access to the debt market and are consequently completely equity financed. The company value firm without debt then coincides with the value of equity. Debt has an influence on the risk profile of a company's equity and therefore on its value.

If we need to value the company's equity, we have to deduct the liabilities from the value of the company. A major implication of debt is leverage. While the value of the company, i.e. the value of the assets is exposed to risks like changing market environment and attrition rates, the value of the debt is only seriously affected by these risks when the company faces bankruptcy. All risks are passed on the shareholders. But the value of equity is smaller than the value of the company, the difference being the debt. Therefore, shareholders bear relatively more risk than the whole company itself. This increased risk is offset by the possibility to achieve a return on investment with more capital, that is to say not only with equity, but equity plus debt. While the shareholders have to pay the creditors the agreed rate, they can keep the excess return for them. This is called leverage. Most young companies are not eligible for debt because they are not creditworthy. The risks stemming from the attrition rates are too high.

Next to plain debt that includes interest payments and the paying back of the principal at maturity or in staged tranches, companies have the possibility to issue convertible debt. A convertible bond yields interest as a normal

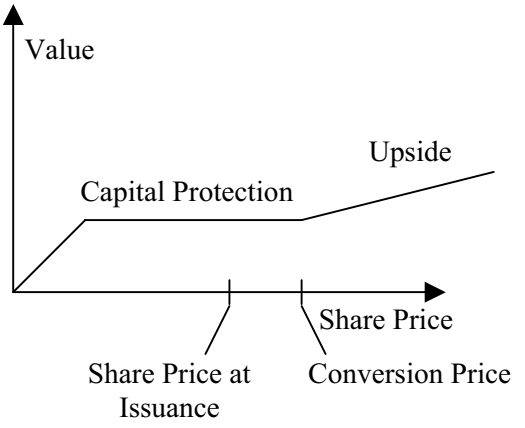


Fig. 4.48. Payoff profile of a convertible bond

bond, but its holder has the right to convert the bond into a specified number of shares, if the share price passes a certain limit. This limit usually lies considerably above the share price at time of issuing, the difference being the conversion premium. A convertible bond therefore has some debt and some equity features. On one hand it offers capital protection; on the other hand it offers the bondholder an attractive upside potential. This upside potential reduces the yield the issuing company has to offer.

The conversion premium offers the company to issue potential shares at a higher price than if it would raise equity. This is in the interest of existing shareholders.

When valuing equity in presence of convertible debt, we have to consider that the convertible bond might turn into shares. Consequently the income has to be distributed among more shareholders. The convertible bondholders potentially dilute the existing shareholders.

Dilution (Employee Stock Option Plans, Ratchets)

Dilution is not only linked to convertible bonds; also employee stock option plans (ESOP) or anti-dilution clauses (ratchets) of some investors provoke dilution. Normally the share price equals the value of equity divided by the number of shares outstanding. ESOP offer the employees of a company the right to buy shares at a fixed price. The shares will be issued at the time of exercise of the employees' option. At the time of exercise the company therefore issues share at a too low price. The value of equity has is divided among the shareholders, but the participants of an ESOP did not have to contribute proportionally, the difference being justified with their value adding work for the company. The ESOP participants bargain is at the expense of existing shareholders. Unfortunately, at the time of valuation it is not clear yet whether the options will be exercised.

In capital rounds investors sometimes insist on protecting its capital by adding anti-dilution clauses to the contract. These clauses are called ratchets and ensure the investor not to be diluted unless the share is valued higher than pre-defined limit. Ratchets can be justified by the information asymmetry between new and existing investors and serve as insurance for new investors.

A proper consideration of the dilutive aspects of convertibles, ESOP, and ratchets requires sound knowledge of quantitative finance. We content ourselves with outlining the consequences.

Company Valuation Manual

1. Define the building blocks of the company.
2. Define the parameters of each building block.
3. Value each building block (except taxes).
4. Combine the valuations of all building blocks.
5. Calculate the tax value.
6. Sum up the value of all building blocks.

Interpretation of Valuation Results

Depending on the purpose of a firm valuation, we want to answer different questions. Most often, we want to learn about the company's value, its risk profile, about the development of its cash balance and its value in the future.

Value. The most important question of the valuation is how much value the company or its shares have.

Risk profile. In addition to the value of the firm today, we might want to know how this value will behave in the future. We want to learn more about the up- and downside potential of the company. We also want to elaborate different scenarios in the future, e.g. what happens to a company when its lead compound in phase two fails? Simulations play an important role in visualising the risk governing the company value. We refer the reader to the section about simulations for more details.

Cash balance. Due to the lengthy and costly process of drug and medical device development, a common question is how long the cash of a company will last, and if and when the company does need to raise further funds. It is again worthwhile to look at particular scenarios, as well as to worst case scenarios.

Value development. A very interesting aspect is the value development of the company. From a theoretical standpoint the company value must grow on average at the assumed discount rate because of the following relationship:

$$V_t = \frac{1}{(1+r)^{(T-t)}} \mathrm{E}[V_T] \Leftrightarrow \mathrm{E}[V_T] = (1+r)^{(T-t)} V_t \tag{4.54}$$

Actually, it does not grow exactly at the discounted rate, because not the entire value is assessed as a discounted expectation. Cash only grows at the interest rate offered by the bank. The expected growth rate is therefore a weighted average of the discount rate and the interest rate.

The growth at the discount rate is owed to the advancement in time. Other factors that influence the value development are:

1. *Trial results*. Either the uncertainty is resolved and we do not have to use the success rate anymore, or the project must be abandoned. By setting the success rate of a project phase to 100% or 0% we can quantify the value jump the trial results should provoke. We will discuss this effect in the following case and in the section on stock valuation in more detail.
2. *Change in discount rate*. The company might enter a new phase of its life cycle, e.g. by diversifying its pipeline. As a consequence, the discount rate falls. This immediately leads to a higher valuation of the company and therefore a higher share price. After this value correction the value then grows at the new discount rate.

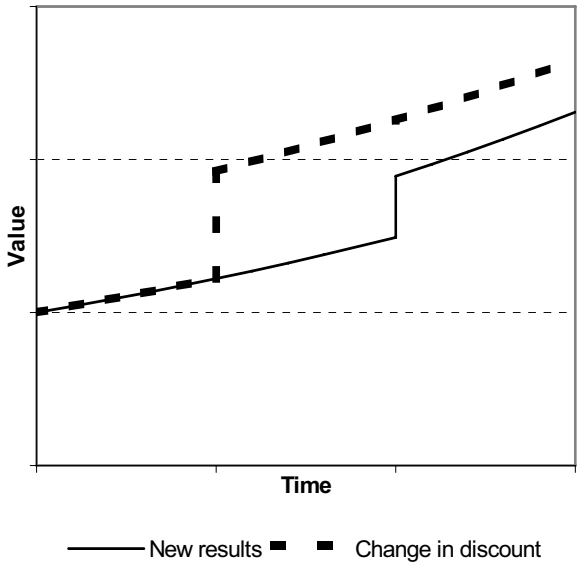


Fig. 4.49. Value development in case of successful trial results or lowered discount rate

Simulation on Company Level

As for portfolio management, simulations provide good insight into the risk profile of a company. They can visualise the company's degree of diversification and chances of success. We then have to check whether these results are in line with the discount rate we have used. If a company is well diversified a high discount rate is hard to justify. Next to the advantages of considering correlations between projects, company level simulations offer the possibility to correctly account for tax effects. Since each scenario represents one possible version of reality; we just account for the taxes as the company would in that specific scenario. Finally, we average over all scenarios and get the value of the taxes.

Case Company Valuation

Mr. Investor has the opportunity to take over a stake in BioComp in a trade sale. The company is specialised in treatments of the cardiovascular system. Currently it has a project in late clinical phase 2, another in clinical phase 1, and two in preclinical phase. On top of that, the management claims to be able to take one project every six months from its research labs into preclinical phase. A brief valuation of the compounds at a discount rate of 17% yields the following results:

Table 4.46. BioComp project values

Project	Phase	Value
BC-1130	Phase 2	$ 25 mn
BC-1140	Phase 1	$ 11 mn
BC-1200	Preclinical	$ 5 mn
BC-1202	Preclinical	$ 5 mn

BioComp's research expenses in addition to the costs allocated to the projects amount to $ 7 mn a year; furthermore it has $ 1.5 mn expenses to maintain operations. The cash position amounts to $ 21 mn, tangible assets are negligible. The tax rate is expected to be 20%, but the CFO of BioComp thinks that tax credits in the near future might lower the effect even down to 16%.

Mr. Investor wants to get an idea about BioComp's value. Furthermore, the company plans an IPO if its lead product passes phase 2. The raised money will then be invested in phase 3 trials. Mr. Investor wants to find out about the potential value increase due to a successful phase 2 trial.

Solution Case Company Valuation

Mr. Investor has already valued the pipeline. In addition, he must quantify BioComp's ability to generate new projects, the unallocated costs, and the tax effect.

BioComp has a feed rate of 2 preclinical projects a year. Assuming the new projects to be as good as the current ones, Mr. Investor calculates the value of the prototype preclinical projects to be $ 5 mn. The cost of the research delivering these projects is $ 7 mn a year. This leads to the following value for BioComp's future projects, i.e. for its technology:

$$V_{tech} = \frac{f \cdot V_{project} - Costs(1+r)}{r} = \frac{2 \cdot 5 - 8 \cdot (1+17\%)}{17\%} = US\$\ 10.6\ mn \tag{4.55}$$

In a similar way we calculate the value of the unallocated costs:

$$V_{unallocated} = \sum_{i=0}^{\infty} \frac{Costs}{(1+r)^i} = \frac{Costs(1+r)}{r} = \frac{1 \cdot (1+17\%)}{17\%} = US\$\ 6.9\ mn \tag{4.56}$$

With this we have all values we need and we can proceed to the final assessment of the company value.

Table 4.47. Value of company components

BC-1130	$ 25 mn
BC-1140	$ 11 mn
BC-1200	$ 5 mn
BC-1202	$ 5 mn
Technology	$ 10.6 mn
Unallocated Costs	$ 6.9 mn
Total	$ 49.7 mn

From these $ 49.7 mn we can subtract 16% for the tax value, i.e. $ 8 mn. We then have to add the cash and end up with a company value of $ 62.7 mn.

The average growth of the company value, assuming an interest rate of 5% for the cash is:

$$\frac{V - Cash}{V} r + \frac{Cash}{V} r_f = \frac{62.7 - 21}{62.7} 17\% + \frac{21}{62.7} 5\% = 13\% \tag{4.57}$$

The more cash is invested, the more this average growth rate approaches the discount rate of 17%.

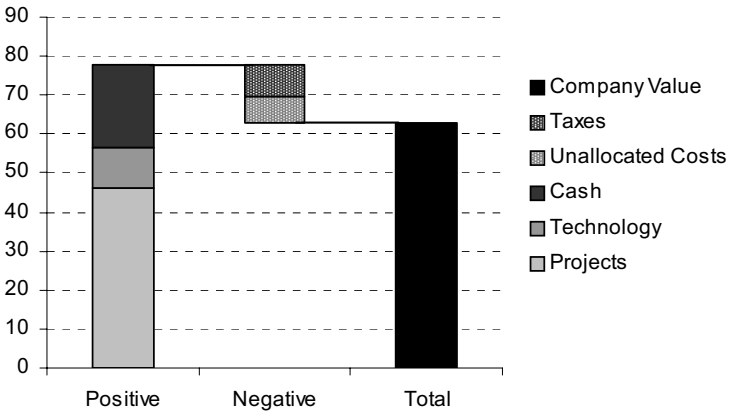


Fig. 4.50. Value of the company

The success rate for phase 2 in cardiovascular diseases is 43%. Consequently, if BC-1130 passes clinical phase 2, its value will increase by a factor $1/43\% = 2.3$ from $ 25 mn to $ 58.1 mn. Taking account of the tax rate this corresponds to a value increase of exactly $ 25 mn on company level, a jump by 80%. In addition, it is reasonable that the company might lower its cost of capital with a project in phase 3 and once on the stock exchange. This would then even increase the value further. On the other hand, a failure would result in loss of a $ 25 mn project.

Stock Valuation

Stock valuation refers to the value of a public company, or more precisely of its equity. We follow the same rules like for company valuation explained above, with some minor differences. In contrast to private companies, the market value of public companies is known at every moment. The market capitalisation, i.e. the current stock price times the number of outstanding shares, stands for the market value of equity in the investor's eyes.

Contrary to the shares of private companies the access to information of public companies is limited. Due to insider trading regulations, we only have access to public data. On the other hand, if we look at a private company we are going to invest in, once we sign a confidentiality agreement we can make use of all sources of internal company information. If we do not have unrestricted access to company information, the valuation of out-licensed products poses a special challenge. As many early-stage and mid-

stage biotech companies base their value on these licensed projects, we need to value them. In the case where we do not know the parameters of the license contract, we have to assume generic contracts. We then have to go back to the time when the contract was signed, and either base the deal terms on comparable transactions or we calculate a possible contract based on the value share principle, as outlined in the section on licensing.

The main difference, however, is that we trade shares of public companies at ease. Investors can quickly react to new information. If we want to sell the shares of a private company, we have to find a counterparty buying them in a trade sale. This can take months and often hinders investors from reacting to news. At the same time the price of the shares does not have to be negotiated, but is given by the market. We even know the market capitalisation since the IPO. We see how the share price reacts to information and what has happened in the past. This will help us to get a feeling how the share might behave to future news. Indeed, before we can judge if the market capitalization is fair, we should get an impression what future events are already anticipated in the stock price.

When valuing public stocks, we want to find out if shares are traded at the right price, if they are overpriced, or if we still have an opportunity to invest. Of course, if we assume perfect markets, we would expect that stocks be always traded at the right price. But as we do not have perfect information flow in the market, it is possible to find attractive investment opportunities.

We will now discuss the influence of clinical trial results on stock price, and consequently, we will show how to predict possible future share price movements. There are situations where we see dramatic changes in the share price: news on successful or failed trials of lead compounds, the withdrawal of drugs, or successful completion of clinical phases. We illustrate such effects with the example of Actelion's share price (ATLN, SWX). On April 20th 2001 Actelion has announced that the phase III clinical trial of Veletri, an intravenous dual endothelin receptor antagonist, did not meet its primary objective of significantly improving symptoms in the treatment of acute heart failure (AHF). On the 7th of November 2004 Actelion has announced the further development of Veletri was stopped.

The news on the negative results from the Veletri trial triggered a share price plunge from CHF 145 to CHF 55, a decrease of 62% in a single day. At that time, Veletri was the lead compound of Actelion. The market potential, if it were to reach market, was enormous. The loss of the project therefore destroyed two third of the market value of Actelion. The announcement in 2004 to stop development of Veletri for futility caused a share price

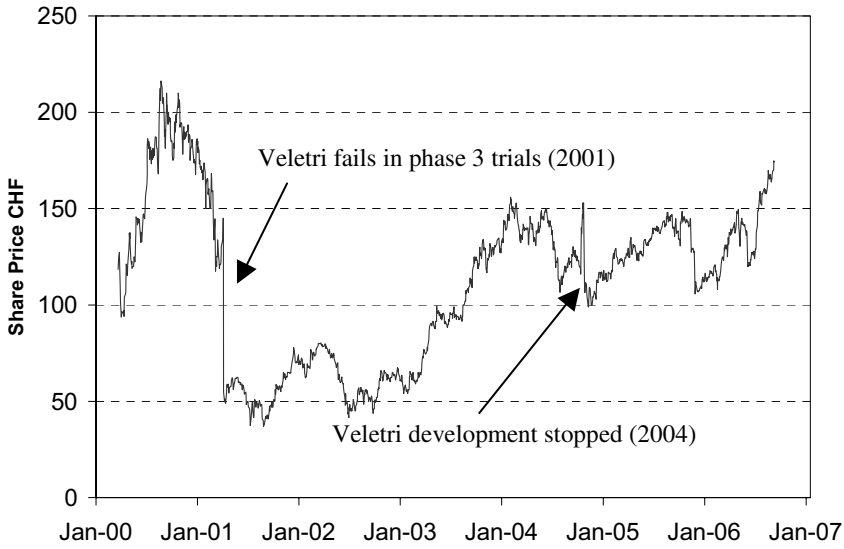


Fig. 4.51. Share price of Actelion (ATLN) since its IPO in April 2000 (Source: SWX)

drop form CHF 153 to CHF 115, a decrease of 24%. Meanwhile, the development of Actelion's second lead compound, Tracleer, proved successful. At the time when Actelion halted the development of Veletri, the company value derived not mainly from this product, but from Tracleer. Furthermore Veletri's value was not the same anymore as in 2001, because the first phase 3 trial has already unveiled some weaknesses, therefore investors have already lowered their expectations with respect to Veletri's sales potential.

The two reactions to bad clinical trial news show how dependent the share price on the clinical development news is. The case of Genentech (DNA, NYSE) displays that positive news can have a significant impact as well. On May 19th 2003 Genentech announced that a phase 3 trial of Avastin plus chemotherapy markedly extended survival of metastatic colorectal cancer patients. The share price skyrocketed by 45%. On March 14th 2004 an interim analysis of phase 3 trial has shown that Avastin plus chemotherapy improves progression-free survival in patients with first-line metastatic breast cancer and on April 14th 2004 an interim analysis of phase 3 trial has shown that Avastin plus chemotherapy extends survival of patients with first-line non-squamous, non-small cell lung cancer. The share price reacted with a 25% and 18% increase, respectively. Of course, we have chosen two prominent examples.

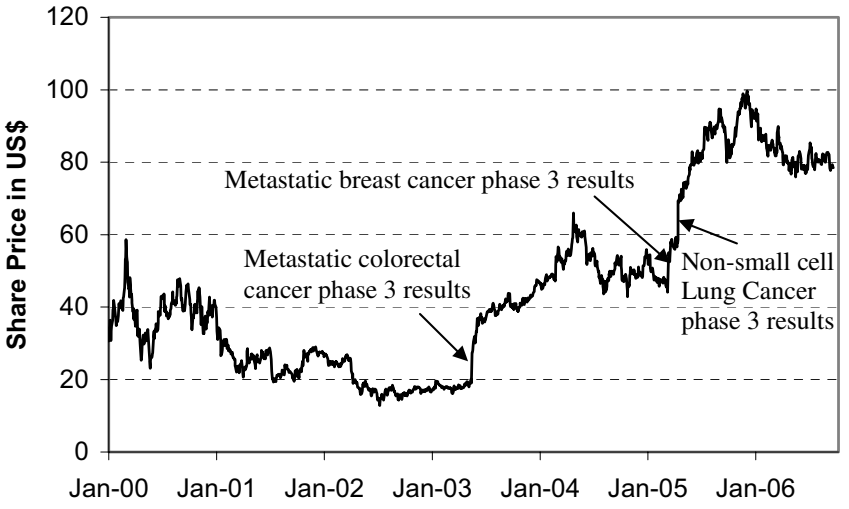


Fig. 4.52. Genentech share price reactions to clinical trial results

These large movements of the share price are interesting, if they can be anticipated, but they involve a fair amount of risk. Due to the information constraints, it is normally not possible to have enough information to predict a positive or negative outcome of the clinical trials.

Above we have seen how to calculate the company value today. If we consider investing in a stock, the calculation of the present value of the company based on the probability adjusted and discounted cash flows helps to judge if the share is priced right. But we often not only want to know the current market capitalisation and the respective share price today; we want to know how the stock will evolve in the future, we want to anticipate the share price's reaction to expected clinical news flow just as seen in the examples about Actelion and Genentech. We know that on average the share price develops at the discount rate, provided our estimates are correct. But in reality the average scenario never happens. There is no trial passed with 60%; a trial is either a success or a failure. The trial results have an immediate impact on the value of the concerned project. Either the trial is passed and we do not have to multiply anymore by the success rate for this trial, or the compound failed and the project value drops to zero. The average scenario, i.e. multiplying the project value with the success rate, lies somewhere in between success and failure. The value of a stock therefore does not follow the average scenario but one specific outcome. But since we cannot predict which outcome will happen, we have to

content ourselves with an expectation, i.e. an average value. As soon as we know more about the scenario that is actually going to happen, we adjust the valuation to this new knowledge. We can elaborate the movement of the stock based on a selection of scenarios, ranging from bad to best-case outcome. To do so we need to value all projects as if they were already one year, two years, and more advanced in their development. This implies that they would also have passed all phases successfully in that period. The projects naturally gain in value with proceeding time, first because earnings come closer and have to be less discounted, second because some investments are sunk and do not have to be considered anymore, and third and most importantly, because of positive trial results. When investigating possible scenarios of a company's value development, we simply have to determine which projects will still be alive at the moments we want to analyse. The company value must then be calculated with these projects' value corresponding to that time. And while the project value usually increases with time, the cash balance decreases. We must also keep track of the cash balance and reduce it by the amount spent, corresponding to the pipeline state. Note that once a project starts earning money, e.g. through revenues or milestones, the project value then decreases but conversely the cash balance increases again. In these cases we then have to consider the milestones or revenues as sunk.

We will now make this exercise with an early stage biotech company, having the following pipeline today.

Table 4.48. Present pipeline of an early stage biotech company

Project	Preclinical	Phase 1	Phase 2	Phase 3	NDA	Market
1						
2						
3						
4						
5						
6						

We consider investing in the stock and want to know what we can expect in terms of share price development.

Table 4.49. Project Characteristics

Project	Mode of conduct	Peak sales
1	Self-conducted	$ 575 mn
2	Self-conducted	$ 653 mn
3	Out-licensed in phase 3	$ 1,790 mn
4	Out-licensed in phase 3	$ 250 mn
5	Self-conducted	$ 1,102 mn
6	Out-licensed in phase 3	$ 375 mn

We consider the following scenarios:

1. Project 1&2 reach commercialisation, all other fail in phase 2.
2. Project 3 reaches commercialisation, all others fail in phase 2.
3. All projects reach commercialisation.

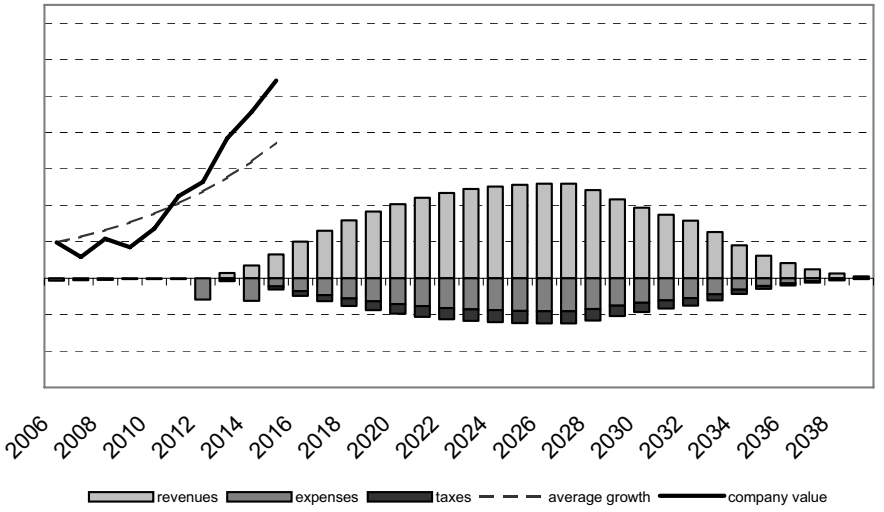


Fig. 4.53. Project 1 and 2 reach commercialisation

If only project 1 and 2 reach commercialisation, and all other compounds fail in phase 2, the share price will first decline and be smaller than the average growth, i.e. the growth at the discount rate, in our case 16%. In this scenario, we would only profit after 4 years from a solid share price increase.

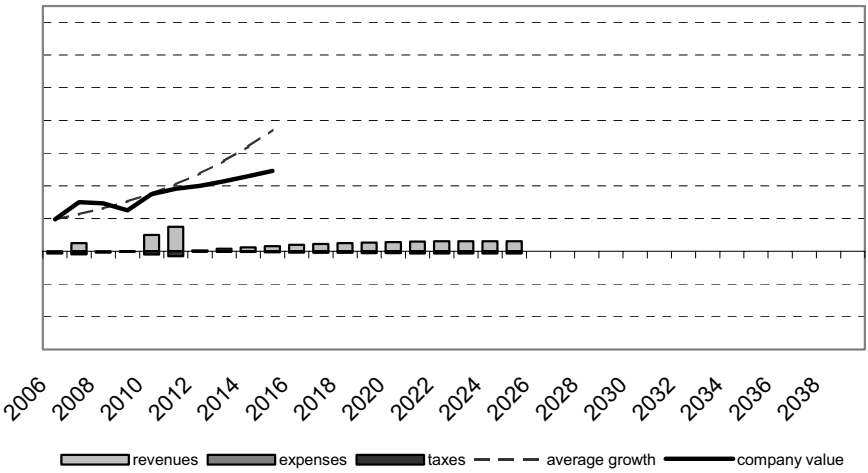


Fig. 4.54. Project 3 reaches commercialisation

In the next scenario, only project 3 passes clinical phase 2. Again all other projects fail in this phase. This bad case scenario does not allow the stock to grow significantly. The increase after four years is due to positive phase 3 results of project 3. Nevertheless, the value drop is not dramatic because, as we can see in the figure, the company has no expenses anymore.

In the third scenario, all projects come to market. The share price rapidly grows at a rate much higher than the average growth of 16%. This, of

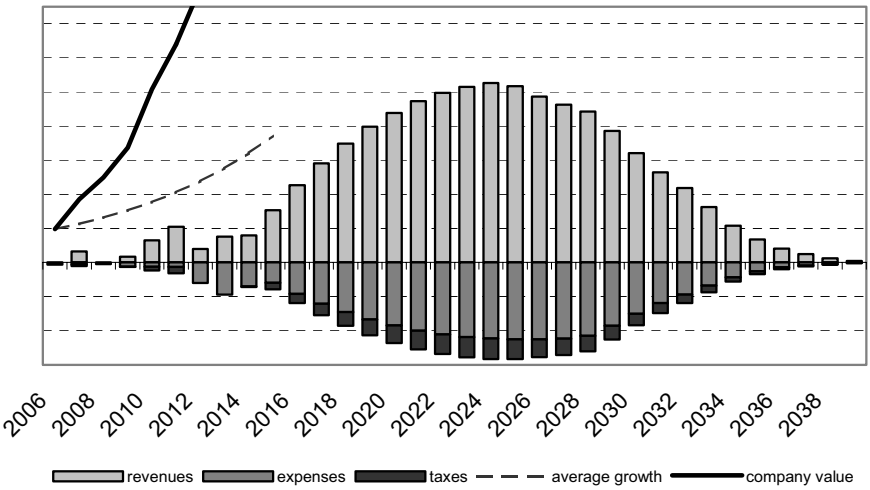


Fig. 4.55. All project successfully pass phase 2

course is a very optimistic scenario, but gives us a feeling what happens in a good case.

Of course, for a thorough study of the share, we would not only look at three, but at many more scenarios. Nevertheless, we get a good impression about the possible development of the stock, in an average, a bad and a good case. We can also undertake such an analysis for a private company. But since it is not listed on a stock exchange we cannot immediately profit from an increase in value.

Exercises

Introduction

In this chapter, the reader has the opportunity to apply what he has learned earlier in the book. Step by step, we will guide the reader through project and license valuation, and repeat important details. We then also discuss more advanced topics by way of exercise. The solutions serve as a blue print and comprehension questions help the reader verifying, whether he has properly understood the topics.

Exercises

Project EXERCISE

In the following exercises, we will use the parameters of the following project that we call EXERCISE:

Table 5.1. Parameters of project EXERCISE

In $ mn	Phase 1	Phase 2	Phase 3	NDA
Length	1 year	2 years	2 years	1.5 years
Cost	4	15	45	2
Success Rate	66%	39%	62%	75%
Peak Sales	230			
Margin	55%			
Growth Rate	1%			
Volatility	25%			
Launch Costs	100			
Discount	15%			

The sales curve is displayed in the following figure. The product will have exclusivity for the 13 first years on the market.

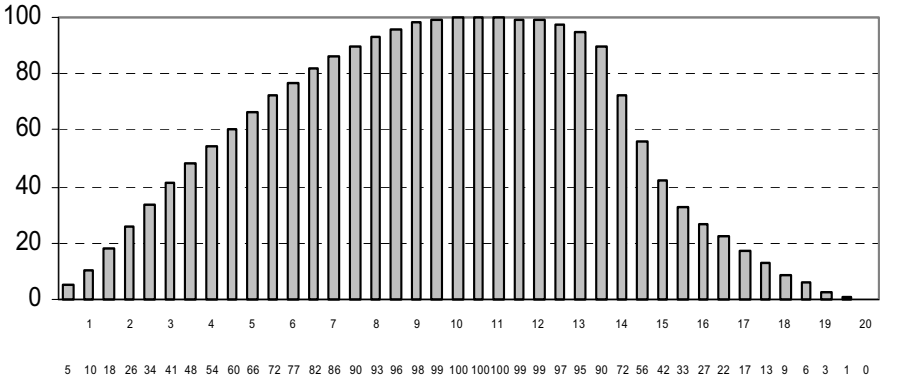


Fig. 5.1. Sales curve for project EXERCISE.

Exercise 1: Project – Getting Prepared

We must set up a spreadsheet with the input parameters. It is important to put all input parameters on a sheet showing all hypothesis. All consecutive calculations must reference on the cells on this hypothesis sheet when making use of the input parameters. Having all input parameters on one sheet allows changing the hypothesis easily.

Exercise 2: Project – Growth Rate

We have assumed a growth rate for the peak sales estimate. We calculate the peak sales estimate corresponding to each semester from now (t=0) to the end of the project's life cycle (t= 26.5). We use half-year time steps because the approval phase is estimated to last 1.5 years. As a rule, smaller time steps yield more accurate results, but require a little more work.

Exercise 3: Project – DCF Value

We now want to calculate the DCF value of project EXERCISE. Consider the use of half-year time steps for the growth rate as seen in exercise 2, for the discount rate, and especially for the sales revenues. Note that the peak sales estimate refers to sales numbers achieved in one year.

Exercise 4: Project – IRR

Usually the value just indicates whether a project is profitable or not. But the value is not a good measure to compare projects between each other. Imagine project A and project B, both having a value of $ 3 mn. Project A requires $ 1 mn investment, and project B requires $ 2 mn investment. Although project A and project B have the same value, project A seems much more attractive, because it requires less investment. The internal rate of return (IRR) is the discount rate that returns a value of zero. This means, that investing the capital a project corresponds to investing the capital in an asset that yields the IRR as annual interest. We now want to know to what return investing in project EXERCISE corresponds.

Exercise 5: Project – Binomial Tree

We now also want to value the project using real options valuation. For this we need to span the tree that models the uncertainty of the peak sales estimate. Assuming the last decision point being at launch, we construct a tree that lasts from now (t=0) until launch (t=6.5). Again, we use half year time steps.

Exercise 6: Project – End States

As the next step, we place ourselves in the end states. In an end state the product is ready to be launched. We assume that all uncertainty has been resolved until then and that we therefore can make an accurate estimate of the product's peak sales. Hence, we know all cash flows and can value the project as if it were at launch, using the peak sales estimate corresponding to the end state we are in. Finally, we do not only need to value the project at launch, we also have to decide whether it makes sense to launch the product.

Exercise 7: Project – Working Back the Tree

In order to get the value of the project today we must work back the tree. At each node lying one time step before the nodes we have already calculated, we must take the expectation, discount for the time step, adjust if in this time step a phase ends, account for the cash flows of this time step, and take a decision if the nodes are at a decision point. Not in every time step we have to account for all these points; in some time steps no phase ends, in some no cash flows are triggered, or no decision has to be made. The expectation and the discounting however applies to every time step.

Comprehension Question 1

We have received different values for DCF and real options. Where does this difference come from? Can we spot this difference somewhere in the calculations?

Exercise 8: License Contract – Getting Prepared

We now assume that the project EXERCISE is licensed to a pharmaceutical company that applies a discount rate of 11%. The license terms are as follows:

Table 5.2. License contract for project EXERCISE

License contract terms	
Phase 1 upfront payment	$ 3 mn
Phase 2 milestone payment	$ 4 mn
Phase 3 milestone payment	$ 8 mn
Filing milestone payment	$ 12 mn
Milestone payment after having sold $ 100 mn	$ 25 mn
Royalty rate for annual sales up to $ 150 mn	6%
Royalty rate for annual sales higher than $ 150 mn	9%

The license terms with respect to commercialisation are a little more exotic than what we have previously seen. The milestone for launch is delayed and only paid once the cumulative sales of the drug exceed $ 100 mn. We call this sort of license payment cumulative milestones. It is not clear from the beginning when the milestone is triggered. If the launch is successful and the sales increase fast, then the milestone arrives early. If on the other hand the sales potential is low or the sales curve not very steep, then it takes longer to the payment of the cumulative milestone.

The royalty rate depends on the amount of annual sales. Usually, the licensor receives 6% of sales, but if they exceed $ 150 mn – the barrier – then the licensor receives 9% of the exceeding amount.

We must now first adapt our input sheet to the license contract.

Exercise 9: License Contract – DCF

Calculating the DCF value of a license contract is not fundamentally different from calculating the project value. Basically, we use milestone payments instead of costs, and royalties instead of sales revenues. Nevertheless, in this case we have to pay special attention to the royalties, because they are stacked, and to the commercialisation milestone, because it is a cumulative milestone.

Exercise 10: License Contract – Real Options

When calculating the real option value we must, of course, consider the same aspects about cumulative milestones and stacked royalties, but this time for each end node. In addition, we must calculate the value not only for the licensor, but also for the licensee, because the licensee decides about the continuation of the project.

Comprehension Question 2

Explain the value differences between DCF and real options. How does the value difference behave with increased peak sales? Try out an initial peak sales estimate of $ 400 mn and explain the observation.

Exercise 11: Technology

Assume that the company owns a technology that allows bringing every 18 months one project like EXERCISE into clinical phase 1. Project EXERCISE is a project that has only a niche indication, usually peak sales are estimated at $ 310 mn for a standard project. As for the project EXERCISE we assume an annual growth rate for the value of the projects and for the costs as well. The company spends $ 3 mn each year for research and preclinical testing that precedes the clinical phases. The technology can probably be exploited for another ten years.

Comprehension Question 3

Put the value of a standard project in relation to the value of the technology. Does it make sense?

Exercise 12: Company – Input Parameters

After having discussed all items of project, license, and technology valuation in detail, we now want to value a company.

Table 5.3. Company pipeline

Project	Phase	Disease Group	Peak Sales	Strategy
ABC102	Phase 1 (Start)	CV	Excellent prec. data	Licensed
ABC107	Preclinical (6 months left)	CV	Too early to tell	Self conducted
ABC201	Preclinical (Start)	Antiinfectives	Too early to tell	Self conducted
ABC111	Lead Opt. (6 months left)	CV	Too early to tell	Self conducted
ABC205	Lead Opt. (1 year left)	Antiinfectives	Too early to tell	Self conducted

The company has five projects in cardiovascular diseases and in antiinfectives.

The company's research laboratories focus on CV and antiinfectives. All four projects have been generated by researchers of the company and it is assumed that the research groups are able to sustain the current feed rate. The company aims at eventually commercialising the projects on its own. But it is in negotiations about licensing ABC102 to a pharmaceutical company. This large player showed also some interest in possibly taking over the whole company.

In a first step we need to find out the input parameters for the projects, i.e. costs, durations, success rates, peak sales, sales curves, and margin.

Exercise 13: Company – Discount Rate

To value the company we must use a discount rate that corresponds to the company's risk profile. The current pipeline is mainly planned to be developed by the company itself. Propose a discount rate.

Exercise 14: Company – License Negotiation

Initially the company planned to develop all projects on its own, since it is backed by very potent and confident investors. Nevertheless, a large pharmaceutical company approached the company whether it is interested in licensing its lead compound ABC102. The company therefore

tries to find out what license terms it can possibly ask for. The targeted structure would be a milestone-royalty ratio of 1:1 and a steadily increasing milestone structure. The deal must be clearly value enhancing for the company, otherwise it would keep sticking to its initial strategy. What deal terms are possible assuming a discount of 10% for the pharmaceutical company?

Exercise 15: Company – Feed Rates

When valuing the company we must also consider the technologies. The company has two fields of excellence, CV and antiinfectives. Both base on a patented technology that can be exploited for 13 more years. All in all the company spends about $ 3 mn each year, however it is not exactly clear how these can be allocated to the single technologies and to general expenses. The projects generated by the antiinfectives technology are similar to ABC205. For the prototype project of the CV technology we use a project with peak sales somewhere in between the peaks sales of ABC102 and the peak sales of the other projects.

Exercise 16: Company – Value

Value the company on a stand-alone basis. Include a dummy corporate tax rate of 15%. The company's current cash balance is $ 13 mn.

More exercises and downloadable spreadsheets can be found on www.avance.ch.

Solutions

Exercise 1: Project – Getting Prepared

If a spreadsheet is arranged that all cells are referenced to the input cells, then we can easily observe the influence of one parameter by changing its value in the input cell. If we would hard code the numbers into the calculations we would have to change every cell that uses this input parameter, most probably forgetting some.

	A	B	C	D	E	F	G
1		Phase 1	Phase 2	Phase 3	NDA		
2	Length	1 year	2 years	2 years	1.5 years		
3	Cost	4	15	45	2		
4	Success Rate	66%	39%	62%	75%		
5							
6	Peak Sales	230					
7	Margin	55%					
8	Growth	1%					
9	Volatility	25%					
10	Launch Costs	100					
11	Discount	15%					
12							
13	Year	0.5	1	1.5	2	2.5	3
14	Sales Curve	5%	10%	18%	26%	34%	41%

input / DCF / ROV

Fig. 5.2. Worksheet "input"

Exercise 2: Project – Growth Rate

Using the discrete compounding formula we can calculate the grown peak sales estimate for every time step. The following figure displays the formula for cell E7, corresponding to the peak sales estimate 1.5 years from now.

	A	B	C	D	E	F	G	H
1	Time	0	0.5	1	1.5	2	2.5	3
7	Peak Sales	230	231.1471	232.3	=input!$B$6*(1+input!$B$8)^E1			236.9692

input / DCF / ROV

Fig. 5.3. Implementation of growth rate

Exercise 3: Project – DCF Value

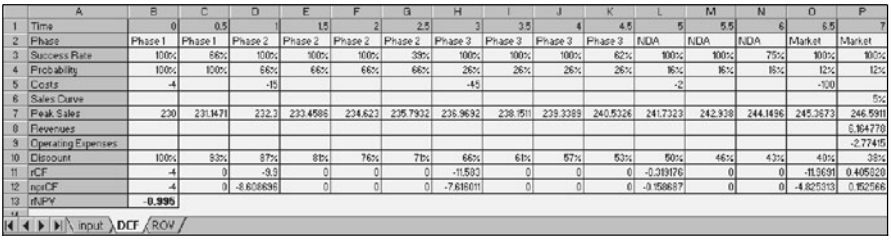
For the solution we display the spreadsheet once with its formulae, and once with its values.

	A	B	C	D	N	O	P	Q
1	Time	0	0.5	1	6	6.5	7	7.5
2	Phase	Phase 1	Phase 1	Phase 2	NDA	Market	Market	Market
3	Success Rate	100%	=input!B4	100%	=input!E4	100%	100%	100%
4	Probability	100%	=B3*B4	=C3*C4	=M3*M4	=N3*N4	=O3*O4	=P3*P4
5	Costs	=-input!B3		=-input!C3		-100		
6	Sales Curve						=input!E17/100	=input!C17/100
7	Peak Sales	=input!$B$6*(1+input!$B$8)^B1	=input!$B$6*(1+input!$B$8)^C1	=input!$B$6*(1+input!$B$8)^D1	=input!$B$6*(1+input!$B$8)^N1	=input!$B$6*(1+input!$B$8)^O1	=input!$B$6*(1+input!$B$8)^P1	=input!$B$6*(1+input!$B$8)^Q1
8	Revenues						=P6*P7/2	=Q6*Q7/2
9	Operating Expenses						=-P5*(1-input!$B$7)	=-Q5*(1-input!$B$7)
10	Discount	100%	=1/(1+input!$B$11)^C1	=1/(1+input!$B$11)^D1	=1/(1+input!$B$11)^N1	=1/(1+input!$B$11)^O1	=1/(1+input!$B$11)^P1	=1/(1+input!$B$11)^Q1
11	rCF	=(B5-B8+B9)*B4	=(C5-C8+C9)*C4	=(D5-D8+D9)*D4	=(N5+N8+N9)*N4	=(O5-O8+O9)*O4	=(P5+P8+P9)*P4	=(Q5-Q8+Q9)*Q4
12	nprCF	=B11*B10	=C11*C10	=D11*D10	=N11*N10	=O11*O10	=P11*P10	=Q11*Q10
13	rNPV	=SUM(B12:BC12)						

input / DCF / ROV

Fig. 5.4. Worksheet "DCF" with formulae

Note that the sales are taken account of half-yearly, the peak sales, however, refer to one full year. We therefore have to account for just half of the peak sales (as displayed in cell P8).



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	Time	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7
2	Phase	Phase 1	Phase 1	Phase 2	Phase 2	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3	NDA	NDA	NDA	Market	Market
3	Success Rate	100%	86%	100%	100%	100%	39%	100%	100%	100%	62%	100%	100%	75%	100%	100%
4	Probability	100%	100%	86%	86%	86%	86%	26%	26%	26%	26%	16%	16%	16%	12%	12%
5	Costs	-4		-15				-45				-2			-100	
6	Sales Curve															5%
7	Peak Sales	230	231.1471	232.3	233.4586	234.623	235.7932	236.9692	238.1511	239.3389	240.5326	241.7323	242.938	244.1496	245.3673	246.5911
8	Revenues															6.164778
9	Operating Expenses															-2.77415
10	Discount	100%	93%	87%	81%	76%	71%	66%	61%	57%	53%	50%	46%	43%	40%	38%
11	rCF	-4	0	-9.9	0	0	0	-11.593	0	0	0	-0.319176	0	0	-11.9691	0.405828
12	nprCF	-4	0	-8.608696	0	0	0	-7.616011	0	0	0	-0.158687	0	0	-4.825313	0.152566
13	rNPV	-0.995														

input | DCF | ROV

Fig. 5.5. Worksheet "DCF" with values

Exercise 4: Project – IRR

The IRR is the discount rate that returns a value of zero. We can consequently try to find the IRR simply by modifying the discount rate on the worksheet "input". We will find a discount rate of about 14.6%. On the other hand, Excel provides a function IRR to calculate the internal rate of return. As in the DCF we have discounted the risk adjusted cash flows, the risk adjusted cash flows in row 11 are the input. When calculating the IRR like this (=IRR(B11:BC11)) we get a value of 7.051%. This is not in line with the 14.6% we have found right before. The reason is that the IRR function calculates the rate for the time step between the cash flows, in this case for 6 months. To get the IRR corresponding to one year the formula would be =(1+IRR(B11:BC11))^2-1, which gives us an IRR of 14.599%. Finally, we could also use the Goal Seek function in the menu Tools as displayed in the figure.

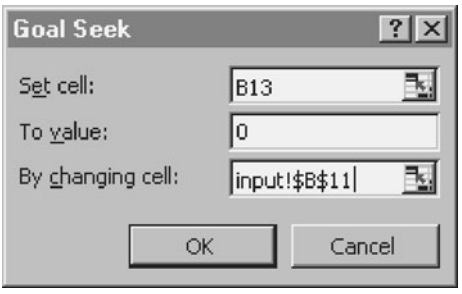


Fig. 5.6. Finding the IRR with the Goal Seek function

Exercise 5: Project – Binomial Tree

In our tree the time steps are half-yearly. The formulae for the binomial tree give us the factor up *u* and the factor down *d*.

$$u = e^{\sigma\sqrt{\Delta t}} = e^{0.25\cdot\sqrt{0.5}} = 1.19$$

$$d = \frac{1}{u} = \frac{1}{1.19} = 0.84$$

With this the tree becomes:

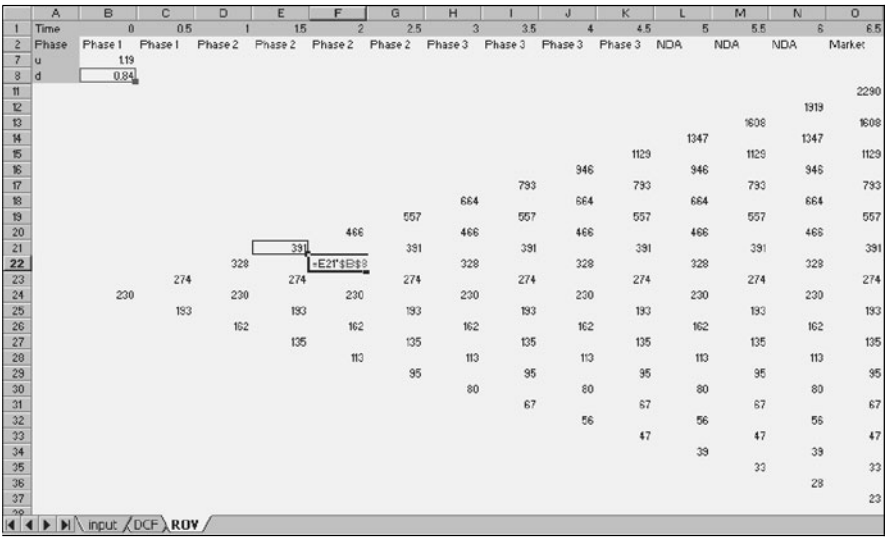


Fig. 5.7. Binomial tree in worksheet "ROV".

Note that for the construction of the tree interestingly the growth rate does not matter. Only when calculating back we use the growth rate as input parameter to the probabilities for step up and step down.

Exercise 6: Project – Calculate the End States

For each end state we have to assume the corresponding peak sales estimate and calculate with this. When projecting the future revenues we must not forget that the peak sales estimate keeps growing every year by the growth rate. These grown peak sales we then multiply with the sales curve

point corresponding to that semester. Note that we have to take just half of the peak sales estimate, because we only calculate the cash flow six months and not for one year. These cash flow must then be discounted back to launch (not back to today!). Summing them up and accounting for the launch costs we get the value for the end states. The following figure displays how the value can be calculated in one line.

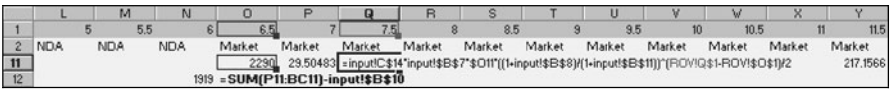


Fig. 5.8. Valuation of project value for top end node

The figure displays the values of the project in the different end states.

Time	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
Phase	Phase 1	Phase 1	Phase 2	Phase 2	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3	NDA	NDA	NDA	Market
														2290
													1919	**4583**
												1608		1608
											1347		1347	**3188**
										1129		1129		1129
									946		946		946	**2209**
								793		793		793		793
							664		664		664		664	**1521**
						557		557		557		557		557
					466		466		466		466		466	**1038**
				391		391		391		391		391		391
			328		328		328		328		328		328	**699**
		274		274		274		274		274		274		274
	230		230		230		230		230		230		230	**461**
		193		193		193		193		193		193		193
			162		162		162		162		162		162	**294**
				135		135		135		135		135		135
					113		113		113		113		113	**177**
						95		95		95		95		95
							80		80		80		80	**94**
								67		67		67		67
									56		56		56	**36**
										47		47		47
											39		39	**0**
												33		33
													28	**0**
														23
														0

Fig. 5.9. Value of end states

We see that in the three lowest states the value of the drug is negative. In these cases we would not launch the drug. Consequently, we can put these values to zero. A much better option however is to do that automatically by using the function *max(.,.)*. This allows afterwards to modify all input parameters and the spreadsheet automatically calculates whether the project would be continued in that state. Taking the maximum of zero and the calculated value returns the value if it is positive and zero if the value is negative.

	L	M	N	O	P	Q	R	S
1	5	5.5	6	6.5	7	7.5	8	8.5
2	NDA	NDA	NDA	Market	Market	Market	Market	Market
31	**38**	67	**45**	67	0.859865	1.611655	2.718669	3.680179
32	56	**25**	56	**36**				
33	**12**	47	**12**	47	0.603787	1.131686	1.909018	2.584179
34	39	**5**	39	=MAX(SUM(P33:BC33)-input!$B$10,0)				
35	**0**	33	**0**	33	0.423973	0.794657	1.340491	1.814581
36		**0**	28	**0**				
37			**0**	23	0.297709	0.557999	0.941277	1.274178
38				**0**				

Fig. 5.10. Implementation of option to abandon

Exercise 7: Project – Working Back the Tree

The easiest method to work back the tree is to create a formula that applies to each time step and then copy-paste it into all nodes. This formula must therefore consider the following five points:

1. Expectation of up and down step
2. Discount for time step
3. Account for success rate
4. Account for cash flows
5. Take decision if we are in a decision point

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	Time	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
2	Phase	Phase 1	Phase 1	Phase 2	Phase 2	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3	NDA	NDA	NDA	Market
3	Success	100%	66%	100%	100%	100%	39%	100%	100%	100%	62%	100%	100%	75%	100%
4	Costs	-4		-15				-45				-2			-100
5	Tree Parameters														
6	dt	0.5													
7	u	1.19													
8	d	0.84													
9	p	47%													
10	1-p	53%													
11															2290
12														1919	**4583**
13													1608	**2688**	1608
14												1347	**2101**	1347	**3188**
15											1129	**1638**	1129	**1867**	1129
16										946	**792**	946	**1456**	946	**2209**
17									793	**617**	793	**1132**	793	**1290**	793
18								664	**479**	664	**545**	664	**1003**	664	**1521**
19							557	**327**	557	**423**	557	**776**	557	**885**	557
20						466	**96**	466	**327**	466	**372**	466	**685**	466	**1038**
21					391	**71**	391	**207**	391	**287**	391	**526**	391	**601**	391
22				328	**52**	328	**53**	328	**220**	328	**250**	328	**461**	328	**699**
23			274	**23**	274	**43**	274	**123**	274	**191**	274	**351**	274	**401**	274
24		230	**0**	230	**30**	230	**34**	230	**145**	230	**165**	230	**305**	230	**461**
25		**0.280**	193	=MAX(([$D$9*E24+$D$10*E26)/(1+input!$D$11)*(ROW!E$1-ROW!D$1)*ROW!D$3-ROW!D$4,0)										**261**	193
26			1	162	**14**	162	**15**	162	**93**	162	**105**	162	**194**	162	**294**
27				**0**	135	**9**	135	23	135	**77**	135	**141**	135	**162**	135
28					**5**	113	**4**	**113**	**56**	113	**63**	113	**117**	113	**177**
29						**2**	95	0	95	**44**	95	**80**	95	**93**	95
30							**0**	80	**30**	80	**34**	80	**63**	80	**94**
31								**0**	67	**22**	67	**38**	67	**45**	67
32									13	56	**14**	56	**25**	56	**36**
33										**8**	47	**12**	47	**12**	47
34											**3**	38	**5**	39	**0**
35												**0**	33	**0**	33
36													**0**	28	**0**
37														**0**	23
38															**0**

Fig. 5.11. Solved tree

The following figure displays how this concept can be implemented in a spreadsheet. For this we need to specify the success rates and the cash flows for every time step (lines 3 and 4). Of course we also have to calculate the probabilities of going up or down (B9 and B10). The implementation of the decision can be applied to all nodes, because a decision is every time necessary when a cash flow occurs. If no cash flow occurs, the project cannot turn negative, because by definition all future values are positive (otherwise the project would be abandoned and the value consequently turns zero, which is not negative). In the cell D25 we see the formula that has been pasted into each cell of the tree. The bold numbers correspond to the values of the project in the corresponding nodes.

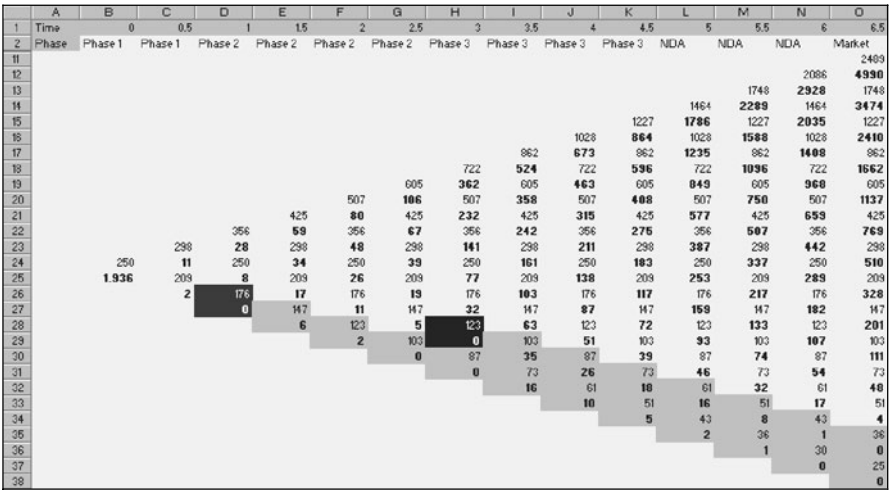
Comprehension Question 1

When valuing the project with real options we have increased the value in some nodes from a negative number to zero. This corresponds to a value increase. In the tree, these value increases translate automatically to the value in the root node by taking the expectation of up and down step. Maybe not the subsequent node is concerned by abandonment, but then it is either one of the next nodes, or even a successor of those. The figure displays where in the tree the project is abandoned because of lack of profitability (black nodes). Some nodes (grey nodes) are then in the shade of these abandonment nodes, i.e. they will never be achieved because the project has already been abandoned beforehand.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	Time	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
2	Phase	Phase 1	Phase 1	Phase 2	Phase 2	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3	NDA	NDA	NDA	Market
11															2290
12														1919	**4583**
13													1608	**2688**	1608
14												1347	**2101**	1347	**3188**
15											1129	**1638**	1129	**1867**	1129
16										946	**792**	946	**1456**	946	**2209**
17									793	**617**	793	**1132**	793	**1290**	793
18								664	**479**	664	**545**	664	**1003**	664	**1521**
19							557	**327**	557	**423**	557	**776**	557	**885**	557
20						466	**96**	466	**327**	466	**372**	466	**685**	466	**1038**
21					391	**71**	391	**207**	391	**287**	391	**526**	391	**601**	391
22				328	**52**	328	**59**	328	**220**	328	**250**	328	**461**	328	**699**
23			274	**23**	274	**43**	274	**123**	274	**191**	274	**351**	274	**401**	274
24		230	**8**	230	**30**	230	**34**	230	**145**	230	**165**	230	**305**	230	**461**
25		**0.280**	193	**5**	193	**22**	193	**64**	193	**124**	193	**228**	193	**261**	193
26			**1**	162	**14**	162	**15**	162	**93**	162	**105**	162	**194**	162	**294**
27				**0**	135	**9**	135	**23**	135	**77**	135	**141**	135	**162**	135
28					**5**	113	**4**	113	**56**	113	**63**	113	**117**	113	**177**
29						**2**	95	**0**	95	**44**	95	**80**	95	**93**	95
30							**0**	80	**30**	80	**34**	80	**63**	80	**94**
31								**0**	67	**22**	67	**38**	67	**45**	67
32									**13**	56	**14**	56	**25**	56	**36**
33										**8**	47	**12**	47	**12**	**47**
34											**3**	39	**5**	39	**0**
35												**0**	33	**0**	33
36													**0**	28	**0**
37														**0**	23
38															**0**

Fig. 5.12. Abandonment of project in the tree

If we change the initial peak sales estimate from $ 230 mn to $ 250 mn, then we get a different picture. Now we are more likely to continue the project if it passes phase 2 and NDA.

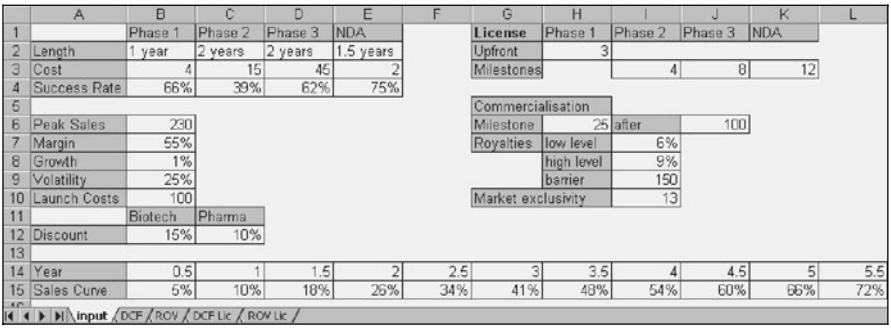


	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	Time	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
2	Phase	Phase 1	Phase 1	Phase 2	Phase 2	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3	NDA	NDA	NDA	Market
11															2489
12														2086	**4990**
13													1748	**2928**	1748
14												1464	**2289**	1464	**3474**
15											1227	**1786**	1227	**2035**	1227
16										1028	**864**	1028	**1588**	1028	**2410**
17									862	**673**	862	**1235**	862	**1408**	862
18								722	**524**	722	**596**	722	**1096**	722	**1662**
19							605	**362**	605	**463**	605	**849**	605	**968**	605
20						507	**106**	507	**358**	507	**408**	507	**750**	507	**1137**
21					425	**80**	425	**232**	425	**315**	425	**577**	425	**659**	425
22				356	**59**	356	**67**	356	**242**	356	**275**	356	**507**	356	**769**
23			298	**28**	298	**48**	298	**161**	298	**211**	298	**387**	298	**442**	298
24		250	**11**	250	**34**	250	**39**	250	**161**	250	**183**	250	**337**	250	**510**
25		**1.936**	209	**8**	209	**26**	209	**77**	209	**138**	209	**253**	209	**289**	209
26			**2**	176	**17**	176	**19**	176	**103**	176	**117**	176	**217**	176	**328**
27				**0**	147	**11**	147	**32**	147	**87**	147	**159**	147	**182**	147
28					**6**	123	**5**	123	**63**	123	**72**	123	**133**	123	**201**
29						**2**	103	**0**	103	**51**	103	**93**	103	**107**	103
30							**0**	87	**35**	87	**39**	87	**74**	87	**111**
31								**0**	73	**26**	73	**46**	73	**54**	73
32									**16**	61	**18**	61	**32**	61	**48**
33										**10**	51	**16**	51	**17**	51
34											**5**	43	**8**	43	**4**
35												**2**	36	**1**	36
36													**1**	30	**0**
37														**0**	25
38															**0**

Fig. 5.13. Abandonment of project if peak sales estimate is $ 250 mn

Exercise 8: License Contract – Getting Prepared

We must put all license parameters on the worksheet "input". It is important also to put in the time of market protection (I10) as well as the licensee's discount rate (C12). We have also prepared two new worksheets "DCF Lic" and "ROV Lic" for the calculation of the value of the license.



	A	B	C	D	E	F	G	H	I	J	K	L
1		Phase 1	Phase 2	Phase 3	NDA		**License**	Phase 1	Phase 2	Phase 3	NDA	
2	Length	1 year	2 years	2 years	1.5 years		Upfront	3				
3	Cost	4	15	45	2		Milestones		4	8	12	
4	Success Rate	66%	39%	62%	75%							
5							Commercialisation					
6	Peak Sales	230					Milestone	25	after	100		
7	Margin	55%					Royalties	low level	6%			
8	Growth	1%						high level	9%			
9	Volatility	25%						barrier	150			
10	Launch Costs	100					Market exclusivity		13			
11		Biotech	Pharma									
12	Discount	15%	10%									
13												
14	Year	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5
15	Sales Curve	5%	10%	18%	26%	34%	41%	48%	54%	60%	66%	72%

input / DCF / ROV / DCF Lic / ROV Lic /

Fig. 5.14. Worksheet "input" for a license contract

Exercise 9: License Contract – DCF

We first approach the problem of the cumulative milestone. It is only triggered after a certain amount of the drug could be sold. We can now simply calculate when this would be the case and find that somewhere between two and two and a half years after launch this limit will be passed. But remember that we want to design the spreadsheet in a way that we can change all input parameters. We therefore have to find a formula that automatically finds out when the cumulative milestone is triggered, independently of the peak sales estimate or the cumulative limit.

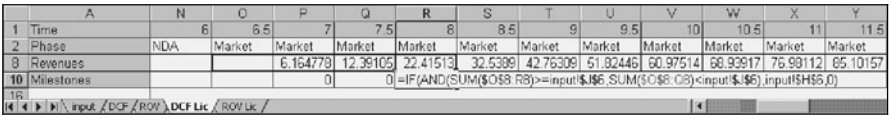


Fig. 5.15. Implementation of cumulative milestone

With the formula in the row 10. in the figure cell R10 is displayed, we must check whether the cumulative sales have exceeded the limit, only then the milestone can be triggered. But we can only trigger the milestone if it has not been triggered already beforehand, i.e. if the limit has not been exceeded in the previous time step already. These two conditions are in the AND-function. If both conditions are verified, then we account for the milestone, otherwise the cell has gets a zero-value.

For the royalties we must check whether annual sales exceed the barrier. Note that the barrier refers to annual peak sales while in the sheet we calculate with semi-annual sales figures. For simplicity we therefore just divide the barrier by two such that we can compare it directly with semi-annual figures. The error resulting from this shortcut is negligible.

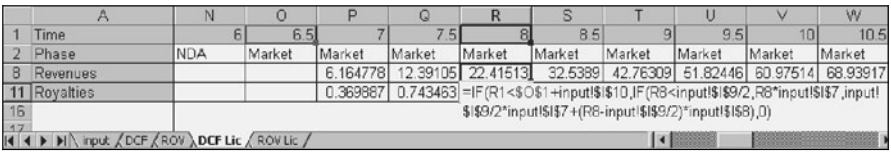
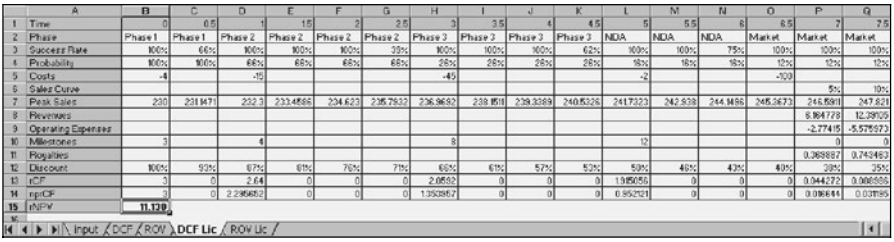


Fig. 5.16. Implementation of stacked royalties

When implementing stacked royalties we have to check whether the sales revenues exceed the barrier. If they don't we simply apply the low royalty rate to the sales revenues. If the sales revenues do exceed the barrier, we

apply the low rate to an amount corresponding to the barrier and the high rate to the part exceeding the barrier. Finally, we have to consider that the royalties are only received as long as patent protection or market exclusivity is valid. In the formula in cell R11 the if clause return the royalties if the product has still market exclusivity and returns zero otherwise.

We do not outline the rest of the calculations since they are similar to the ones already discussed in the case of a self-conducted project. We content ourselves with providing the final result.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Time	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
2	Phase	Phase 1	Phase 1	Phase 2	Phase 2	Phase 2	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3	NDA	NDA	NDA	Market	Market	Market
3	Success Rate	100%	66%	100%	100%	100%	39%	100%	100%	100%	62%	100%	100%	75%	100%	100%	100%
4	Probability	100%	100%	66%	66%	66%	66%	26%	26%	26%	26%	16%	16%	16%	12%	12%	12%
5	Costs	-8		-15				-45				-2			-100		
6	Sales Curve															5%	10%
7	Peak Sales	230	231.971	232.3	233.4586	234.623	235.7932	236.9692	238.1511	239.3389	240.5326	241.7323	242.938	244.1496	245.3673	246.5911	247.821
8	Revenues															6.864778	12.39106
9	Operating Expenses															-2.77415	-5.575673
10	Milestones	3		4				8				12				0	0
11	Royalties															0.069887	0.743462
12	Discount	100%	93%	87%	81%	76%	71%	66%	61%	57%	53%	50%	46%	43%	40%	38%	35%
13	rCF	3	0	2.64	0	0	0	2.0552	0	0	0	1.985056	0	0	0	0.044272	0.068556
14	rpCF	3	0	2.296682	0	0	0	1.353857	0	0	0	0.952721	0	0	0	0.036644	0.037195
15	rNPV	11.139															
16																	

Input / DCF / ROV / DCF Lic / ROV Lic /

Fig. 5.17. DCF calculation of license contract

The DCF value of the license for the licensee is $ 11.1 mn.

Exercise 10: License Contract – Real Options

Since we must calculate not only the licensor's but also the licensee's value at the end nodes we arrange for a little more space when constructing the tree. The calculation of the end nodes then follows the same lines as in the DCF calculation. We provide in the following a table the formulae for the uppermost end node.

Table 5.4. Formulae for uppermost end node

	A	O	P
1	Time	6.5	7
2	Phase	Market	Market
3	Success Rate	100%	100%
4	Costs	–100	
13		2,290	=$O13*(1+input!$B$8)^(P$1-$O$1)*input!B$15/2

Table 5.4 (continued)

	A	O	P
14		=MAX(SUM(P15:BC15) +O$4,0)	=IF(P$1<input!$I$10+$O$1, IF(AND(SUM($P13:P13)>= input!$J$6,SUM(O13:$P13)< input!$J$6),input!$H$6,0)+ IF(P13*2<input!$I$9,P13* input!$I$7,input!$I$9/2*input!$I$7+ (P13-input!$I$9/2)*input!$I$8),0)
15		=IF(O14=0,0,SUM(P16:BC16))	=(P13*input!$B$7-P14)/ (1+input!$C$12)^(P$1-$O$1)
16			=P14/(1+input!$B$12)^(P$1-$O$1)

In the column O lie all the end nodes, cell O13 being the peak sales estimate of the uppermost end-node. In the cells left of column O in row 13 we calculate the sales revenues corresponding to the time in row 1. In row 14 we calculate the license payments, i.e. the cumulative milestone plus the royalties. Row 15 then corresponds to the cash flows to the licensee discounted back to the end node, row 16 corresponds to the cash flows to the licensor. In the cell O14 we calculate the value of the license for the licensee, which is the sum of the discounted cash flows plus the launch costs. In O15 we calculate the value for the licensor. Note that the licensor's value is zero if the licensee decides not to continue the project.

The value of the license contract is $ 3.6 mn for the licensee and $ 9.2 for the licensor.

Comprehension Question 2

In the figure above, we can see that the licensee refuses to continue the project in the lowest node at the beginning of phase 2 and in the lowest two nodes at launch. In these scenarios the licensor does not receive any license payments anymore, although they have a positive value. This implies that the value for the licensee is lower when calculated with real options than with DCF. We can attribute this difference to the flexibility that was handed over from the licensor to the licensee. The licensor is short in flexibility while the licensee is long in flexibility.

If we use a peak sales estimate of $ 400 mn we get a DCF value of $ 13.69 mn and with real options $ 13.75 mn. Surprisingly, the real option

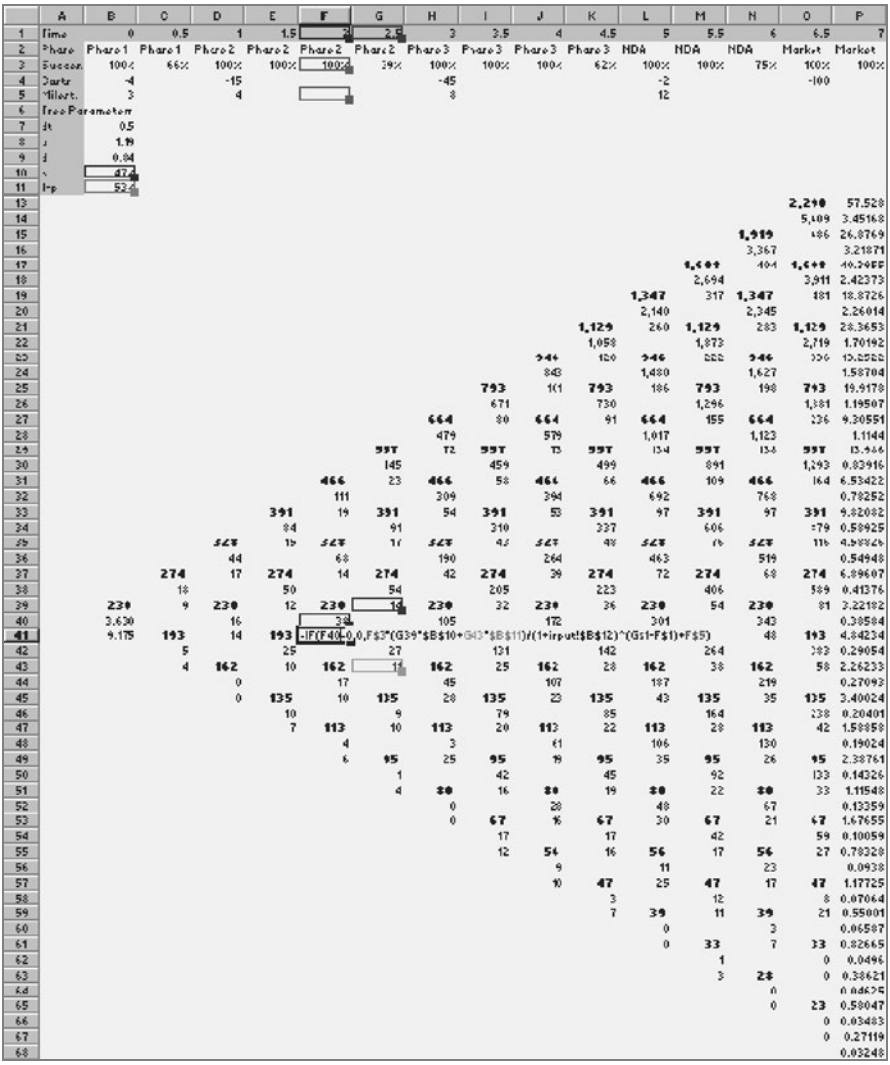


Fig. 5.18. Calculation of the real options value for licensee and licensor

value is now higher. The real option value is now higher because a second effect now covers the lack of flexibility. In the binomial tree, we have now a lot of scenarios where most of the sales revenues are compensated at the high royalty rate. This finally leads to a higher average royalty rate than when using DCF. Furthermore, the flexibility is not as valuable at $ 400 mn than at $ 230 mn because it is much less probable that the projects gets abandoned.

Exercise 11: Technology

We have to use the same discount rate as for the company, i.e. 15%. This gives us a project value of $ 7.42 mn with DCF and $ 7.47 mn with real options. If the company can put every 18 months one project into clinical phase 1, it can consequently put 0.66 projects per year into clinical phase 1. Using the formula for valuing technologies, we can calculate the value of a technology producing 0.66 projects at a growth rate of 1% over an infinite time horizon.

$$V_{tech}^{\infty} = \frac{\left[fV_{project} - (1+r-g)Costs\right]}{r-g} = \frac{0.66 \cdot 7.4 - (1+15\%-1\%)\cdot 3}{15\%-1\%} = \$\,10.6\ mn$$

But since the technology is only exploited over ten years we have to subtract the discounted value of it after ten years.

$$V_{tech} = \frac{\left[fV_{project} - (1+r-g)Costs\right]}{r-g}\left(1-\frac{1}{(1+r)^n}\right) = 10.6\left(1-\frac{1}{(1+15\%)^{10}}\right) = \$\,8.0\ mn$$

The technology has a value of $ 8.0 mn when calculated with the DCF value of the standard project. The real options approach yields a value of $ 8.1 mn.

Comprehension Question 3

A value of $ 8 mn seems moderate when compared to the $ 7.4 mn of a project generated by the technology. Nevertheless, it will take 18 months until a new project enters the pipeline, until then the company will spend $ 4.5 mn. The first project therefore has an approximate value of $ 1.7 mn (we must discount the $ 7.4 mn for the 18 months time difference and also part of the costs). This number now compares well to the value of the technology.

Exercise 12: Company – Input Parameters

Since project ABC102 has excellent preclinical data we are confident in using average sales numbers for this compound. For above average sales numbers it is still a bit early to tell, normally proof of concept studies in man then justify further adjustments towards blockbuster status. For all other projects we use the median numbers of the respective disease group.

Not knowing better we assume the other input parameters to correspond more or less to industry standards. We use overall numbers mentioned in the chapter about fundamentals in life sciences. The costs of the current phase must be adjusted to the remaining length. Usually we would need to assume higher launch costs for the first compound that reaches commercialisation, accounting for the setting up of a marketing and distribution network. Unfortunately we do not know which project will be the first one; therefore we use a standard assumption of the half of the peak sales estimate as the launch costs.

Table 5.5. Parameters of project ABC102

In $ mn	Phase 1	Phase 2	Phase 3	NDA
Length	1.5 years	2 years	2.5 years	1.5 years
Cost	4	10	45	3
Success Rate	63%	43%	76%	84%
Peak Sales	466			
Margin	65%			
Growth	0%			
Launch Costs	233			

Table 5.6. Parameters of project ABC107

In $ mn	Preclinical	Phase 1	Phase 2	Phase 3	NDA
Length	0.5 year	1.5 years	2 years	2.5 years	1.5 years
Cost	1.5	4	10	45	3
Success Rate	65%	63%	43%	76%	84%
Peak Sales	145				
Margin	65%				
Growth	0%				
Launch Costs	73				

Table 5.7. Parameters of project ABC201

In $ mn	Preclinical	Phase 1	Phase 2	Phase 3	NDA
Length	1 year	1.5 years	2 years	2.5 years	1.5 years
Cost	3	4	10	45	3
Success Rate	65%	71%	51%	80%	97%
Peak Sales	265				
Margin	65%				
Growth	0%				
Launch Costs	133				

Table 5.8. Parameters of project ABC111

In $ mn	Lead Opt.	Preclinical	Phase 1	Phase 2	Phase 3	NDA
Length	0.5 years	1 year	1.5 years	2 years	2.5 years	1.5 years
Cost	1.2	3	4	10	45	3
Success Rate	70%	65%	63%	43%	76%	84%
Peak Sales	145					
Margin	65%					
Growth	0%					
Launch Costs	73					

Table 5.9. Parameters of project ABC205

In $ mn	Lead Opt	Preclinical	Phase 1	Phase 2	Phase 3	NDA
Length	1 year	1 year	1.5 years	2 years	2.5 years	1.5 years
Cost	2.5	3	4	10	45	3
Success Rate	70%	65%	71%	51%	80%	97%
Peak Sales	265					
Margin	65%					
Growth	0%					
Launch Costs	133					

$ 145 mn peak sales is very moderate for CV drugs. Many CV drugs report sales below $ 100 mn and there is no clear sign yet that the projects are superior to other approaches. Nevertheless, the promising preclinical results of ABC102 justify peak sales of about $ 300 mn for the prototype project of the CV technology.

We will use the following sales curve (quarterly):

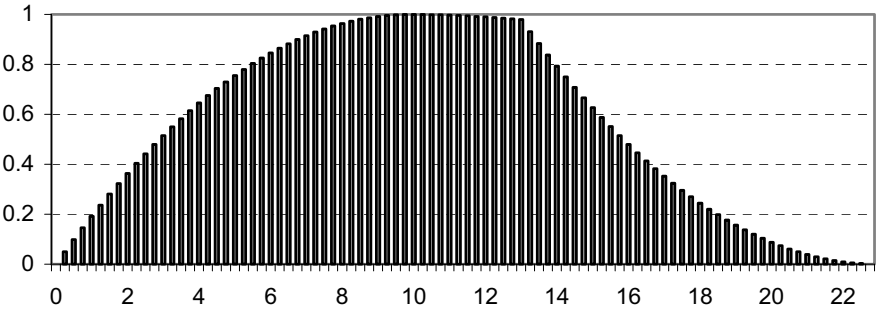


Fig. 5.19. Sales curve for projects

Exercise 13: Company – Discount Rate

The discount rate is a critical input parameter to the valuation of a company. The company has only one project at the beginning of clinical phase 1, all others being in preclinical phase or lead optimization. Our proposed framework in the discount section suggests a discount rate of around 20%. Higher success rates in CV and antiinfectives compared to the average success rates used in the mentioned discount model justify lowering the discount rate to 18%. Success rates have an important influence on the discount rate. Since we have made conservative assumptions for the peak sales we can feel comfortable with this lower success rate. The license deal would allow lowering the discount rate to 17.5%.

Exercise 14: Company – License Negotiation

Since for our company the deal must be clearly value enhancing we must compare the value of a possible license with the value of the project if developed in-house. We do not consider any aspects like steeper sales curve or better marketing of the pharmaceutical company. First, we need to value the project as in-house project at a discount rate of 18%. To estimate the leeway in the negotiations we should also calculate the same project in the pharmaceutical company's eyes. The values are $ 26.7 mn for our company and $ 74.2 mn for the pharmaceutical company.

We then can produce the numbers corresponding to a generic license contract that has a milestones-royalty ratio of 1:1 and milestone weights of 1 for clinical phase 1, 2 for clinical phase 2, 3 for clinical phase 3, 4 for filing and 5 for approval. The minimum contract must correspond to $ 26.7 mn when valued at a discount rate of 17.5%, the maximum contract to $ 74.2 mn at 12%.

Table 5.10. Extreme license contracts delimiting the negotiation leeway

In $ mn	Minimum Contract	Maximum Contract
Upfront payment	4.5	12.1
Phase 2 milestone	9.1	24.1
Phase 3 milestone	13.6	36.2
NDA milestone	18.2	48.3
Launch milestone	22.7	60.4
Royalty rate	16.5%	25.3%

The license contract should therefore lie somewhere in between if the premises of the generic license contract should be respected. Especially the royalties seem very high for a phase 1 deal. For the pharmaceutical company it is more advisable to pay a larger upfront payment, reducing all future payments. An alternative would be buying the whole company, which is apparently the option the pharmaceutical company also decided to consider.

Exercise 15: Company – Feed Rates

We can subdivide the company in two parts, a CV part and an antiinfective part. The CV part is composed by three projects in phase 1, preclinical phase, and lead optimisation as well as a technology. Displayed on a time axis we have the following picture:

Table 5.11. CV projects

Time	1	2	3
Phase	Lead opt	Preclinical	Phase 1
Probability	100%	70%	45.5%
Project	ABC111	ABC107	ABC102

Table 5.12. Antiinfective projects

Time	1	2	3
Phase	Lead opt	Preclinical	Phase 1
Probability	100%	70%	45.5%
Project	ABC205	ABC201	

Assuming that ABC111 has just been produced by the technology we have to find the feed rate that is most likely to end up with one project in preclinical and another in phase 1. This leads to the following problem, where p_i denotes the probability of phase 1 and n_i the number of projects in phase i (the n_i describe the current pipeline):

$$\max_f \left\{ \sum_i \binom{f}{n_i} \left(\prod_{j=1}^{i} p_j \right)^{n_i} \left(1 - \prod_{j=1}^{i} p_j \right)^{(f-n_i)} \right\} \tag{5.1}$$

This method yields a feed rate between one and two for both technologies. Staying conservative we use feed rates of 1.

The CV prototype project (with 1 year lead optimization at $ 2.5 mn, $ 330 mn peak sales, and $ 165 mn launch costs) has a value of $ 0.3 mn with DCF at 18%, project ABC205 has a value of $ 2.3 mn with DCF. As an overall technology for the company we receive:

$$V_{tech} = \frac{\left[f_{CV} V_{CV} + f_{anti} V_{anti} - (1+r) Costs \right]}{r} \left(1 - \frac{1}{(1+r)^n} \right)$$

$$V_{tech} = \frac{\left[1 \cdot 0.3 + 1 \cdot 2.3 - 1.18 \cdot 3 \right]}{0.18} \left(1 - \frac{1}{1.18^{13}} \right) = -\$\ 4.6\ mn$$

Note that the technology has a negative value. This does not necessarily mean that the technologies do not generate any value, because part of the costs is general and administrative which is also spent to manage the existing five projects.

Exercise 16: Company – Value

To value the company we must value its parts. Using DCF we get:

Table 5.13. Value of the company

Asset	Value ($ mn)
ABC102	26.7
ABC107	8.2
ABC201	-2.9
ABC111	-3.9
ABC205	2.3
Technology	-4.6
Sum	**25.8**
Tax (15% of sum)	-3.9
Cash	13
Total	**34.9**

Interestingly, the company also conducts negatively valued projects. We have included these in the final value, because the company plans to go ahead with them without caring about their value. If somebody wants to take over the company, these should not be included in the final value, because the new company would not need to continue them if it considers them loss making. This increases the value by $ 6.8 mn, neglecting also a part of the technology the value increases even more. Considering further that the overtaking company can value the same projects at a much lower discount rate, the shareholders could be offered a nice premium on the current share price.

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