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Finding the value of biotechnology

a risk-adjusted net present value approach

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Finding the value of biotechnology - a risk-adjusted net present value approach

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Abstract

The objective of the project was to develop and evaluate a risk-adjusted net present valuation model; to examine how proceedings in clinical development, different indications and different market assumptions affect the value of biotechnology and products. According to the developed model, based on sensitivity analysis, scenario analysis and Monte Carlo simulation, the most important parameters are: market share, price, transition probabilities and time spent in development. Monte Carlo simulation was found to be a good but time-consuming method to quantify uncertainty in underlying estimates.

Keywords

Biotechnology, risk-adjusted net present value, Monte Carlo simulation, scenario analysis valuation

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GRADUATE THESIS PROJECT • BIOINFORMATICS ENGINEERING PROGRAM
UPPSALA UNIVERSITY SCHOOL OF ENGINEERING

Finding the value of biotechnology

A RISK-ADJUSTED NET PRESENT VALUE APPROACH

FREDRIK KÄLLGREN

Finding the value of biotechnology
-a risk-adjusted net present value approach-

Fredrik Källgren

Sammanfattning

Läkemedelsutveckling är en tidskrävande, kostsam och riskfylld process. Kostnaden för att ta fram ett nytt läkemedel brukar grovt uppskattas till 800 miljoner dollar och endast en läkemedelskandidat av fem tusen lyckas ta sig från labboratoriet till marknaden. Av de svenska bioteknikbolagen har de allra flesta inte någon försäljning från egna produkter och är därmed helt beroende av att investerare skjuter till kapital som kan finansiera deras verksamhet.

Investeringar i forskningsintensiva bioteknikföretag sker med avsikten att utvecklingen av produkterna i bolagets pipeline fortskrider med målet att slutligen nå marknaden och därmed generera en tillfredsställande avkastning. För att bedöma om en investering är lönsam krävs någon form av värdering. Traditionella värderingsmodeller fungerar inte tillfredställande på bioteknikföretag som går med förlust och som dessutom har en stor osäkerhet i de närtida kassaflödena. Värderingsmodellen måste anpassas efter de utvecklingsrisker som bolaget är behäftat med.

I detta projekt utvecklas en sannolikhetsjusterad kassaflödesmodell som tar hänsyn till läkemedelskandidaternas specifika utvecklingsrisker. Modellen ska på ett enkelt sätt möjliggöra för modellering av hur värdet för bioteknikbolag påverkas vid olika tänkbara händelser. Det kan exempelvis handla om förseningar av projekt, att bolaget skriver licensavtal, förändrade marknadssituationer, etcetera. Modellen testas genom konstruktion av ett presumtivt bioteknikbolag med upp till tre olika produkter under utveckling, vilket värderas utifrån olika scenarion. Med hjälp av modellen identifieras de viktigaste parametrarna som påverkar ett bioteknikföretags utveckling; marknadsandel, produktens framtida pris, utvecklingstid och sannolikheten att produkten når marknaden.

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ABBREVIATIONS

ASR	Age-Standardized prevalence Rate
CAPM	Capital Assets Pricing Model
DCF	Discounted Cash Flow
DD	Dividend Discount Model
EMEA	the European Medicines Agency
eNPV	expected Net Present Value
FCF	Free Cash Flow Model
FDA	the Food and Drug Administration
IND	Investigational New Drug Application
IRR	Internal Rate of Return
mAb	monoclonal Antibody
NDA	New Drug Application
NPV	Net Present Value
OECD	Organisation for Economic Co-operation and Development
RE	Residual Earnings Model
ReOI	Residual Operating Income Model
R&D	Research and Development
rNPV	risk-adjusted Net Present Value
WACC	Weighted Average Cost of Capital

1 INTRODUCTION – THE IMPORTANCE OF VALUATION

Valuation is the process of assessing a value to products and programs (Villinger & Bogdan, 2005). Valuation is no exact science, rather a process allowing companies and investors to interact (Villinger & Bogdan, 2005). Attributing a value to biotechnology companies through an economically valid, communicable, evaluation methodology is important since it allows investors to find out if and under what condition they should participate in a venture, it emphasizes the financial impact of the acting of senior management and is a necessity in order to understand deals and co-development agreements (Bode-Greuel & Greuel, 2005).

Assigning a value to biotechnology companies and drug development in general is especially difficult because of the long and risky development process and uncertain market conditions (Villinger & Bogdan, 2005). The value is derived from expected future revenue streams from products, which in many cases are not on the market, and from the potential of the companies' technology platform (Bode-Greuel & Greuel, 2005; Villinger & Bogdan, 2005). The risk of development failure in drug development is of great concern, especially with respect to the significant investments made. It is therefore argued that financial valuation models should reflect both the uncertain outcomes in clinical trials as well as managerial decisions (Bode-Greuel & Greuel, 2005; Stewart et al., 2001). Among professionals such as analysts, venture capitalists, pharmaceutical- and biotechnology companies, the most frequently used financial models are risk-adjusted Net Present Value models, rNPV, followed by non risk-adjusted Net Present value models, comparables and scenario methods (Puran, 2005). In interviews with 44 CEO/business developers Muscho et al. (2000) finds that when evaluating deals[1] and co-development agreements only two thirds uses economic models, 21% simply added an arbitrary chosen margin to their expected cost and 12 % evaluate deals based on best guesses.

This project was conducted at Kaupthing Bank, Stockholm at the department for Equity Research. The principal objective of this study was to develop and evaluate a risk-adjusted net present valuation model; to examine how proceedings in clinical development, different indications and different market assumptions affect the value of biotechnology companies and products and hence

[1] The average deal value in 2007 exceeded USD 90 million (Medtrack, 2008)

understand how different values may be derived. Model constraints are that it should be user friendly and easy to work with. The model should in an easy manner allow for analysis of commonly occurring events announced by biotechnology companies such as delays/advancements in R&D activities and entering/terminating collaboration and partnership agreements.

1.1 REPORT LAYOUT

Based on content, this report is divided into two main parts, consisting of seven sections. The first part, section 2 to 4, discusses valuation methodology and drug development. Section 2 discusses biotechnology and drug development and section 3 and 4 discusses valuation from a drug development perspective and how the valuation model is implemented. The second part is a case study which makes use of the developed valuation model. The case study is presented in section 5. The results are presented in section 6 followed by conclusions in section 7.

1.2 DEFINITIONS

According to the Secretariat of the Convention on Biological Diversity, Article 2, Biotechnology may be defined as: "Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or process for specific use". This is basically the same definition held by OECD with the exception that OECD specifies the need for production of either knowledge, good or service (OECD Biotechnology statistics, 2006, pp. 7). Since these definitions are broad, including everything from nanobiotechnology products to baking, they tend to be rather unpractical to use (Miller, 2007). More precise divisions in use are the segmentation in accordance with the biotechnology techniques, DNA/RNA, proteins and other molecules, cells and tissue culture engineering, process biotechnology techniques, gene and RNA vectors, bioinformatics and nanobiotechnology, or by the scope of the biotechnology such as, human health, animal health, plant, food and beverage, industrial and environmental (OECD, 2005; Cloete, 2006). The biotechnology

industry as a whole is also sometimes referred to as a discovery industry rather than a biotechnology industry (Drews, 1998).

In this study a biotechnology firm is defined as a firm within human health engaged in at least one of the above mentioned techniques. A biotechnology product target primary humans and the development requires the use of at least one of the above mentioned techniques.

2 BIOTECHNOLOGY AND DRUG DEVELOPMENT

2.1 HISTORICAL BACKGROUND

Developing substances to improve human health has been done for hundreds of years. In the beginning, plant extracts where used as medicines but as the first patent appeared in the 19th century following significant improvements in biology and chemistry, a more systematic way of extracting new drugs took form. During the first half of the 20th century, development efforts were primary focusing on vaccines and antibiotics. In the 1970s and 1980s advances in technology made it possible to rationally target diseases and focusing on specific therapeutic areas. In the 1980s and 1990s further improvements in chemistry and molecular biology made it possible to direct molecules to specific targets which role in disease etiology[2] where more precise known (Datamonitor, 2007c).

2.2 BIOTECHNOLOGY PRODUCTS

Biotechnology has been used in drug development during the last thirty years and the resulting products, vaccines excluded, are often referred to as biologics (Datamonitor, 2007a; Brown, 2001). Other segments used to describe the pharmaceutical market are vaccines and small molecules, see Table 1. Vaccines, even though they are often proteins, are not referred to as biologics since their mechanisms of action are different to biologics. Vaccines mimic the target and stimulate the production of endogenous antibodies, as opposed to biologics which

[2] The process of identifying the cause of a particular disease or disorder.

elicit its effect by binding directly to the target (Datamonitor, 2007a). Biotechnology companies get 82% of revenues from biologics and 18% from small molecules (Datamonitor, 2007b).

TABLE 1: SEGMENTATION OF THE PRESCRIPTION PHARMACEUTICAL MARKET

Type	Description
Biologics	Therapeutic proteins and monoclonal and polyclonal antibodies
Small molecules	Therapeutics with a molecular weight of less than 500 Daltons
Vaccines	Often proteins but unlike vaccines biologics do not elicit their effect directly through binding a target

Source: Datamonitor (2007a)

2.4 CLINICAL TRIALS

Before any pharmaceutical products such as new human drugs, medical devices, veterinary drugs, and food additives are allow to be sold, manufactures need a marketing permit. The permits precede an extensive drug review process involving clinical trials and exist to ensure drugs are safe and effective. In the US the Food and Drug Administration, FDA, and in the EU the European Medicines Agency, EMEA, approve these permits. (Davis, 1999; FDA)

In the United States[3], preclinical studies need to be conducted before any product may be tested on humans. Within the scope of preclinical tests, enough information must be provided so that agency can decide if it is reasonable safe to move forward with testing the drug in humans. If the drug is considered safe an Investigational New Drug Application (IND) may be submitted. The IND describes the type of people who may participate and the dosage to be studied. The application is reviewed by both FDA and a local institutional board. If the IND is found acceptable clinical trials on humans are allowed to begin. Clinical trials in humans are usually divided in three different phases. Phase I aims to determine what the drug's side effects are. Phase I trials are conducted on 20 to 80 healthy volunteers and only if the drug still is considered to be safe and no evidence for unacceptable toxicity were found are the drug candidate allowed to proceed to phase II. Phase II trials involves a few dozen to about 300 patients. The primary focus is effectiveness and to show whether the drug works in patients

[3] The procedure is similar in Europe.

with the targeted disease. If shown effective, and if the drug candidate is still considered safe, the drug candidate is allowed to proceed to phase III trials. Phase III studies are usually set up after in-depth discussion with the FDA regarding the set-up and clinical endpoints. Phase III trials involves hundreds to about 3000 patients and the trials aims to further investigate effectiveness and side effects by studying different populations, different dosages and different combinations of drugs. After positively finishing phase III trials, a formal application called New Drug Application, NDA, containing all post- and clinical data, is submitted. The FDA may refuse to file a NDA application if it is incomplete, or if some required data is missing. Even if approved, the FDA may require additional postmarketing studies, often called phase IV studies. The review process is summarized in Figure 1 below. (FDA, 2008)

A drug may be eligible to a fast track approval review if the drug candidate is targeting a life-threatening illness that lacks satisfactory treatments, and if the drug has the potential to treat a serious aspect of the disease. Fast-track approval might shorten approval times significantly. Between 1998 and 2005 around 500 drugs were designated to accelerated approval, representing 13% of all approved drugs. The rate of designated fast-track approval differs between therapeutic areas. Most HIV drugs have been approved under accelerated approval provisions and 40% of all provisions have been for oncology therapeutics. In the US, if the drug targets an indication with fewer than 200 000 potential patients or is not found to be profitable until more than seven years since launch, then the drug may be classified in accordance with the Orphan Drug Act. If a drug receives Orphan status, it is eligible for grants and tax credits for trials and seven years of market exclusivity. Orphan act intends to stimulate not speed up approval (FDA, 2008; Datamonitor, 2007c).

Drug Review Steps

1) Preclinical (animal) testing.

2) Investigational new drug application (IND) - outlines the aims and objective of the clinical trials.

3) Phase I studies (20 to 80 people).

4) Phase II studies (few dozen to about 300 people).

5) Phase III studies (hundred to about 3,000 people).

6) Pre-NDA period - the FDA and drug sponsors meet.

7) Submission of a New Drug Application (NDA).

8) After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.

9) If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.

10) The FDA reviews information regarding the drug's professional labeling.

11) The FDA inspects the facilities where the drug will be manufacture.

12) FDA reviewers will find the application either "approvable" or "not approvable."

13) The FDA may require additional postmarketing studies (phase IV).

FIGURE 1: SUMMARY OF THE DRUG REVIEW PROCESS
Source: FDA, www.fda.gov (2008-01-17)

3 VALUATION

Investments are made with the aim of generating a return and the price or value put on any investment will reflect the risk-adjusted rate of return that can be earned. The return is comprised of three factors: the amount of money the investment is likely to generate, the point in time when money is received and the effect of inflation (Baker, 2001). In turn, risk-adjustments reflect that some investments are considered to be riskier than others, i.e. some assets tend to have a higher variance around the expected mean of future returns (Baker, 2001). When valuating biotechnology companies and their products, two primary valuation methods has been suggested, discounted cash flow, DCF, and real option[4] methods (Villinger & Bogdan, 2006; Stewart et al., 2001). It is argued that real

[4]An option grants the option-holder the right but not the obligation to exercise their rights in respect of an asset

options methods better handles uncertainties in model parameters and better captures the possibility to avoid losses by cancelling projects (Villinger & Bogdan, 2005; Villinger & Bogdan, 2006). Real options address these possibilities by applying financial option theory on the drug development process. Drawbacks with real options are that they are more demanding and complex than DCF models (Villinger & Bogdan, 2006; Stewart, 2002b). Stewart (2002b) argues that many of the so called real options aren't real at all because they can't be exercised in practice.

This thesis uses a risk-adjusted DCF model. The primary reason why real option models are left out is because a simple non-complex model is desirable. Also, investors, venture capitalists and analysts are more familiar with DCF models than real options. I also argue that it is easier to communicate changes in development time and increased risk in terms of transition probabilities and time spent in clinic (risk-adjusted DCF) than volatile measures, growth factors and rote nodes (real options).

In literature, four discounted cash flow models are commonly occurring: Dividend Discount Model (DD), Free Cash Flow Model (FCF), Residual Earnings Model (RE) and Residual Operating Income Model (ReOI). All models can be derived from the DD model and should in theory result in the same value (Smith, 2008). In practical applications however, they might differ a few percentage points (ibid). Within the biotechnology valuation literature the technique is simply called discounted cash flow, without being more precise (Villinger & Bogdan, 2005). The same technique is sometimes, referred to as net present value (NPV), risk-adjusted net present value (rNPV), augmented net present value or expected net present value (eNPV) (Bode-Greuel & Greuel, 2005; Rajapakse et al., 2005; Stewart et al., 2001; Villinger & Bogdan, 2005). The value of biotechnology companies often lies in projects which are not yet commercial launched. Hence, the valuation methodology for biotechnology companies is often similar with the valuation of single projects and entrepreneurial start-ups (McKinsey & Company, 2005).

The valuation method used in this study is referred to as net present value when no additional risk adjustments are added to specifically capture the development risk and risk-adjusted net present value, rNPV, when R&D risk is separately handled.

3.1 NET PRESENT VALUE

The NPV algorithm discounts the future net cash flow generated by an investment to today's value. The sum of the discounted cash flows equals the derived value of the investment. A positive value indicates that the investment is likely to create value, while a negative value indicates that the investment is value-destroying. (Bode-Greuel & Greuel, 2005)

The NPV algorithm is:

$$NPV = C_0 + \frac{C_1}{1-r} + \frac{C_2}{(1+r)^2} + \ldots + \frac{C_t}{(1+r)^t} + \frac{C_{TV}}{r(1+r)^t}$$

Where

C = net cash flow

r = discount rate

t = time period for which the future cash flows are valued

$\frac{C_{TV}}{r(1+r)^t}$ = terminal value

The discount rate *r* from an investors perspective reflects the opportunity cost of capital, that is what an investors demand in return for investing in other projects with similar risk, while for the part seeking funds the discount rate reflects the cost of capital (Bode-Greuel & Greuel, 2005; Puran, 2005). A company seeking funds might have hundreds or thousands of ways of sourcing capital but most professionals and most of the literature delimit their discussion to only two forms of capital: the interest bearing debt, D, and risk bearing capital, EQ, (mostly equity) (Bode-Gruel & Gruel, 2005; Bodie & Merton, 2000, pp. 436; Hamberg, 2004, pp. 284). The reason behind this classification is the conceptual differences between the contracts with the company which give rise to different risks. Interest bearing capital relies on a fixed legal contract, which gives certain

rights, whereas risk bearing capital relies on a residual contract (Hamberg, 2004, pp. 284). The resulting, weighted average cost of capital, WACC, is expressed as:

$$WACC = w_{eq} r_{eq} + w_d r_d$$

$$r_d = r_f + rp_d$$

Where

w_d = D/(D+EQ)

w_{eq} = EQ/(D+EQ)

r_{eq} = cost of debt

r_d = cost of equity

rp_d = risk premium for debt

The capital assets pricing model, CAPM, usually serves as an estimate for the cost of equity (Bodie & Merton, 2000, pp. 343-354; Dimasi & Gramowski, 2007; Hamberg, 2004). This gives:

$$r_{eq} = r_f + \beta(r_M - r_f)$$

Where

r_f = risk free rate

β = beta value

r_M = market risk premium

Since 1990 the long term debt for biotechnology companies has made up less than 1% of its market value, therefore the debt component is usually negligible and the weighted cost of capital in practical applications often equal to

the cost of equity (Dimasi & Grabowski, 2007). WACC and CAPM are theoretical frameworks for determining discount rates but other ways of determining discount rates exists. Venture capitalists tend, to some extent, to use the internal rate of return, IRR, expected by their fund investors as a benchmark for the discount rate (Puran, 2005). The IRR has a tendency to be higher than the WACC and the reasons provided are the high risk associated with biotechnology, the low liquidity of the underlying asset, and compensation for management services provided by venture capitalists (Puran, 2005).

3.1.1 RISK-ADJUSTED NET PRESENT VALUE

Before a drug is allowed to be distributed to the market, the manufacturer needs to prove through clinical trials that the new drug is safe and efficient. The clinical trial process may be seen as a series of discrete events; either a positive result in one phase is obtained and the project is allowed to proceed to the next phase or the result is negative resulting in a failure. Such transition probabilities, i.e. the probability of moving from one phase to the next, have been estimated for different industries and therapeutic areas (Dimasi, 2003; Dimasi & Grabowski, 2007; Reichert et al., 2005). When valuating biotechnology products and drug development in general, the development risk, i.e. the risk of failure before reaching the market, is commonly separated from the market risk (Bode-Greuel & Gruel, 2005; Puran, 2005, Stewart, 2002). The development risk is modelled by adjusting cash flows with an appropriate probability of the likelihood that they will appear. The market risk which is the normal market risk faced by all products at the market is captured through the use of an appropriate discount rate (Bode-Greuel & Gruel, 2005; Puran, 2005, Stewart, 2002). The risk-adjusted net present value methodology is illustrated in Figure 2 and 3.

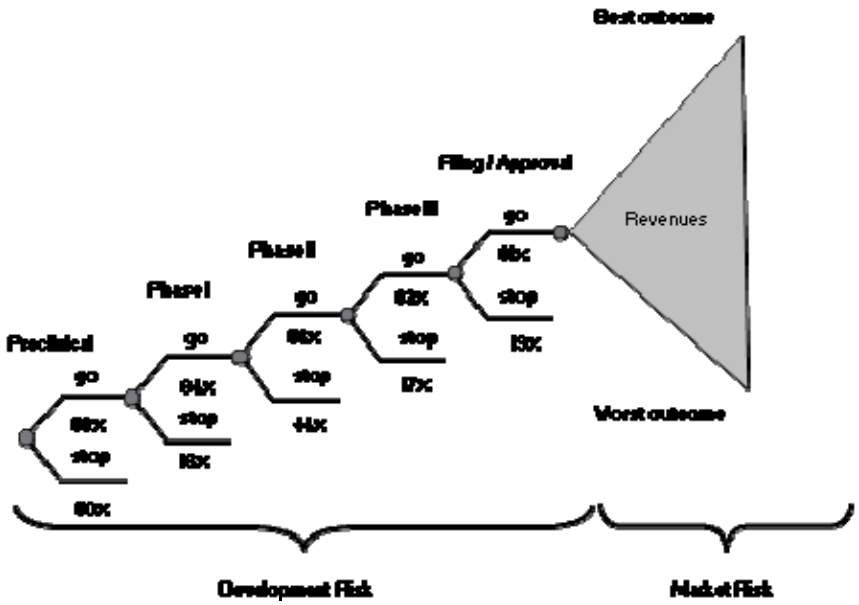


FIGURE 2: DEVELOPMENT AND MARKET RISK

The development risk can be seen as a series of discrete events where each clinical trial represents a necessarily requisite with probability *p* for future advancements and a probability *1-p* that the whole project will be cancelled. The market risk is the risk that the value of an investment will diverge due to market factors. Source: Dimasi & Gramowski (2007) and Stewart (2002).

	Phase I	Phase II	Phase III	Filing	Launch
Net Cash Flow	-25	-30	-80	-10	600
Transition probability	84%	56%	83%	81%	
Cumulative probability	100%	84%	47%	39%	32%
Risk-adjusted net cash flow	-25	-25	-38	-4	190
Years from now	0	2	4	5	6
Discount rate	15%	15%	15%	15%	15%
Risk-adjusted present value	-25	-19	-22	-2	82
Risk-adjusted NPV	15				

FIGURE 3: EXAMPLE OF R-NPV CALCULATIONS

In this example a project is about to enter phase II. The net cash flow of each stage is adjusted by the corresponding probability of reaching that state onto which a 15% discount rate is applied.

3.2 CASH FLOW PROFILE

From a cash flow perspective, drug development is a quite unique process. The lengthy and costly development process and the high probability of a substantial sales drop when a patent expires, results in a distinctive cash flow profile,

summarized in Figure 4. It must be stressed that the figure only represents a schematic and simplified view of a likely drug development process. The figure is derived from an evaluation of relevant literature and databases (Arojarvi, 2001; IMS; Medtrack). In the following subsections the different parts of the cash flow profile are discussed in greater detail.

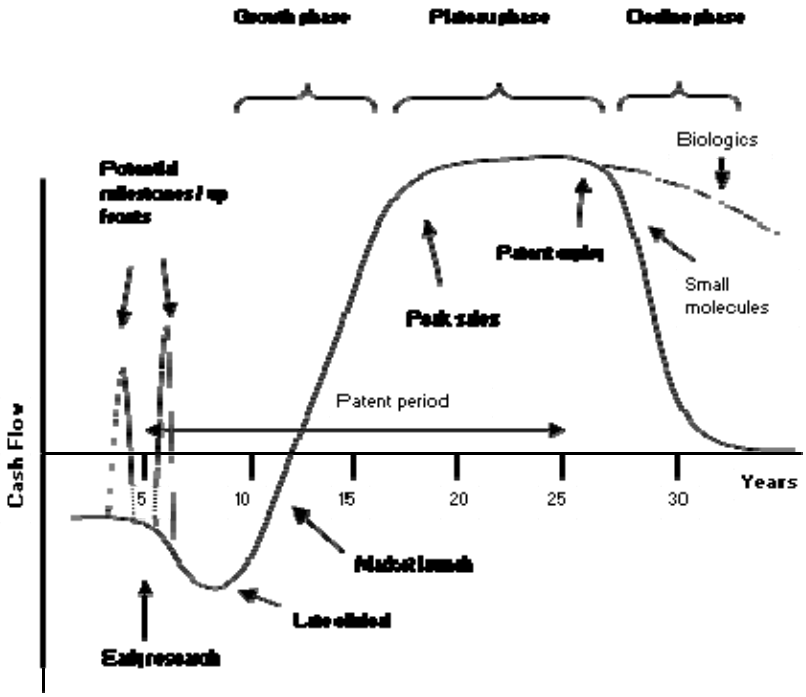


FIGURE 4: CASH FLOW PROFILE

The cash flow profile represents a schematic description of cash flows generated by a single drug candidate. A slower drop of sales after patent expiry is probably more likely for biologics than small molecules, indicated by the dotted line.

3.2.1 FORECAST PERIOD

For the valuation of biotechnology projects it is recommended that the forecast period should at least cover the project's patent period (Bode-Greuel & Greuel, 2005). Brand-name drugs are generally given patent protection for 20 years from the date of submission of the patent but may be granted five years of extended patent protection resulting in a total of 25 years of legal protection (FDA, 2008-03-24; eu-upplysningen.se, 2008-03-24). Since drugs need to undergo rigorous and time consuming clinical trials and patents are filed long before the product

reaches the market a novel drug is usually only protected between 8 to 15 years after being approved (www.astrazeneca.se, 2008-03-24). Patent protection may differ substantially among biotechnology products since the patent protection is complex and unique to each project. In addition, patents could in excess of only covering the product also protect manufacturing processes and delivery techniques and thereby extend the legal protection and delay competition (Datamonitor, 2007c). The ability to protect the product even after the product patent expires is something which affects the cash flow profile of a company. Due to the complexity of patent protection, and with the entering of preclinical trials as starting-point, a 20 to 30 year long forecast period is used.

3.3.2 EXPENDITURES AND DEVELOPMENT TIME

Drug development is a long-lasting and costly process (Dimasi, 2002). With the preclinical phase as starting point, based on earlier studies, the development process for a typical biotechnology company can be estimated to last for 9.6 years costing roughly USD 230m (Dimasi & Grabowski, 2007; Stewart, 2001). Clinical trial costs increase with the consecutive phases (Dimasi & Grabowski, 2007). Project cost and development time are unique for each project but seem to correlate with the choice of therapeutic area and industry (Dimasi & Grabowski, 2007; Reichert et al., 2005). Biotechnology companies tend to have somewhat lower clinical trial costs than pharmaceutical companies but their development and approval times are longer (Dimasi & Grabowski, 2007; Reichert et al., 2005).

Different to small molecules are biologics not available for oral self administration; instead they are often administered intravenously with assistance from medical personnel. From this follows that biologics sales force tend to be smaller, since they only need to focus on the hospital sector instead of the prescribing primary care physicians. Biologics also tend to be more expensive to produce than small molecules because of the lack of available high throughput chemical processes, which increases the cost of goods sold. (Datamonitor, 2007a)

Time spend in development can to some extent be shortened. Clinical development involves regular meetings with authorities and increased contact and improved dialogue can speed up clinical trials. Also, target indications that lack

satisfactory treatment can make a drug electable to accelerated approval programs. (Datamonitor, 2007c)

3.3.3 REVENUES

An average biotechnology company receives 82% of revenues from biologics and 18% from small molecules (Datamonitor, 2007b). Regardless of market size, revenues from pharmaceuticals seem to generate revenues in a similar pattern (Arojarvi, 2001; Lehman Brothers, 2004; Medtrack, 2008). A pattern characterized by three distinctive phases here referred to as growth, plateau and decline phase. The growth phase usually last for 7 – 12 years, depending on the potential of the drug. A fast adoption can be seen by novel and blockbuster drugs targeting therapeutic areas with great unmet needs entering a known market. A slightly slower adoption can be represented by a drug entering many different markets, for instance different countries in Europe, or a drug which continues to target new indications and thereby gradually increases sales. The growth phase ends when the products sales have reached a somewhat more stable market share, here referred to as peak sales. After peak sales the plateau phase starts, characterized by almost no or limited growth (ibid). After the patent exclusivity expires the onset of generic competition dramatically changes the revenue stream from products. This is especially true for small molecules which basically face generic competition the same day as the patent expire. Merck's Zocor, a small molecule cholesterol-lowering drug, lost almost its entire 20% market share to generic Simvastin within six month from its patent expiry, see Figure 5.

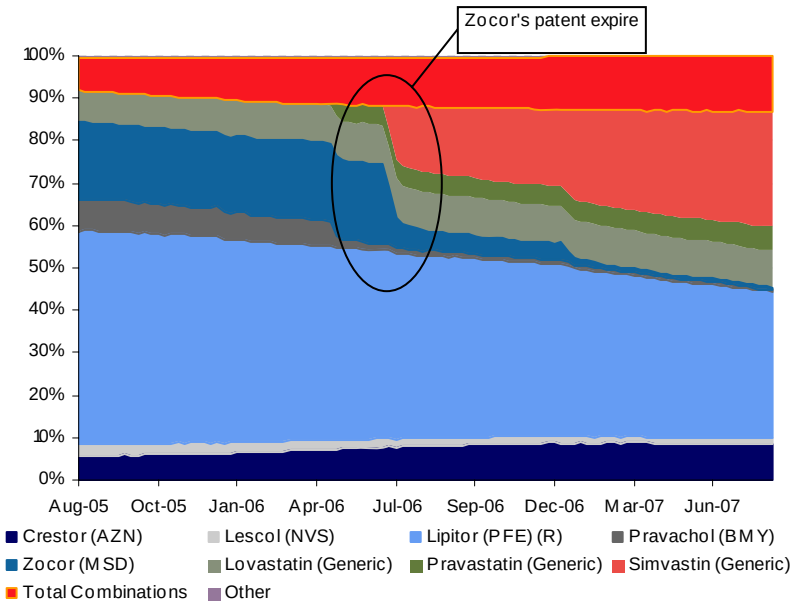


FIGURE 5: STATINS MARKET SHARE IN THE USA

This graph shows prescriptions data for statin products in the United States. In mid 2006 Zocor's patents expired and already after six month the drug lost almost its entire market share to generic simvastins. This graph clearly demonstrates the great impact generics have on the market for small molecule products.
Source: IMS America

Biologics are believed to face less generic competition compared to small molecules given the same regulation frameworks as of today. Generic drugs manufacturers duplicate the active ingredient[5] of the branded originator and hence do not have the same development costs and can therefore afford to sell the drug at substantial discounts. This is regulatory possible because it has been shown that a generic small molecule is identical both structurally and functionally to its branded originator (FDA, 2007). This has not been shown for biologics; there does not exist unambiguous evidence that a generic protein is structurally and functionally similar to a branded product (FDA, 2007). As a consequence there are no abbreviated approval pathways for protein products licensed under Public Health Service Act (FDA, 2007; Datamonitor, 2007a, pp. 14). Generic companies developing biosimilars need to perform full length clinical trials, significantly lowering the advantage of the imitator in favour of the branded originator. An intensified debate regarding the increasing cost of biologics together with its commercial success might speed up both the development of mimic technologies

[5] In the United States in accordance with section 505(b)(2) of the Food, Drug, and Cosmetic Act, which permits an applicant to rely on published information or on information from approved drugs.

and the simplification of the regulatory framework (Datamonitor, 2007c; Szabo, 2004). Nevertheless, patent protection of biologics is complex. Apart from the basic product, biologics are usually protected by several other patents (Datamonitor, 2007). A slower erosion of sales after patent expiry is probably more likely for biologics and not an abrupt end as seen among small molecule products, indicated by the dotted line in Figure 4.

3.3.4 OUT-LICENSING, DEALS AND ROYALTIES

Out-licensing deals are essential elements of biotechnology companies' strategy as they often do not have the money to fund the whole drug development and marketing process or do not want to bear the whole development risk themselves. Licensing agreements offers a biotechnology company risk sharing and access to external expertise and resources. The deal structure usually involves a first one time up-front payment followed by milestone payments when goals are met. There exists other agreement structures where costs and revenues are shared more equally, such as co-developing and/or co-marketing agreements but they occur much less frequently. An out-licensing deal most often involves a large pharmaceutical company taking on all future development activities and costs, but deals could also result in contract research opportunities with the licensee. Out-licensing deals are usually viewed positively by investors and could generate additional revenue streams by attracting new investors or boosting venture capital founding, which reduces the financial risk. The main drawbacks with licensing deals are loss of control and lower future revenues. Some deals only involve the marketing right where the licensee has no influence over the remaining development process. A more likely scenario, however, is the licensee taking the greater role in the development and/or marketing process; resulting in the licensor losing control. When the products reach the market, the licensor usually receive royalties on top of up-fronts and milestones. (Datamonitor, 2005; Datamonitor, 2007c; discussions with industry experts)

Deals with biotechnology companies are usually conducted in clinical phase I or II, see Figure 6. Deals between earlier-stage companies and the top 50 largest

pharmaceutical companies are usually done during phase I, while deals between the 200 largest companies are usually done later in phase III (Datamonitor, 2007c). Deals tend to be single-product agreements and selected based on therapeutic area (Datmonitor, 2007c). This result in a strategic aspect of the deals in excess of only the drug and its market potential, in order to get a deal with a large pharmaceutical company the drug candidate must fit the licensee's overall strategy. Up-fronts and milestones give rise to positive revenue peaks in the schematic cash flow profile in Figure 4. Royalties does not change the above mentioned outline, it only affects the magnitude of the revenue stream.

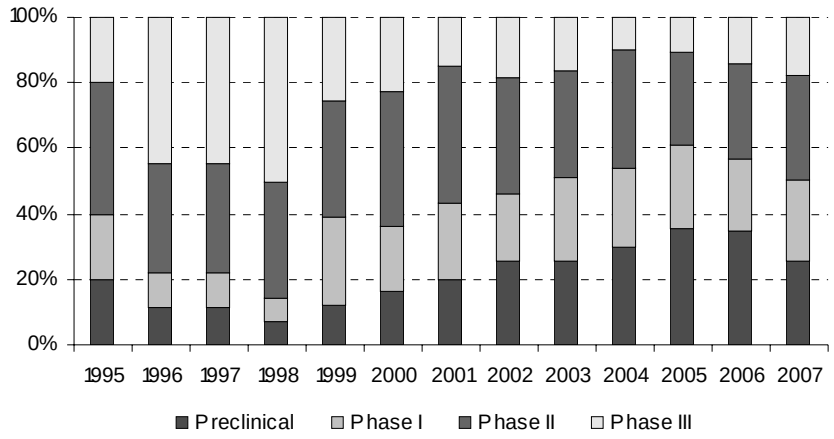


FIGURE 6: WHEN DEALS ARE MET WITH BIOTECHNOLOGY COMPANIES
This diagram show the proportion of deals met in each clinical stage with at least one biotechnology company during 1995-2007.
Source: Medtrack 2008-01-14

3.3.5 LOSS CARRYFORWARD

Drug development is a costly process resulting in negative cash flow over many years. If the development cost is carried by a single small biotechnology company it is likely that the company as a whole will show negative earnings. These losses may be carried forward and reduce tax liabilities on future capital gains. These loss carryforwards will affect cash flows positively as the company starts to generate positive earnings.

3.4 SIMULATION – OBTAINING RELIABLE ASSUMPTIONS

Estimating variables always involves uncertainty and an exact estimate will most often turn out wrong (especially for events occurring many years ahead). A commonly used method to represent uncertainty in more than two estimates is to use different scenarios. For instance, if a product achieves both better sales and lower costs than expected, that is called a best case scenario, if everything turns out as expected it is a most likely scenario and if clinical trials is delayed followed by lower sales than expected, this is a worst case scenario. Reasoning in terms of scenarios may be useful when the assumptions reflect possible and likely events. The different cases usually results in rNPVs covering a wide range of values, which do not reveal anything about the underlying uncertainties, see Figure 7.

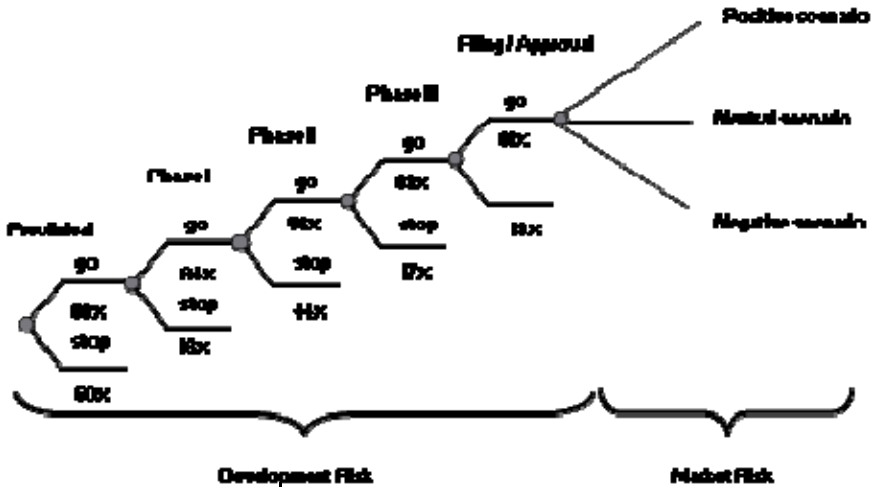


FIGURE 7: MARKET SCENARIOS

A commonly used method to capture uncertainly in estimate is reasoning in terms of scenarios; each scenario results in independent rNPVs.

In many cases one may have a good feeling for a single estimate or good statistics supporting a given choice. Such information could be used to describe uncertain estimates in terms of probability distributions. To capture and quantify this uncertainly to an aggregated level, Monte Carlo simulations can be used[6]. Monte Carlo simulations works by repeated sampling from the probability distributions of each input parameter. The number of times an rNPV is occurring within an

[6] see for instance Bode-Greuel and Greuel (2005) and Puran (2005)

interval with equally length is calculated. The resulting output is a graph showing a range of possible rNPV:s and their occurrence. The methodology is schematically exemplified in Figure 8.

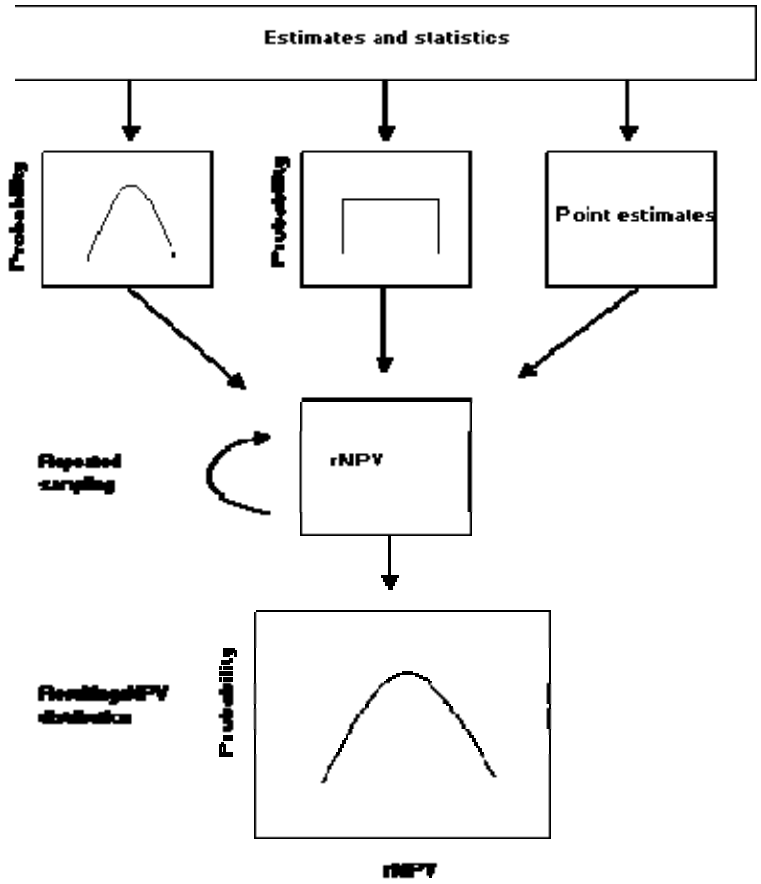


FIGURE 8: MONTE CARLO SIMULATION METHODOLOGY

Monte Carlo simulations allow for key parameters to be estimated either by probability distribution or single point estimates. The resulting rNPV distribution reflects the uncertainly in the underlying estimates. Source: Adapted from Puran (2005)

3 IMPLEMENTATION

The rNPV model was implemented in Microsoft Excel. Excel was chosen since it is probably the most used computer tool when valuating companies and the spreadsheet layout allows the user to easily follow each calculation step. Excel is also widely spread which increases the portability. The main drawbacks with using Excel instead of implementing the valuation model in a programming language such as C/C++ or Matlab (Mathworks) is its low calculation capacity.

The time loss when performing simulations is argued to be of less importance compared with the gain of having an easy used highly portable model; therefore Excel was chosen as the program of use. Simulations are performed using the Visual Basic programming language with the rNPV Excel model acting as calculation engine. Cash flows are calculated over a 32 years time period and data to populate the model was obtained from literature (Datamonitor, 2006& 2007; Dimasi, 2002; Dimasi, 2007; Lehman Brothers, 2004; Reichert et al., 2005; Schrag, 2004; Kerins et al., 2004; Stewart et al., 2001), databases (Medtrack; IMS health; IARC) and industry experts.

4 CASE STUDY

A hypothetical case study based on available data was set up in order to validate the functionalities of the model and gaining understanding in how different scenarios and valuation assumptions affect valuation. The study was based on mAb projects targeting one single indication, colon cancer. Limiting the study to mAb targeting only one indication was done firstly because relatively good and detailed market data and data from mAb products already on the market are available. Secondly, only considering one indication and one type of therapeutic product makes it easier to both understand and analyze the interaction effects when a company's research portfolio consists of more than one project.

The case study was divided into three different analyses; sensitivity analysis, scenario analysis and Monte Carlo simulations. In the sensitivity analysis each input was varied within an interval while keeping all of the other parameters constant. The analysis aims to illustrate single parameters effect on the rNPV. The scenario analysis allows two parameters to be changed simultaneously, and their combined effect on rNPV to be studied. Monte Carlo simulations, which has no upper limit with respect to number of parameters allowed to changed simultaneously, is used to study the combined effect when more than two parameters are changed at once. Monte Carlo simulation offers a way to represent a combined view on rNPV due to the uncertainly in underlying estimates.

4.1 BASE CASE SET UP

The case study was built upon a base case from which the effect of parameter changes is tested on. The base case was based on both relevant literature sources and estimates; its set up is discussed in the following section.

4.1.1 CLINICAL TRIALS

Total R&D costs and clinical development time follows from literature (Datamonitor, 2007b; Dimasi, 2007; Stewart et al., 2001). After consulting experienced people within the industry, some adjustments were done with respect to the currency exposure. It is not likely that the development costs for a Swedish biotechnology company conducting clinical trials, to be exposed only to a single currency. If for instance two independent phase III trials are requested by the authorities, commonly one is usually done in the US and one in Europe. It is also more likely the US market is the primary market to be targeted. Hence, it is more likely that a majority of clinical trials are performed in the US. Therefore 70 % of development costs are estimated to be connected to the US dollar and the remaining 30 % connected to the Euro.

According to Medtrack (2008-01-14) roughly 50% of all deals in 2007 were done during phase I and II, see Figure 6. In general, if a deal is done during preclinical trials the licensor is compensated with 10% royalties, 15% if deal is done in phase I or II and 30% if met in phase III (Datamonitor, 2005). These suggested royalty rates are only rough guidelines, royalty rates and the entire agreement structure may vary considerably between projects. As the base case, it is assumed that a deal with a large pharmaceutical company is done in the beginning of phase II and that the licensor thereafter takes on all of the development cost. The royalty rate is assumed to be 15% and a one time upfront payment of USD 40m[7] is to be paid when the agreement is signed. Even though milestones are usually part of a licensing deal, they are not included in the base case. The reason is that they are uniquely determined for each project, are rather complex in structure and do not add much to the interpretation of single variables, if included in the base case.

[7] This follows from disclosed deals, see appendix 1

4.1.2 DISCOUNT RATE

When valuating biotechnology companies the risk component in the discount rate represent the risks remaining after accounting for the risks involved in clinical trials (Stewart, 2002; Bode-Greuel & Gruel, 2005). The discount rate varies considerably in literature and among practitioners. Lehman Brothers (2004) uses 10 % as a basic risk free discount rate for the pharmaceutical industry. Dimasi (2002) uses a real rate of 11 %. Using CAPM Dimasi & Grabowski (2007) estimates the cost of capital for biotechnology firms during 1994 – 2004 to be in the range of 10 – 12.5 % in real terms and 13 – 17 % in nominal terms. Stewart (2002) observes that when clinical-trial risk is excluded, an appropriate discount rate for biotechnology firms seems to be in the range of 9 – 15 %. Stewart et al. (2001) estimates the discount rate to be equal to the internal rate of return generally available by primary sources to biotechnology companies, which they estimate to 20%. This is in line with Kerins et al. (2004) who find the cost of capital available from venture capital funds, which often are the primary source of capital available to biotechnology firms, to be between two to four times as expensive.

Without taking into consideration specific company characteristics, a 15 % discount rate is used as base case. A 15% discount rate is in the upper limit of reported clinical risk free discount rates reported when deriving the discount rate from WACC/ CAPM, reflecting the more likely venture capital funding and its higher cost of capital.

4.1.3 REVENUES

According to Schrag (2004) the yearly mAb cancer therapy cost exceeds USD 160 000 per patient for which 56 000 patients in the United States will receive treatment at this cost. The International Agency for Research on Cancer (2008-01-

09) estimates an age-standardized prevalence rate[8], ASR, for colon cancer in more developed regions to be 0.04 % and 0.01 % in less developed regions. From this follows that about 50 % of all colon cancer patient in the US will get mAbs treatment. Datamonitor (2006) estimates the treatable population size worldwide for five different colorectal cancer drugs between 163 000 – 326 000 patients. In addition, I estimate the fraction of patients to get mAbs treatment in emerging markets to be 10 times lower than in the USA, Europe and Japan. This results in a treatable patient group consisting of 202 600 patients.

There are today more than 21 mAb drugs available on the market, making it harder for new mAbs to capture market shares. Datamonitor (2006) estimates the penetration rate of five colon cancer mAbs to be in the range of 3 – 70%. As the market gets more saturated and thereby making very high market share more unlikely, a 10% market penetration is used as the base case. The market uptake is assumed to come at normal speed; 10% market share is assumed to be reached after 10 years. After peak sales a 2% annual growth is assumed, following an assumed average growth rate of the targeting markets. The patent protection is estimated to last for 20 years after entering preclinical trials. The likely sales drop after patent expiry is modelled as being abrupt with a 70% year over year sales drop during 5 year and thereafter having constant sales for the remaining forecast period.

4.1.4 TAX – LOSS CARRYFORWARD

Loss carryforwards differ substantially between companies depending on many different reasons. In this study it is assumed that the company will start to pay tax 5 years after the product reaches the market.

All base case assumptions are summarized in tables 2, 3 and 4.

[8] ASR is a summary measure of a prevalence rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age. (International Agency for Research on Cancer, 2008-01-09)

TABLE 2: BASE CASE – CLINICAL DEVELOPMENT

Phase	Transition probabilities	Development Time(years)	Development costs (USDm)	(EURm)
Preclinical	50%	1.6	-29.9	-20.7
Phase I	84%	2.4	-16.1	-11.2
Phase II	56%	2.7	0.0	0.0
Phase III	83%	1.3	0.0	0.0
Filing	81%	1.5	0.0	0.0

Source: Dimasi, 2007 & Stewart et al., 2001 and estimates

TABLE 3: BASE CASE – REGIONAL DIFFERENCES

Region	Population (m)	Growth rate	Patient Population (t)
EU (27 countries)	493	0.4%	99
USA	303	0.9%	61
Japan	127	-0.1%	25
Emerging markets	3682	1.1%	18

Source: Eurostat, U.S. Census Bureau (2007-08-23), Schrag (2004), The International Agency for Research on Cancer and estimates

TABLE 4: BASE CASE – REVENUES

# years to peak sales	10
Yearly drug cost per patient ($)	160000
Royalty (%)	15%
Market share (%)	10%
Patent expiry from phase I	20
Loss carried forward (years with no tax)	5
Sales drop after patent expires	70% sales drop for 5 years
Exchange rates (SEK/ foreign currency)	
Exch. Rate (USD* - USA)	6.3
Exch. Rate (EUR - Europe)	9.1
Exch. Rate (YEN - Japan)	0.06
Exch. Rate (USD* - ERM)	6.3

*USD is used as currency in emerging markets
ERM - Emerging Markets

Source: Kaupthing research, Schrag (2004) and estimates

4.2 SENSITIVITY ANALYSIS

Within the rNPV model there are many parameters to be considered, each of which affects the value unequally much. Important parameters are varied within a likely interval while keeping the other parameters constant. The percentage

change in rNPV relative to the base case is calculated in order to highlight their inter-relationship and relative importance. The following section discusses how the intervals, for each parameter, were chosen.

4.2.1 CLINICAL TRIALS

In accordance with Rajapakse et al. (2005), time spent in each clinical phase was varied within ±50% from the base case.

Following from that estimates in literature vary between 30 – 70%, clinical cost estimates were varied within a ±50% span (Rajapakse et al., 2005; Stewart et al., 2001).

Since the base case makes use of a drug targeting only one indication developed by a biotechnology company, a 70% interval is believed to be too wide and the cost is instead varied within the average reported difference, i.e. ±50%. Also, transition probabilities are estimated differently in different studies (Dimasi, 2007; Reichert et al., 2005). Hence, in order to capture roughly all earlier propounded transition probabilities, when there is no obvious reason, due to company characteristic, to exclude some values, a ±50% interval is used.

The impact on rNPV with respect to different deal structures is tested in two ways. First, the base case scenario where a deal is met in the beginning of phase 2 is tested with different royalty rates. A span is chosen to cover all royalty rates reported as good guidelines when a deal is done while the project is in clinical phase, resulting in that the royalty rate is varied within a ±5% interval. Second, the impact on the rNPV is tested with respect to different agreement entry points; entering an agreement in phase I, phase II or phase III, respectively. An agreement met at a later stage is assumed to follow the royalty rate guidelines as discussed above and assumed to have an up-front payment of the same size as for deals met in earlier phases (i.e. an USD 40m up-front).

4.2.2 REVENUES

Two main revenue drivers are price and market share. A drug's price is one of the most difficult parameters to estimate. Even with a product consisting of the same mAb, the price may differ considerably. Schrag (2004) finds that the yearly drug cost per patient for different regimen containing the same mAb stretches between USD 21 000 to 31 000. Following from the uncertainty of the pricing of drugs, the price component is varied within ±50%. The market share is varied within 5% – 20%, with 10% as the base case. Although Datamonitor (2006) estimates the potential penetration rate for five different colorectal cancer mAbs to be within 3% - 70%, I argue that for practical applications it is more useful and realistic to test a model within a somewhat more limiting span of values. That is because each product has unique properties and short term after market analyses have been conducted, changes in market share estimates from 3% to 60% are probably very rarely seen among professionals.

4.2.3 DISCOUNT RATE

The discount rate is set to vary as to include almost the entire spectra of different discount rates observed to be in use, as described above. From this follows that the discount rate is varied within a ± 5 % interval.

4.2.4 PATENT PROTECTION

The patent protection period is seen as a relatively uncertain parameter and is therefore tested within a ±5 year interval compared to the base case. This follows from that biologics tend to have a rather complex patent structure and the future outlook for generic competitions is unclear.

The generic threat, i.e. generic products enters the market resulting in a sales drop, is modelled by two different scenarios: either smooth or abrupt. The smooth sales drop reflects the expected less dramatic sales drop if the patent protection for biologics remains different from small molecules. The abrupt sales drop mimics

the substantial generic threat faced by small molecules today (used as base case). The smooth drop is modelled by assuming a constant 15% year over year sales drop as market exclusivity rights expire, while an abrupt sales drop is modelled through a 70% year over year sales drop.

TABLE 5: SENSITIVITY ANALYSIS

Changes made to the different parameters compared to the base case

Input	Change to base case
WACC	±5ppt
Development time	
Time - Phase I	±50%
Time - Phase II	±50%
Time - Phase III	±50%
Time - Filing	±50%
Development costs	
Cost - Phase I	±50%
Cost - Phase II	±50%
Cost - Phase III	±50%
Cost - Filing	±50%
Transition probabilities (%)	
Prob - Phase I	±20ppt
Prob - Phase II	±20ppt
Prob - Phase III	±20ppt
Prob - Filing	±10ppt
Time to peak sales	±2 years
Price ($)	±50%
Royalty (%)	±5ppt
Market share (%)	+10ppt / -5ppt
Patent expiry from phase I	±5 years
Loss carried forward	±5 years
Sales drop after patent expires	abrupt /smooth
Exchange rates (SEK/ foreign currency)	
Exch. Rate (USD* - USA)	±50%
Exch. Rate (EUR - Europe)	±50%
Exch. Rate (YEN - Japan)	±50%
Exch. Rate (USD* - EM)	±50%

*USD is used as currency in emerging markets

EM - Emerging Markets

4.3 SCENARIO ANALYSIS

The scenario analysis, where two variables are changed simultaneously, were constructed to represent key decisions in biologic drug development and on variable sets identified as important in the sensitivity analysis. Below follows a short discussion of the choice of each set of parameters.

Market share and price: Market penetration may require considerable advertising and public efforts, and price setting strategies may be limited by government regulations (Rajapakse et al., 2005). This scenario investigates how different strategies with respect to both price and market penetration affect the rNPV.

Price and patent protection: Government regulations and the possibility that a patent will not hold in court may effect the patent protection period. This scenario captures how a company may need to adjust the price component in order to compensate for changes in the right to market exclusivity.

Time spent in development and development cost: Clinical trials may be afflicted with both delays and increased development costs. This scenario relates development time losses/gains to development time. It also captures the strategic issues related to clinical trials and currencies exposure. The base case assumes that 70% of development costs are connected to USD and the remaining to EUR. Therefore costs are varied within USD ± 8m and EUR ± 5m, with USD -16m and EUR -11m as mean values.

4.4 MONTE CARLO ANALYSIS

The Monte Carlo approach is applied on two different portfolios; one consisting of one project and a second consisting or three projects in different clinical phases.

Parameters set to be represented by a statistical distribution are: parameters describing transitions probabilities, market share, development cost and yearly costs. These parameter sets are chosen as they are more uncertain than other parameters, or data supporting estimates are build upon partly subjective and partly unequivocal data. In addition, using parameters describing both pre and post marketing approval periods highlight the versatility of the Monte Carlo approach. Assumptions are as follows: Transition probabilities, price and market share are assumed to be uniformly distributed spanning over ±20%, ±50% and -

5% to +10%, respectively. Development costs are assumed to be normally distributed so that a 95% confidence interval spans over the ±50% range used in the sensitivity analysis. Tables 6 and 7 summarize the model inputs.

TABLE 6: DEVELOPMENT COSTS

Parameters represented as normal distributions.

	USD		EUR	
Phase	**Mean cost (m)**	**Std. Dev**	**Mean cost (m)**	**Std. Dev**
Preclinical	-30	7.6	-21	5.3
Phase I	-16	4.1	-11	2.9
Phase II	-19	5	-13	3
Phase III	-48	12	-33	8
Filing	-1	0	-1	0

TABLE 7: TRANSITION PROBABILITIES, MARKET SHARE, PRICE

Parameters represented as uniform distributions.

Input	**Change to base case**	**Base Case**	**Values** +	-
Transition probabilities (%)				
Prob - Phase I	±20%	80%	100%	60%
Prob - Phase II	±20%	54%	74%	34%
Prob - Phase III	±20%	64%	84%	44%
Prob - Filing	±10%	90%	100%	80%
Market share (%)	+10% / -5%	10%	20%	5%
Price ($)	±50%	160,000	240,000	80,000

5 RESULTS AND DISCUSSION

5.1 SENSITIVITY

The tornado diagram in Figure 9 shows the sensitivity of rNPV to single input parameters. The single most important input parameters are market share and price, followed by royalty, the transition probabilities and time spent in development. These results are in line with Bode-Greuel and Greuel (2005) who finds that the value of R&D projects is most sensitive to sales forecast and in particular for projects being in clinical trials. Important difference is that this model does in addition to Bode-Greuel and Greuel (2005), also recognize development time as an influential value driver.

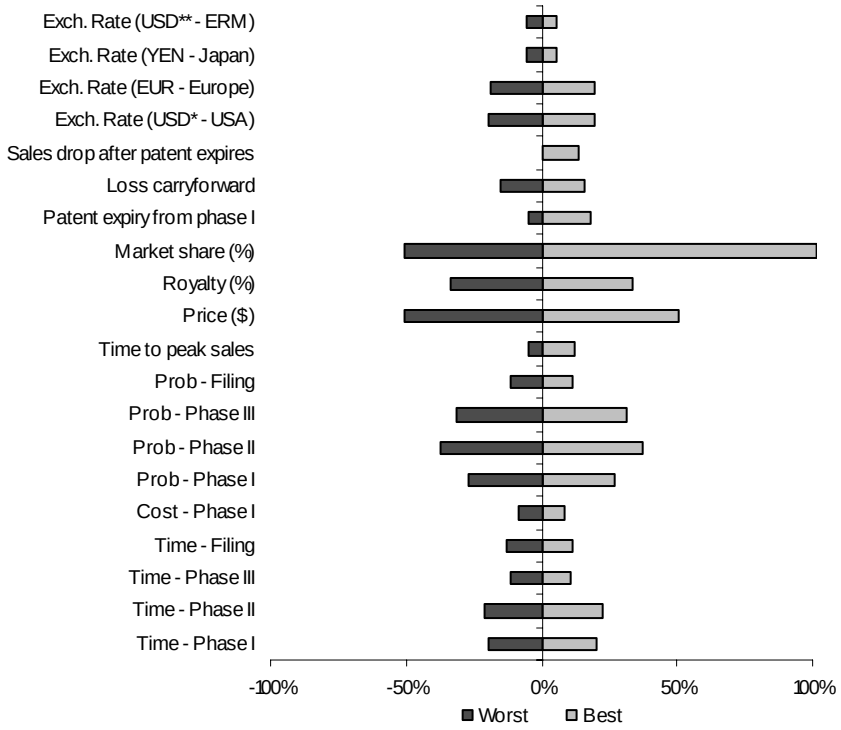


FIGURE 9: SENSITIVITY TO RNPV TO INPUT PARAMETERS

The vertical axis intersects the horizontal axis at the base case. The most influential parameters are: market share and price.

The two most important parameters, price and market share, are based upon strategic pricing decisions as well as sales force and marketing strategies. Since it

is assumed that the projects are being out-licensed these parameters will reflect the partner company's strategy and sales skills.

The third most important set of parameters are the transition probabilities, the company's and the partner company's ability to succeed in clinic. This indicates that if the originator company or the partner company has a track record better than average, i.e. have succeeded in bringing products to the market more often than the average company, drug candidates originating from such companies should be valued with a premium and vice versa.

Time spent in development is important even though it is assumed that a deal is met in phase I and that the partner takes on all development cost thereafter. The reasons for this are that most of the revenues will be generated during a limited period of time and a delay in development lowers the time to capitalize on the product. This highlights the importance of a dedicated partner; a partner with both the resources, skills and the intention to carry out clinical trials rapidly and correctly. It also stresses the importance of having a good continuous dialogue with the authorities as having to redo a study or send in additional information, hence delaying the project, will have large negative impact on the rNPV of the project. The tornado diagram is based on that a deal is met in phase I but the development time seems to almost be as important regardless of in what development phase a deal is done as indicated in table 8.

TABLE 8: RNPV DUE TO CHANGES IN DEVELOPMENT TIME

Changes in development time affects the rNPV value almost as much regardless of in what development stage a deal is met.

		deal phase II		deal phase III	
Input		+	-	+	-
Development time					
Phase I	±50%	-19%	20%	-20%	24%
Phase II	±50%	-21%	22%	-22%	27%
Phase III	±50%	-12%	11%	-13%	12%
Filing	±50%	-13%	12%	-15%	13%

Time spent in development seem to more critical in earlier phases. These results are based on relative changes to input parameters where phases with longer development times have been evaluated within a larger absolute value span

compared to phases with shorter development times, resulting in that the result is biased toward more time-consuming development phases. However, it highlights that even though a project has many years in clinic before reaching the market, every delay seriously affects the rNPV negatively.

Biologics are generally considered to be less exposed to generic replication after patent expiry than small molecules are. This has been seen as a great advantage. Only considering the effect that biologics may experience a less steep sales drop after patent expiry, the effect does not seem to be that important for early stage projects. The sales drop effect will of course be more important as time for patent expiry getting closer, but according to this model there are many other factors that are more important for early research projects.

Exchange rate fluctuation tends to be of less importance. It is however important to remember that sales revenues in the base case are spread among four different currencies and therefore are the currency risk is relatively low. If instead the majority of revenues were coming from one market the impact of currency fluctuations would probability look much different.

5.2 SCENARIO ANALYSIS

The result of changing the yearly drug cost (price) and market share is shown in Figure 10. Small price changes roughly correspond to an equal relative change in market share. In Figure 10 points A, B and C have the same rNPV, derived from different pricing and market shares which could be the result of different market and pricing strategies. By moving to point B from A, a 12% price increase together with a 12% lower market capture will result in about the same rNPV as the base case. As changes grows larger market share gets more important. It is for instance worth more to capture 40% more market share than being able to price the product with a 40% premium. This analysis can be useful for evaluating different sales and marketing strategies and evaluate their impact in different markets.

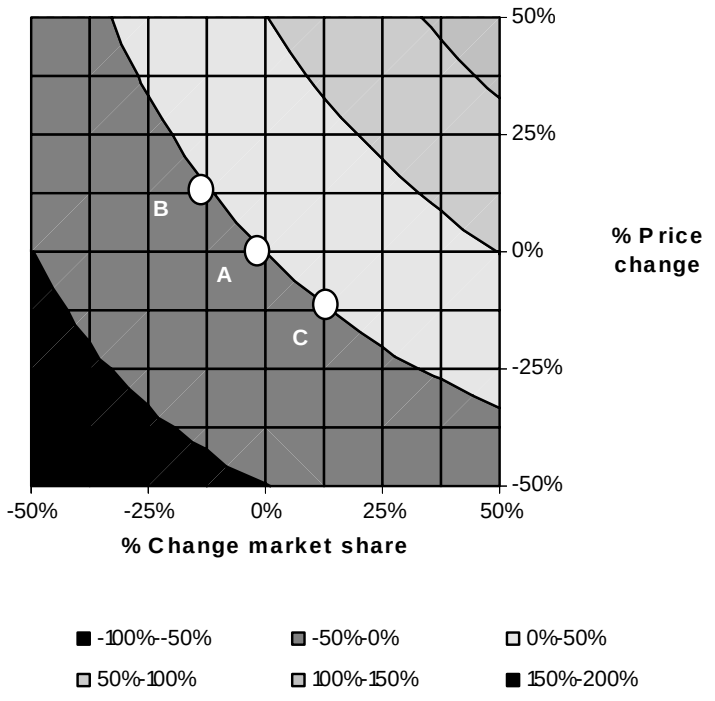


FIGURE 10: MARKET SHARE AND PRICE

Portfolio rNPV for simultaneous variations in market share achieved and yearly drug cost (price). Small price changes do roughly correspond to an equally large relative change in market share but as changes gets larger market share get more important.

In this model, for products in early clinical trials, a few years extended or shorten patent period only marginally affect the derived rNPV. Figure 11

illustrates the price adjustments a company need to conduct in order to compensate for changes in the patent protection period and the right to market exclusivity. When being in phase I, a two year shorter market exclusivity period may be compensated with approximately an eight percent price increase. In my view, this is a relatively moderate future price adjustment needed to compensate for two entire years of market exclusivity.

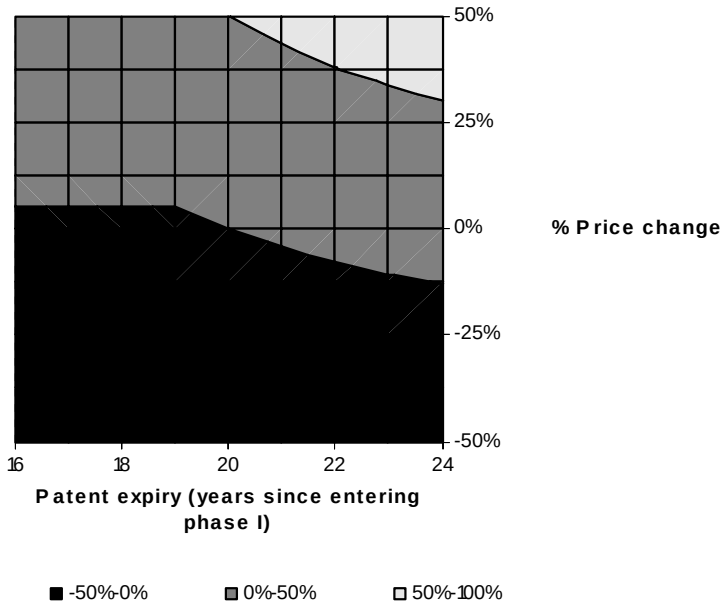


FIGURE 11: PRICE AND PATENT PROTECTION

Portfolio rNPV for simultaneous variations in yearly price per patient and patent protection period achieved. Early clinical stage drug projects can compensate the loss of a few years of guaranteed market exclusivity by a small price increase. A two year shorter patent protection period is compensated by approximately 8% price increase.

Delays in the clinic are value destroying and clinical development time reductions are value creating. Figure 12 describes the combined effect on rNPV of cost changes in total development time and changes in development costs while being in phase I. From Figure 12 follows that development time is a powerful value driver. A 12 % delay is compensated by as much as a 25% cost reduction and if trials are delayed with more than 13% then not even a 50 % cost reduction will be enough to compensate for the delay. This emphasizes the importance of well grounded development time estimates and the importance of companies being well aware of the true cost of research activities.

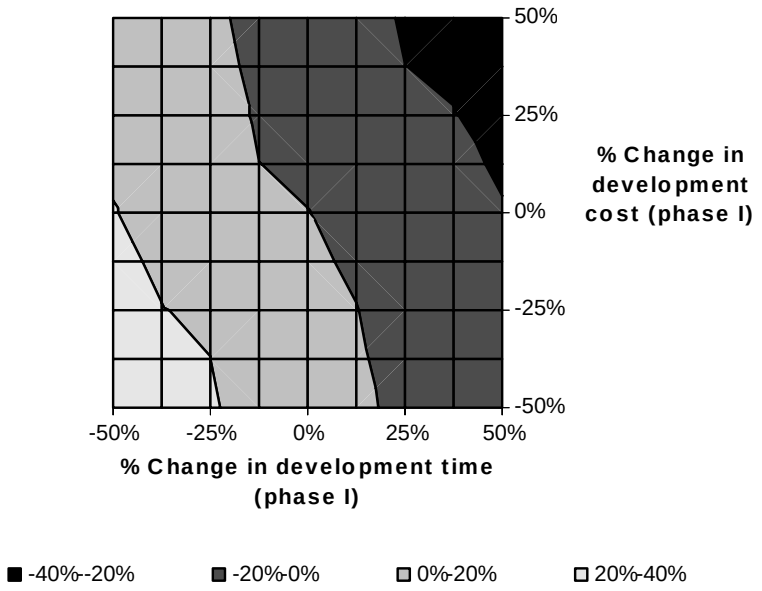


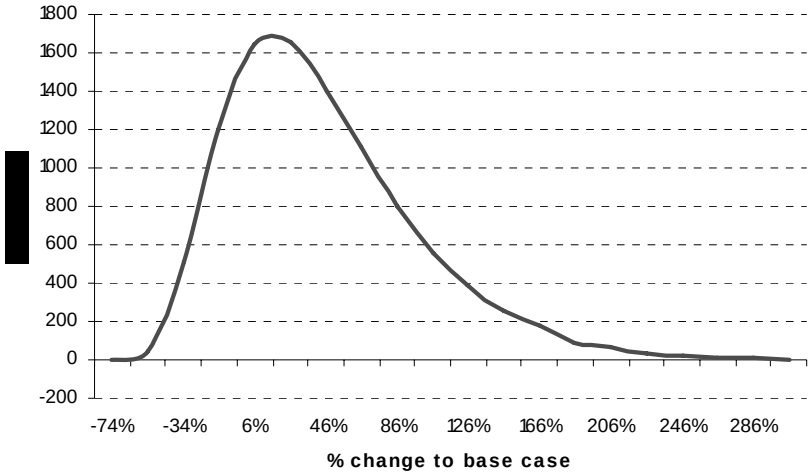
FIGURE 12: TIME SPENT IN DEVELOPMENT AND DEVELOPMENT COSTS

Portfolio rNPV for simultaneous variations in development time and development costs. Relatively changes in development time affects the rNPV more than changes in development cost.

5.3 SIMULATION

Monte Carlo simulations were conducted by repeated sampling of each of the uncertain estimates specified in section 4.4. Each probability distribution is generated through 10 000 iterations, a procedure which takes around 45 minutes to complete on an ordinary 2.6 GHz home computer. Figure 13 shows the probability distribution from a single portfolio. The underlying uncertainty gives

rise to a wide variety of possible values of which most lie between -70% up to +200% compared to the base case. This emphasizes the uncertainty involved with determining a value for single drug development candidates in early development stages. The uncertainty of costs, transition probabilities and sales forecast will decrease as more information becomes available and hence narrow the span of the project's rNPV.



N	10000
Max	416%
Min	-84%
Median	15%
Average	25%
Std. Dev.	55%

FIGURE 13: ONE PROJECT

Frequency of portfolio rNPV based on a portfolio containing one drug candidate. Monte Carlo simulations indicate that a correct rNPV for the portfolio, based on the uncertainly in the underlying estimates, can be in the range of -70% to +200% compared to the base case. The average rNPV is 25% greater than the base case and the shape of the probability curve is biased toward a larger rNPV compared to base case.

There is less variation in the rNPV with a portfolio consisting of three projects in different clinical phases, as indicated by Figure 14. The total portfolio value containing three projects spans over values from -40% to +130% compared to -70% to +200% for the single project portfolio. The variations and the risk in estimates are still large but due to risk reduction through diversification it is less than when compared to a non-diversified research portfolio. As a consequence, a calculated rNPV of a company with a well-filled diverse pipeline should be more stable and hence more correct compared to a company having only a few projects in the pipeline.

If the distribution in Figure 14 represented the value of a company listed on some stock exchange then the x-axis would be the rNPV value per share instead of percentage change to some base case. If the stock is then traded within the range of likely values the market price would equal the value from the model. Otherwise, if the stock is traded with a price exceeding the value range then the stock would be considered fundamentally expensive or vice versa.

N	10000
Max	148%
Min	-50%
Median	22%
Average	24%
Std. Dev.	29%

FIGURE 14: THREE PROJECTS

Frequency of portfolio rNPV based on a portfolio containing three different drug candidates. Monte Carlo simulations indicate that a correct rNPV for the portfolio, based on the uncertainly in the underlying estimates, can be in the range of -40% to +130% compared to the base case. With more projects the effect of uncertain estimates decreases.

6 CONCLUSIONS

According to the valuation model developed in this project, the most important parameters are: Market share, price, transition probabilities and time spent in development. For early stage drug candidates, time spent in development are almost as critical as the price to the risk-adjusted net present value. This indicates that news regarding proceedings in development, both with respect to development costs and time spending, are the most important events for early stage research projects.

Biologics are believed to be better off after patent expiry compared to small molecules since it has not been proven that generic biologics are structurally and functionally identical to their branded original, which is a prerequisite to being granted reduced clinical trials procedures. The impact on the rNPV of a branded early stage biologic drug candidate from this advantage is relatively low.

Monte Carlo simulations are a useful method to quantify uncertainty in underlying estimates. The resulting probability facilitates the interpretation of the resulting rNPV value. The weakness of the method is its time consuming simulations which are partly a consequence of the model being implemented in Microsoft Excel.

7 ACKNOWLEDGEMENTS

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APPENDIX

APPENDIX 1 – CANCER DEALS WITH BIOTECHNOLOGY COMPANIES

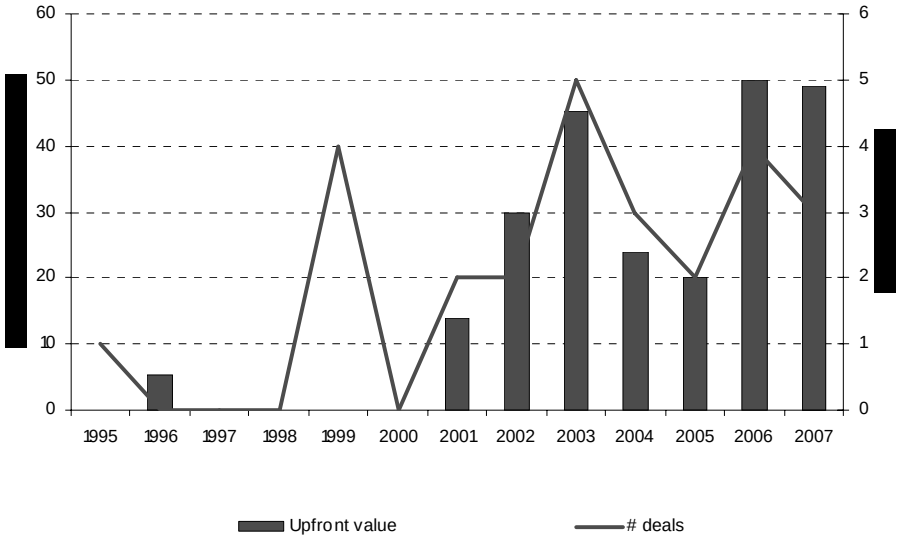

FIGURE 15: AVERAGE UPFRONT VALUE

Shows the average upfront value of disclosed cancer treatment deals met with biotechnology companies during 1995 – 2007. Source: Medtrack (2008-01-14)

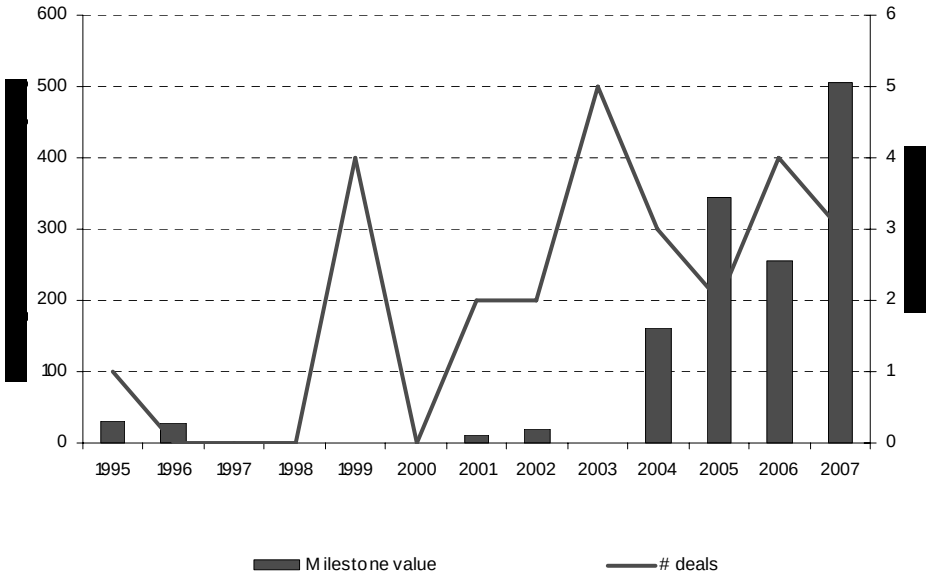

FIGURE 16: AVERAGE MILESTONES VALUE

Shows the average milestone value of disclosed cancer treatment deals met with biotechnology companies during 1995 – 2007. Source: Medtrack (2008-01-14)