Determining the value of drug development candidates and technology platforms

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Abstract

This paper explains a comprehensive and systematic approach to evaluate drug development projects and technology platforms, using an augmented version of net present value (NPV). The benefits of financial models for value-driven project and portfolio management, licensing negotiations and investors' decisions are discussed.

INTRODUCTION

The value of biotechnology companies is driven by anticipated future product and revenue streams, or by the impact that a technology platform is expected to have on the value of assets. Furthermore, ownership of intellectual property rights, well-educated scientists and extensive experience of the management team add to the value of the company by reducing R&D and market risk. This paper focuses on the quantitative financial evaluation of technologies and product development candidates, the major determinants of company value.

Quantitative financial evaluation of biotechnology investments is not an easy task. Biotechnology companies are typically dealing with innovative and, therefore, particularly uncertain technologies and drug development candidates. The applications and the impact of a technology are often not clearly defined, and new drug development targets are not validated. However, financial evaluation and risk analysis are essential for the following reasons:

- Investors request financial indicators and defined value propositions to fund biotech operations.
- Senior management of biotech companies needs to understand the risk and expected financial impact of their projects for prioritisation and maximisation of company value.
- While establishing technology partnerships and licensing agreements, the involved parties need to understand the financial value generated by a deal, and to ensure market-conformity and fair deal terms.

The determinants of value in the biotechnology industry are expected cash inflows from marketed assets, R&D and market uncertainty, cost and speed of development, and strategic opportunities arising from technologies and projects. The revenue-generating products of biotechnology companies are usually not marketed drugs, because the financial power to support late stage development and launch is often lacking. Instead, development candidates are licensed out or developed with a partner, leading to various models of cost/revenue share. Sometimes, more than two partners are involved. Only quantitative financial analysis that properly reflects the risks and the choice of projects will reveal to what extent the involved parties benefit from overall project value.

This paper describes a widely accepted financial model, an augmented version of the net present value (NPV) algorithm which is adapted to the needs of R&D-

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The augmented NPV algorithm represents risk and decision points adequately in financial models

driven industries.[1–7] It is sometimes also called risk-adjusted NPV or expected NPV. The authors prefer the term 'augmented NPV' because as well as representing R&D and commercial risk in NPV models, such models are also used to investigate the impact of operating options and alternative development strategies on the value of R&D projects.[8,9] Augmented NPV better describes the value of managerial flexibility. If based on solid assumptions, the augmented NPV provides the required information to support value-driven decisions of managers in biotechnology companies, investors and parties involved in licensing and technology partnerships.

EVALUATION OF EARLY STAGE R&D PROJECTS: CAPTURING UNCERTAINTY AND THE VALUE OF FLEXIBILITY IN FINANCIAL MODELS

Before financial models can be created, R&D portfolios may require some structuring

Before financial models can be created, R&D portfolios may require some structuring. For example, several drug discovery projects (eg addressing different targets) may be undertaken in parallel to support the development of one new product, thereby increasing the probability of success. The structuring process would outline reasonable decision points at which research progress would be assessed and activities focused on the most promising path. Projects with low priority may be licensed out or terminated, leading to incremental licence value in the earlier or zero value in the latter case. Conversely, one drug discovery project (eg based on a new target) may give rise to several development candidates for a variety of therapeutic indications. Again, companies would select some therapeutic indications for in-house development, while drugs for other indications may be licensed out. In summary, the structuring process would create a transparent portfolio of projects with different commercialisation strategies and value propositions. Financial modelling can, in a reiterative process, support project prioritisation.

Project target profile

Once therapeutic indications of interest are identified, project target profiles (PTPs) should be established to define the deliverables of preclinical and clinical development. PTPs should represent products that are both approvable and competitive enough to ensure sufficient revenues. PTPs are useful not only for clinical but also for preclinical projects even when development candidates are to be licensed out because the screening cascade can be optimised with respect to the features needed to make a future product competitive.

PTPs are the basis for the product development plan on the one hand and for the sales forecast on the other hand. The PTP facilitates the definition of patients eligible for treatment and determines the clinical trial end-points. Furthermore, PTPs allow the identification of relevant competitors, the assessment of market risk, and the generation of a meaningful sales forecast even in early stage development.

The net present value (NPV) algorithm as a commonly used tool to evaluate investments: Theoretical background

The NPV represents the value generated by an investment. NPV is a forward-looking financial indicator to support the allocation of resources if maximisation of value is the objective.[10] The NPV algorithm requires assumptions on all incremental cash inflows (eg revenues, royalties) and cash outflows (eg R&D and marketing costs, costs of goods sold) associated with a project. Cash flows that occurred in the past are excluded as they are sunk and cannot be retrieved by any decision. For the evaluation of biotechnology projects it is suggested that a project's cash flows at least up to the end of patent protection should be included. Cash flows beyond patent protection can

be represented as a terminal value, assuming that a continuous revenue stream can still be expected beyond patent expiry (usually at a reduced level). The impact and kinetics of generic competition can be assessed individually, or a categorisation (eg low, moderate, high generic impact defining a percentage reduction of net cash flow from the last years' level) could be applied, reflecting the expected characteristics of the product (eg ease of manufacturing, sales level before patent expiry) in a formalised way, as uncertainty for the remote time of patent expiration is high and often does not allow more precise estimates.

The NPV equation is:

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

where C = net cash flow

r = discount rate according to capital asset pricing model/ weighted average cost of capital (see below)

t = variable for the period in which the remaining future cash flows are valued as terminal value

$\frac{C_{\mathrm{TV}}}{r(1+r)^t}$ = terminal value (assuming steady-state cash flows)

Net cash flows are usually determined for yearly intervals. The NPV is determined by discounting net cash flows to today's value by applying a discount rate *r*. The sum of the discounted cash flows represents the value of the project: a positive value indicates that a project is likely to create value and is worth funding (with preference for higher NPV projects); projects with a negative NPV are unlikely to create value and should be terminated.

The discount rate *r* reflects the opportunity cost of capital or, in other words, the return an investor would demand for an investment of similar risk.[11] Risk in this context means capital market risk (not the risk of development or market failure). Investors wish to generate at least the same return they would expect from investing in stock with similar systematic risk.

From the perspective of a company, the discount rate is the cost of the capital with which operations are funded. The capital asset pricing model (CAPM) is commonly used to derive an appropriate return on equity, although it does not reflect investors' behaviour perfectly:

$$r_{\mathrm{e}} = r_{\mathrm{F}} + \beta \times (r_{\mathrm{M}} - r_{\mathrm{F}})$$

where r_{e} is the expected return on equity, r_{F} is the risk-free rate, β is the beta value of the security and $r_{\mathrm{M}} - r_{\mathrm{F}}$ is the difference between the expected return on the market and the risk-free rate.

The CAPM assumes that a risk premium (defined as the difference between the average capital market return and the risk-free rate) is requested by investors for accepting the risk to invest in assets whose value is highly volatile. The risk premium is given an appropriate weight through beta. The beta factor is company-specific and describes the covariance of a company's equity with the market. For example, if a company's beta is greater than 1, the volatility of its stock is larger than that of the market, making the stock more risky. In such a case, CAPM would result in a higher discount rate by giving the risk premium more weight.

If a company has not only issued equity but also debt, an extension to the CAPM is applied, reflecting the usually lower return requirement for debt, the weighted average cost of capital (WACC). The WACC also accounts for the tax shield provided by debt.

$$r_{\mathrm{WACC}} = \frac{E}{E+D} r_{\mathrm{e}} + \frac{D}{E+D} r_{\mathrm{d}}(1 - T_{\mathrm{C}})$$

where E = equity
D = debt
r_e = expected return on equity
$r_d(1 - T_C)$ = after tax cost of debt

What would be a typical discount rate for a biotechnology company today? Benchmarks indicate that discount rates used for big pharmaceutical companies are in the order of 10 per cent, those for public biotechnology companies are in the range of 20 per cent, and those for private biotechnology companies (venture capital funded) are in the order of 30 per cent. Analyses of the European Private Equity & Venture Capital Association (EVCA) indicate, however, that annualised net returns for private equity investments were only around 10 per cent for the time period from 1980 to 2003,[12] demonstrating that return expectations are not always achieved.

The difference of discount rates between major pharmaceutical companies versus mid-size or biotechnology companies, according to the logic of CAPM, would be driven by differences in beta. The authors investigated beta values of different categories of listed pharmaceutical companies (drug discovery, early development, mid-size and fully integrated pharmaceutical companies) over the years 1997 to 2002. Our results indicate a strong correlation of beta with the average risk of the respective R&D/marketing activities (correlation coefficient: 0.98).[13] Average beta values per category ranged from 1.70 (discovery focus) to 0.39 (fully integrated), supporting the significant differences between the applied discount rates. Analogous conclusions were drawn by Myers.[14]

Decision trees are a useful tool to represent options

Using an augmented version of NPV that reflects the uncertainty and decision options of pharmaceutical R&D

Originally, the NPV algorithm has been developed for 'static' investments where managerial actions have virtually no impact on value. The situation is, however, different for the development of new drugs. In R&D, the risk of development failure is a great concern, especially in view of the significant investments to be made. It is therefore essential that the financial models used to evaluate R&D projects reflect the uncertain outcomes of preclinical and clinical studies and the respective managerial decision options. In the presence of risk, managerial options have value because they minimise the impact of negative outcomes (for example, by minimising costs), and they allow managers to maximise the value of the project by taking advantage of the new information.

Decision trees are a useful tool to represent development risks and decision options (see Figure 1). They illustrate the step-wise investment reflected by R&D milestones. Decision trees should focus on those activities that are essential for the completion of development and for the achievement of a competitive product profile. They illustrate decision points, ie the time at which the arrival of new results is expected. Typically, decision points occur at completion of essential preclinical and clinical trials. Decision-relevant potential outcomes are outlined with a level of differentiation driven by the decision options managers have. Probability estimates are assigned to each potential outcome (see below). There may only be the choice between 'stop' and 'go'; however, sometimes 'go' options may come along in several different ways. It may also be relevant to differentiate the result of the pivotal clinical trials with respect to the impact on product profile and competitiveness. It is often useful to create more than one sales forecast to link the commercial potential of a drug to distinct trial results. The financial evaluation will more accurately reflect the value of a project if not only the minimum registration-relevant results, but also potential upside scenarios based on superior efficacy are included in the evaluation.

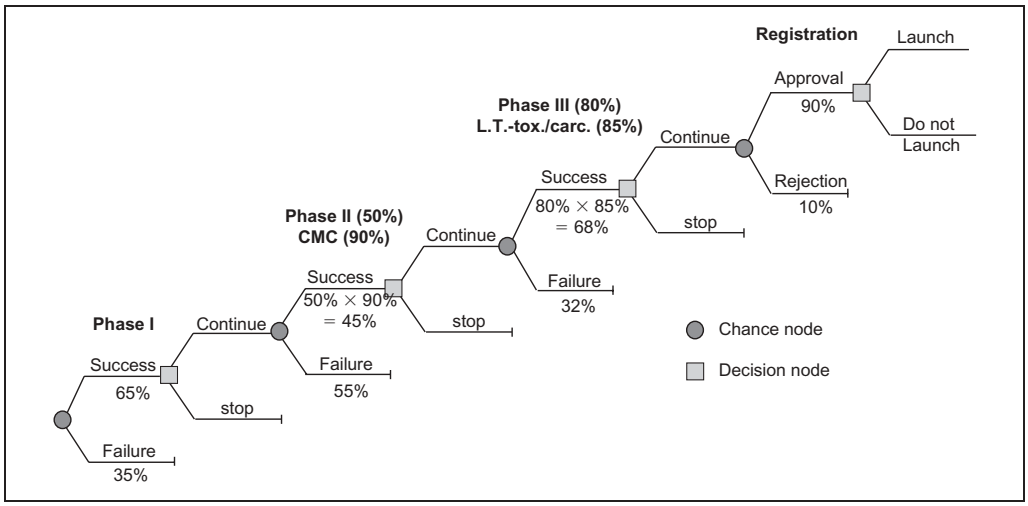

Figure 1: Example of a decision tree for a clinical development candidate. Decision trees should include those uncertain outcomes that drive managerial actions and have an impact on value. Information from different independent studies completed in parallel (eg clinical and long-term animal toxicology) is grouped in development milestones, reflecting the project's optionality. Chance nodes indicate potential outcomes, whereas decision nodes represent possible managerial actions. Decision trees should be modelled individually and may differ with respect to level of detail and number of decision points. Probabilities for independent outcomes, eg clinical and chemical and manufacturing control (CMC), are multiplied to reflect the overall probability of success at a development milestone

The augmented NPV model does not only represent project value, but also illustrates the value of individual scenarios

Decision trees illustrate alternative project scenarios. These scenarios are evaluated individually and probability-adjusted in a way that they receive their appropriate weight in the overall augmented NPV, which is the 'value tag' assigned to the project. However, the augmented NPV model also reveals the value of individual scenarios, or the value that a project may have in the future, depending on possible trial results or changes in the marketplace. The case study below illustrates how the augmented NPV is obtained.

Case study

The company BestBiotech is developing an innovative drug (BB1) for the treatment of ovarian cancer. The initial label at launch is assumed to be second line treatment in patients who relapse after first-line treatment with a taxane and/or *cis*-platinum. The project is currently in advanced preclinical development. The evaluation is based on the label mentioned above.

For the sake of simplicity, the decision tree (Figure 2) illustrates only chance nodes, assuming that the project will have an intrinsic value if development milestones are successfully completed; should BestBiotech decide not to complete development, the project could be sold to another company which would continue development. Stage-related probabilities of success are indicated in the decision tree. In Phase II, individual probabilities are assigned to both clinical and chemical and manufacturing control (CMC) activities that are independent from each other (60 and 90 per cent, respectively), but similarly important for the decision to go to Phase III. The tree gives rise to six development scenarios. The probability of a particular scenario is calculated by multiplying its stage-related probabilities; each stage-related probability is conditional on the success of previous stages.

The epidemiology-based market model contains probability distributions for uncertain variables such as fraction of patients receiving first- and second-line drug treatment in the USA and the five

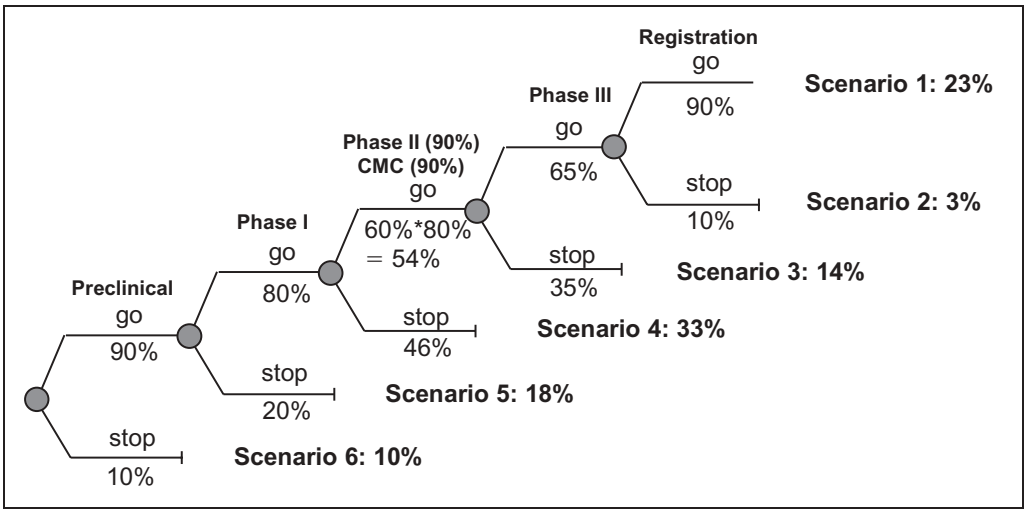

Figure 2: Decision tree for the case study

major European countries. The analysis of competitors in development suggests that two or three strong new products will be launched earlier than or at the same time as BB1. BestBiotech developed a systematic algorithm to determine a potential patient share assuming no new competition and to correct this number for the impact of assumed strong competitors, depending on the amount of compounds in development (eg 30–60 per cent (uniform distribution) of potential share could be lost to two future competitors). A PERT distribution was applied to model the ex-factory price per treatment (ranging between €10,000–15,000 in the USA and €5,000–11,000 in the EU). Launch is projected to the year 2012, and peak patient penetration is expected five years after launch.

Calculation of NPV: Table 1 illustrates the cash flows forecasted for BB1, assuming successful completion of development and marketing. Net cash flows were inflated at a rate of 2 per cent and discounted at the company's discount rate of 15 per cent. Expiry of market exclusivity is assumed for the end of 2022. It is assumed that net cash flows decrease by 75 per cent in the following year owing to generic competition. The sum of discounted net cash flows (including terminal value) indicate a mean NPV of €178m for the launch scenario (scenario 1, Figure 2 and Table 2). The augmented NPV comprising all scenarios can be obtained through two ways. The first approach consists of determining individual NPVs for all scenarios that are weighted by their respective scenario probabilities. Probability-weighted scenario NPVs are then added, resulting in an overall augmented NPV of €31m for BB1 (Table 2). The second approach works by calculating values backwards: (1) value of BB1 at the time of launch, taking into account the cash flows from launch onwards; (2) value at the time of submission, while both outcomes (approval and rejection) are taken into account according to their respective probabilities; (3) value at start of Phase III; continue rolling back across all milestones until the project's present value is obtained. Both methods lead to identical results, if applied at the same level of detail and accuracy of discounting. However, the first approach may be more comfortable for complex decision trees with more than two outcomes at decision points, and for complex cash flow profiles.

Monte Carlo simulation: If uncertain variables are defined as probability distributions, simulation software supports the generation of frequency histograms, probability plots, and other statistical data such as mean, mode or standard deviation. The standard deviation and minimum and maximum values of BB1's augmented

Table 1: Cash flows (€000) of project BB1

	Year																		
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	
Preclinical development	−431	−500	−500	−500	−500															
Phase I		−400	−400																	
Phase II			−1.275	−1.275																
Phase III					−7.000	−7.000														
Registration							−500	−500												
Internal costs	−87	−158	−158	−158	−158	−158	−158	−158												
Techn. product dev.	−2.323	−1.500	−1.500	−6.333	−1.167	−1.167	−333	−333												
Launch/ marketing exp.							−18.120	−36.240	−36.240	−36.240	−27.180	−27.180	−25.602	−25.886	−26.186	−26.501	−26.833	−27.180	−26.993	
G&A costs 5%									−821	−3.313	−5.434	−7.178	−8.534	−8.629	−8.729	−8.834	−8.944	−9.060	−8.998	
CoGS									−1.020	−4.119	−6.757	−8.923	−10.607	−10.722	−10.843	−10.970	−11.102	−11.240	−11.156	
Sales									16.417	66.255	108.688	143.559	170.680	172.572	174.571	176.675	178.885	181.202	179.951	
Net cash flows	−2.841	−2.558	−3.833	−8.266	−8.824	−8.325	−19.111	−37.232	−21.665	22.583	69.317	100.277	125.936	127.335	128.813	130.370	132.006	133.721	132.805	
Inflation rate 2%	*1,00*	*1,02*	*1,04*	*1,06*	*1,08*	*1,10*	*1,13*	*1,15*	*1,17*	*1,20*	*1,22*	*1,24*	*1,27*	*1,29*	*1,32*	*1,35*	*1,37*	*1,40*	*1,43*	
Inflated net cash flows	−2.841	−2.609	−3.988	−8.772	−9.552	−9.191	−21.523	−42.767	−25.384	26.989	84.497	124.682	159.718	164.722	169.967	175.461	181.217	187.242	189.678	
Discounted cash flows	−2.841	−2.269	−3.015	−5.768	−5.461	−4.570	−9.305	−16.078	−8.298	7.672	20.886	26.800	29.852	26.772	24.021	21.563	19.366	17.400	15.327	
Scenario NPV	177.600																			25.545 Terminal value

Terminal value assumption: net cash flows are reduced by 75 per cent after expiry of market exclusivity.
CoGS = costs of goods sold; G&A = General and Administration cost.

Table 2: Calculation of augmented NPV: €31m

Scenario	Probability (%)	Scenario NPV (€000)	Expected scenario NPV (€000)	
1	23	177,600	40,395	Launch
2	3	−49,305	−1,246	Stop after failure of registration
3	14	−23,923	−3,255	Stop after failure of Phase III
4	33	−11,627	−3,851	Stop after failure of Phase II
5	18	−6,143	−1,106	Stop after failure of Phase I
6	10	−2,841	−284	Stop after failure of preclinical
			sum: 30,653	

Monte Carlo simulation: NPV (€m)

Minimum	−68.60
Mean	30.21
Maximum	388.44
Standard deviation	84.23
Mode	−11.63

The value of R&D projects is highly sensitive to uncertainties related to the sales forecast

NPV are shown in Table 2. However, the graphical representations in Figures 3–5 may be more informative than a standard deviation. For example, the cumulative ascending probability plot in Figure 3 illustrates the uncertainty of project value. Quantitative information can directly be derived from the graph, such as the probability of a particular NPV. Similar information can be obtained for the sales forecast. Figure 4 shows a cumulative ascending plot for expected sales in year 5, indicating, for example, that the probability of exceeding €175m is about 35 per cent. Figure 5 illustrates the uncertainty of the sales forecast up to patent expiration, depicting mean, standard deviation and the 5/95 per cent percentiles.

How to obtain credible assumptions

The creation of an NPV model may appear straightforward for a trained financial expert. However, the generation of credible assumptions requires considerable effort. Financial project evaluation includes assumptions on future costs and revenues. In addition, risk must be assessed in a quantitative way as probability distributions. The value of R&D projects is most sensitive to uncertainties of the sales forecast (in particular, for projects in the clinical stage) and the probability estimates in the

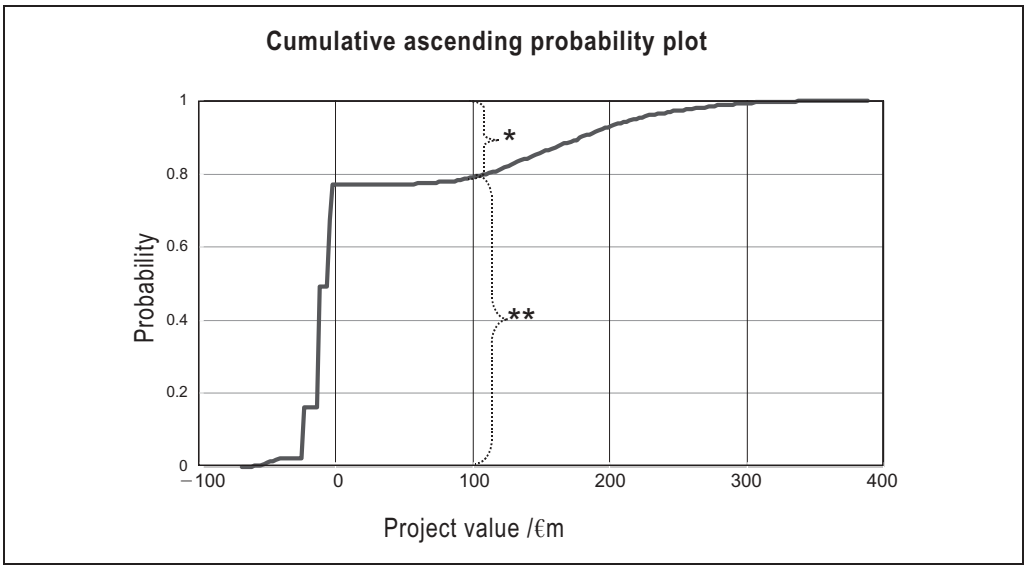

Figure 3: Monte Carlo simulation: uncertainty of NPV (*probability that the NPV > €100m = 20 per cent; **probability that the NPV ≤ €100m = 80 per cent)

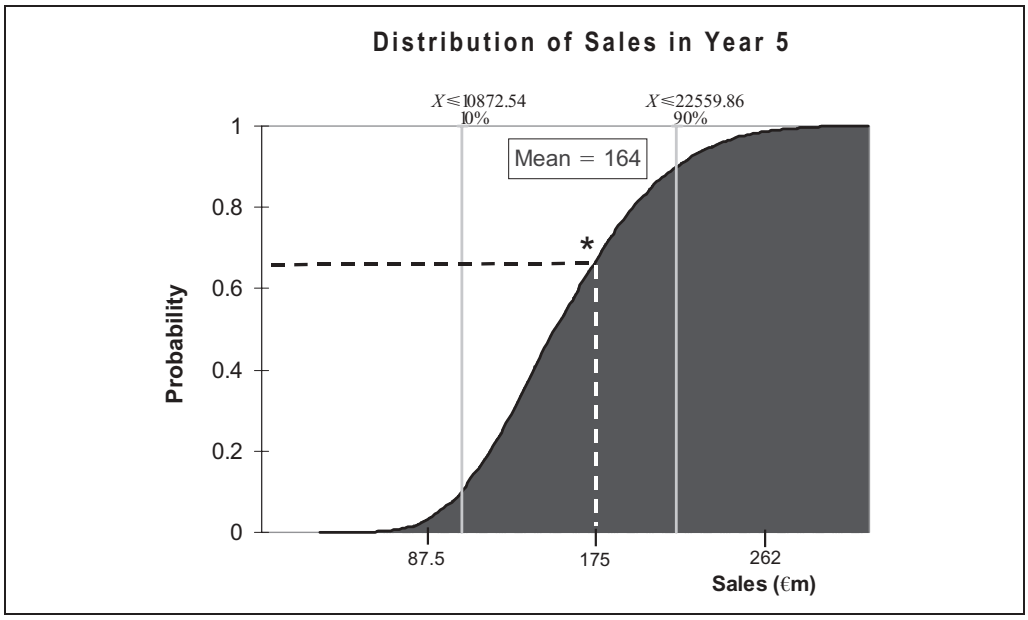

Figure 4: Monte Carlo simulation: probability of achieving defined level of sales (*probability that sales in year 5 > €175m ≈ 33 per cent)

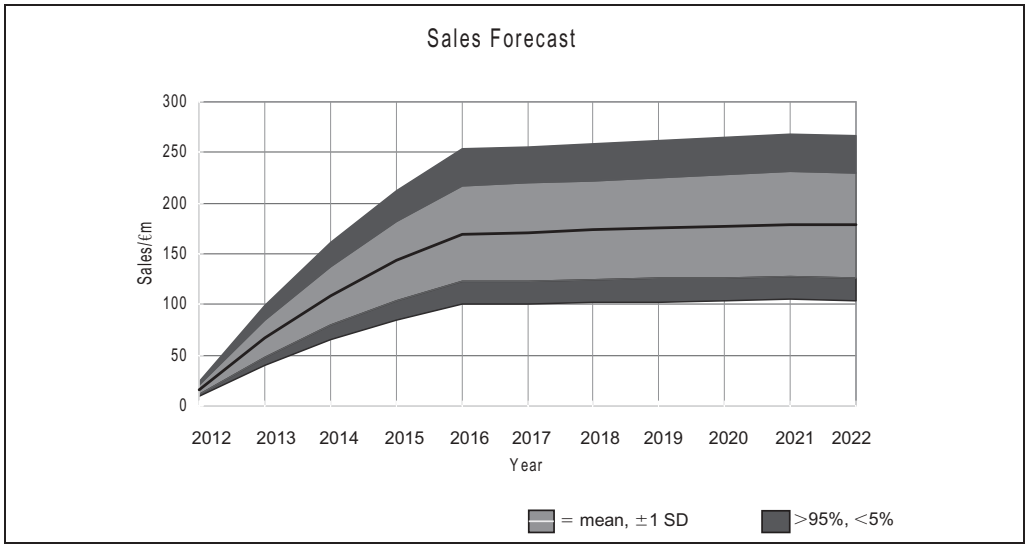

Figure 5: Monte Carlo simulation: uncertainty of sales

decision tree. The following gives some recommendations on how trustworthy assumptions could be generated, with special emphasis on early stage projects.

Sales forecast

The uncertainty of sales forecasts decreases with progressing development, as more information becomes available about the properties of the development candidate in comparison to existing and future competitors. Sales forecasts are more difficult to prepare for preclinical and early clinical candidates, because the spread of potential outcomes is larger, and the health political environment is more likely to change. However, trustworthy sales forecasts can be generated for early stage projects if the following approach is applied:

- Create epidemiology-based forecasts whenever possible.
- Use the project target profile for the identification of the patients eligible for treatment and for the definition of patient subgroups for which market penetration may differ.
- Estimate the positioning of the future product in the context of treatment alternatives based on medical need on the one hand and on anticipated

efficacy profile on the other hand.

- Consider alternative market scenarios and product profiles.
- Investigate the acceptance of the new product through focused surveys.
- Do conjoint analyses to obtain information on physicians' preferences for particular product attributes in relation to product price.
- Use probability distributions (eg triangular, uniform, Poisson, programme evaluation and review technique – PERT) instead of single point estimates for uncertain variables, such as prevalence, diagnostic rate or patient penetration.
- Make assumptions on a feasible price range based on thorough analysis of competitors, extensive market research and the future availability of generics.
- Apply Monte Carlo simulation to investigate the probability of achieving a particular level of sales, properly taking into account the uncertainty of assumptions.

Probability distributions

When we throw a die, we can exactly calculate the probability (in other words, frequency) of a particular outcome. We are able to predict the probability based on our knowledge of the die, and we could prove that our calculation is correct by throwing the die many times. Unfortunately, such a 'frequentist' approach does not apply to pharmaceutical R&D. We have no knowledge about the frequency of random events in drug development. There is, however, some information on attrition rates for particular clinical development stages,[15,16] but those benchmarks do not disclose the targeted clinical indication or the reason for failure, and they may not be representative for small biotechnology companies. Furthermore, therapeutic area specific information is limited and does not allow conclusions about particular indications.

Databases provide information about stage-related attrition rates

Overall, benchmarks define a range of reasonable probability estimates. For the evaluation of individual projects, however, probabilities should be judged by experts for each individual project. In addition, not only are stage-related probabilities defined, but probabilities are differentiated with respect to independent variables, such as clinical versus long-term toxicology, that may similarly contribute to the success of a development milestone (see example in Figure 1).

Experts sometimes feel uneasy about making probability estimates based on judgment, as the accuracy of such numbers cannot be proven. Furthermore, senior managers may not trust the estimates, being suspicious about overly optimistic assumptions. Risk analysis strongly benefits from the involvement of an experienced and independent moderator who facilitates the interactive discussion among experts. Different perspectives would come to light, and it is our experience that probability estimates converge among experts with increasing level of information exchange. Finally, it has proven useful to involve senior experts in a peer review process: probability estimates would be compared across projects and checked for consistency. This improves the reliability of probability estimates, and the involvement of senior managers in the process increases the acceptance of the analysis.

Cost estimates

In the absence of detailed plans, cost estimates can be derived from benchmark information.[15,16] For a defined preclinical development strategy and for Phase I, contract research organisations (CROs) would provide proposals indicating the budget requirements. The costs for clinical development beyond Phase I may be more difficult to estimate because they differ considerably depending on

therapeutic indications. Such differences are driven by the number of patients needed in a trial, and by the treatment costs per patient (eg outpatient versus intensive care treatment, cost of diagnostic procedures and co-medications, duration of treatment and requirements for follow-up). The project target profile is useful to obtain information on the clinical development cost, because it outlines the objectives of development, the mode of treatment and the clinical end-points.

Sensitivity analysis illustrates how the uncertainty of particular assumptions influences the valuation

The cost of commercialisation is often underestimated in the biotechnology industry. Salesforce and promotional expenses vary depending on the target market. Hospital products are characterised by lower marketing expenses than products promoted to specialists or primary care physicians, driven by the required number of physician contacts. However, promotional costs are also strongly driven by the competitive environment in a particular therapeutic area. For example, although oncology mostly represents a specialist market, marketing expenses have considerably increased in the past years based on an increasing number of companies active in this field, some of them having strong marketing power. The environment for hospital products has also become more difficult after the introduction of formularies.

Monte Carlo simulation shows the impact of all uncertain variables moving at random

Financial valuations are sensitive to assumptions on costs of goods sold (CoGs), as these have a direct and permanent effect on profits. CoGs may be difficult to estimate in early development. If CoGs become a threat to profitability, an acceptable CoGs range could be defined by investigating a feasible market price for a given product and this range be used in the valuation model. The risk of missing the defined CoGs target could then be addressed at the end of Phase II, when finalised market material should be available for the start of Phase III. Failing the CoGs target would thus be considered as a significant development risk.

Project and portfolio valuation must reflect a company's business strategy

Augmented NPV: Interpretation of results

The case example is given above. BestBiotech's project BB1 has a mean value of €31m, which is encouraging for a preclinical project. Depending on the overall risk and risk structure of projects >in relation to revenues and cost, projects at such an early stage range between €–10 and 35m. The value may be higher if expansion options exist and are quantified.[9]

Detailed analysis helps to explain the valuation results. Is the value driven by high expected sales, by low development risk, by an unusual cost structure or by low CoGs? Sensitivity analysis illustrates how the uncertainty of particular assumptions influences the valuation. While sensitivity analysis isolates the impact of single risky elements, Monte Carlo simulation shows the impact of all uncertainties. Monte Carlo simulation provides probabilities for particular NPV values or sales levels; it tells us how likely particular outcomes are if all uncertain variables move at random.

Quantitative financial valuation as described here provides the 'intrinsic' project value. The objective is to use facts-driven and agreeable assumptions to arrive at a valuation that is transparent and generally acceptable. In principle, the valuation of a portfolio of projects represents to a great extent the value of a biotechnology company (the value of technologies, patents or financial assets may have to be added). However, care must be taken to make realistic assumptions regarding the size of the R&D budget and other resources: not all projects may be supported by internal resources, some may only be realised in partnerships or would have to be licensed out. Consequently, the project and portfolio valuation must reflect a company's business model and portfolio strategy, meaning that for some projects only a fraction of value would be owned by the originator, while the remainder would be assigned to a licensee. To accomplish a realistic valuation, such

projects would be valued as future licence candidates (see below).

Financial valuations are used for value-based project and portfolio management. Furthermore, financial valuation results serve to communicate project and portfolio value to investors and potential corporate partners. In addition to present value, investors are particularly interested in the value uptake that will occur if the project passes development milestones successfully. Figure 6 illustrates the present and future value of BB1, assuming successful completion of milestones. This is a particularly useful representation in our experience. Time lines could be added to each milestone to illustrate when particular development results are expected. The same analysis could also be completed for the value uptake of the overall portfolio as opposed to single projects, and uncertainty could be analysed by Monte Carlo simulations. Such an analysis supports investors to judge a company's portfolio with respect to their exit strategies.

The potential value uptake of projects, assuming successful completion of development milestones, is useful information both for investors and for R&D managers

EVALUATION OF TECHNOLOGY PLATFORMS

So far, the valuation of R&D projects for which therapeutic applications can be envisioned has been discussed. However, the value of biotechnology companies is not only driven by drug development projects, but also by proprietary technologies. Such technologies are usually not limited to particular therapeutic applications, and they do not directly result in marketable drugs. Instead, technologies serve to facilitate the discovery of new drugs or the R&D process, for example:

- Discovery of innovative development targets (eg genomics, proteomics) that may support the development of new drugs with improved efficacy and/or safety.
- Chemical technologies in order to
  - — create structurally optimised development candidates with higher potency and selectivity;
  - — increase efficiency of chemical synthesis decreasing the time to start of preclinical development;
  - — optimise the production process and decrease the cost of drug substance.
- Preclinical profiling of development candidates in order to
  - — reduce development risk by

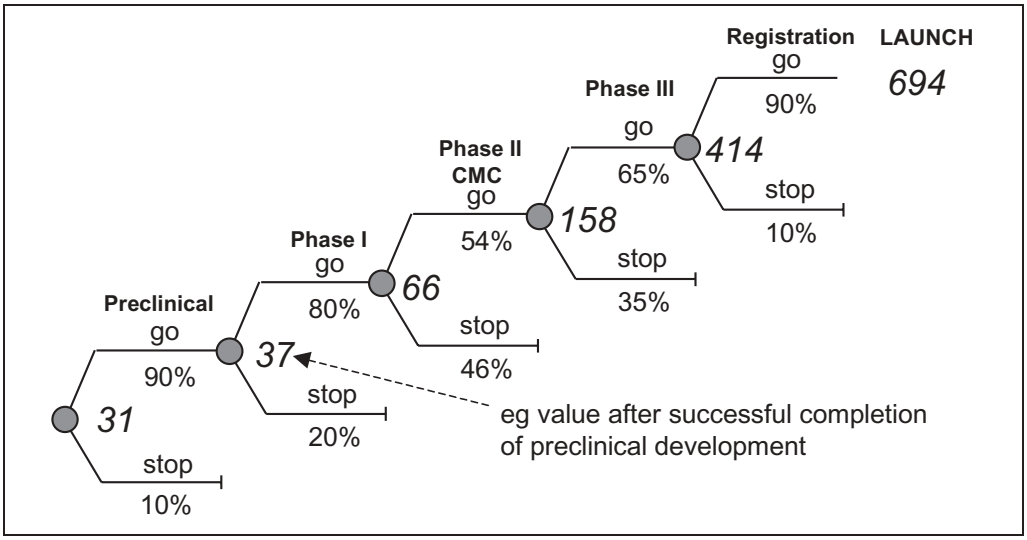

Figure 6: Value (€m) after successful completion of development milestones. The large italic numbers indicate the present and future values of the project, assuming successful completion of previous milestones (sunk costs are eliminated and discounting is adjusted)

investigating toxicity or drug–drug interactions;

— optimise efficacy and/or safety in particular patient subgroups classified by pharmacogenetics (resulting in reduced development risk, reduced development cost and increased market penetration in that subgroup);

— reduce attrition in the clinical phases.

Technology platforms add value to R&D projects

Overall, technologies add value to R&D projects by reducing time and cost to identification of a new drug candidate, by reducing R&D risk, and by improving the quality and validity of data. The effect of risk and cost reduction, reduced development time and improved product profile can be quantified. Figure 7 exemplifies how a technology that reduces development risk in Phases II and III could increase the value of BB1. One of our clients uses their extensive in-house statistics detailing the reasons of project failure to evaluate the impact of, for example, toxicology screening technologies on reducing the risk of failure in particular development stages.

If a technology is exclusively applied to in-house projects, its value is already included in the value of the R&D portfolio. If, however, technologies are offered as a service to other companies, they have a value distinct from internal projects. For the valuation of traded technologies, assumptions are needed on the capacity dedicated to external services, and on the number of deals that could be managed in a year. The value of the services could then be quantified as follows:

- Determine the financial value of the partner's development candidate if information is available, or use average assumptions on sales volume, costs, risks and time lines.

- Estimate the effect of the technology with respect to risk reduction and/or development cost and time and/or changes of product profile.

- Determine the increase of project value induced by the technology.

- Determine a market conformity fraction of the value added by the technology that should be assigned to the provider as price for the service:

  — identify deals made for technologies that are comparable with respect to their impact on R&D projects and market exclusivity/intellectual property status;

  — calculate the present value that would be captured by the provider using the terms of the reference deals;

  — draw conclusions with respect to deal terms and negotiation strategy.

In our experience, companies are willing to pay around 2–15 per cent of the present value increase to the provider of the technology (payments may be staged and related to the progress of the project).

The valuation of new drug development targets without clear association with therapeutic areas, such as those arising from genomics or proteomics research, is most difficult. It is sometimes not possible to determine the intrinsic value of such technologies. The analysis of reference deals may provide useful information about how the market values such assets.

EVALUATION OF LICENSING DEALS

The augmented NPV model is applied as basis for determining fair prices for licensing candidates. Overall, four steps are recommended to prepare for deal negotiations:

- Create a quantitative financial model (augmented NPV) to calculate overall project value.

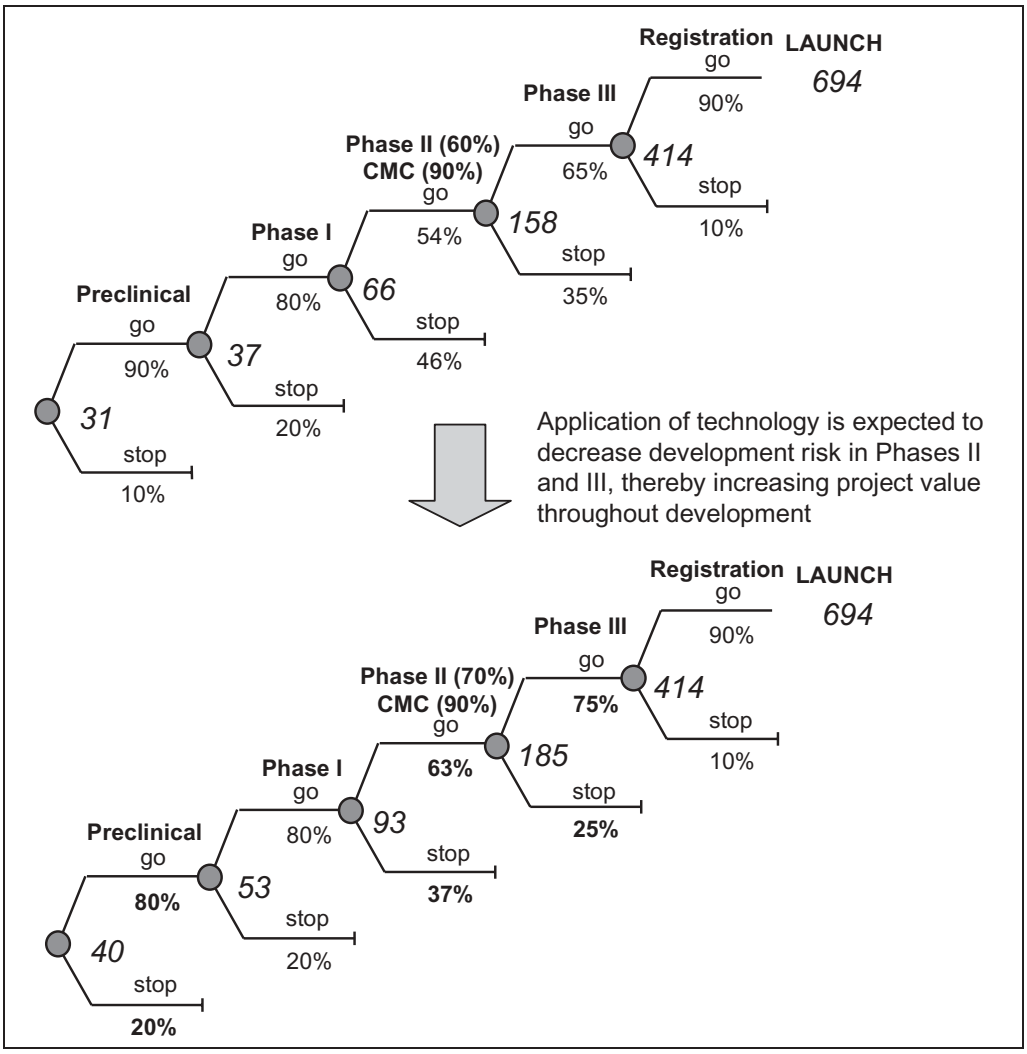

Figure 7: Value increase (€m) by application of risk-reducing technology. Let us assume that BestBiotech has identified a technology provider offering an *in vitro* model for ovarian cancer, investigating the potential of drugs to inhibit metastatic spread. BestBiotech would like to test BB1 and four back-up candidates in this model. The compound ranking best in this model would be chosen for clinical development. BestBiotech estimates that the probability of identifying a compound with sufficient activity in the metastasis model is 80 per cent; if none of the compounds was active in the test, development would be terminated although virtually all other preclinical tests have already been completed. Since clinical experience with drugs screened in the metastasis model is limited, statistical data on the frequency of successful clinical trials are not available. After extensive discussions with the technology provider, BestBiotech concluded that the probabilities of clinical success in Phases II and III should increase to 70 and 75 per cent, respectively. Upon application of the *in vitro* test, the present value of the project increases by €9m. Assuming successful completion of Phase I, the value of the project would be increased by €27m if the development candidate had proven to be active in the metastasis test. This indicates that measures to reduce risk may increase present and future portfolio value considerably. The price of such activities is often lower than the value it adds to development candidates

- Define a rationale for splitting the value between the licensor (LOR) and the licensee (LEE).
- Translate the desired deal value in financial terms (upfront, milestone payments, royalties, . . .).

- Determine alternative deal terms of similar NPV that would be acceptable (eg high stage-related payments/low royalties versus moderate early stage payments/higher royalties).

Augmented NPV facilitates the definition of fair prices for licensing candidates

It is worth being as detailed as possible with respect to the product target profile of licensing candidates. Information obtained in the due diligence stage usually provides the information needed to profile the candidate and to create meaningful financial models. The rationale for the value split, defined as the percentage of present value captured by the LOR versus the LEE, can be derived from the analysis of reference contracts with published financial details. This will frame the negotiation range and provide supportive arguments; it also sets the stage for discussing deal terms. The authors have observed a great variety of deal terms, indicating that the involved parties try to accomplish their individual financial needs. Our analyses indicate also, however, that not all published deals create value for the involved parties. The authors therefore suggest supporting the negotiation process by financial LEE/LOR models, based on augmented NPV, which can be used to investigate the impact of suggested deal terms almost immediately.

The augmented NPV algorithm is widely accepted in the pharmaceutical and other R&D-intensive industries

CONCLUSIONS AND OUTLOOK

A methodology has been described to evaluate drug development candidates and technology platforms as they are typically pursued by biotechnology companies. The augmented NPV algorithm properly takes into account the major drivers of value and the relevant uncertainties of such business activities. The suggested evaluation approach is beneficial for

Highly uncertain early stage projects strongly benefit from the establishment of project target profiles

- internal project prioritisation purposes, as the approach reveals the financial impact of all parameters that drive decisions;
- licensing negotiations;
- investors who wish to facilitate financing discussions and to support the definition of exit strategies.

The augmented NPV algorithm is widely accepted for the evaluation of R&D projects in the pharmaceutical (and other R&D intensive) industry(ies), because it reflects the risk, the optionality and the staged investment policy of such projects. If valuations of future follow-on opportunities were added that depend on the success of current projects, the strategic value of the portfolio would be captured adequately, eliminating concerns of some managers who fear that financial models might miss the long-term benefit of costly projects with an initially small commercial potential.

Managers sometimes believe that the suggested approach to financial project evaluation is not so useful for discovery projects because the range of possible outcomes may be too wide, leading to valuation results that do not really support project differentiation and prioritisation. It may sometimes be difficult to outline the expected properties of, for example, an innovative drug that is developed based on a newly discovered enzyme or receptor. The role of the drug development target in the respective disease may still be unclear, and there may be as yet unknown applications that are only revealed through future research. In such cases, valuations would be highly uncertain. The structuring process described in the second section can strongly improve the understanding of the value drivers of such projects: what are the therapeutic applications the company is actually pursuing in research (because efficacy will only be proven in the indications investigated) and what are the required deliverables in terms of efficacy and safety that lead from an innovative target to an innovative drug? Such reasoning results in project target profiles that provide guidance to scientists at each R&D stage to optimise their research tools and decision criteria. The financial valuation could then be built on the

project target profile and the development strategy. Even if managers prefer not to conduct a complete financial valuation for early discovery projects, the definition of research objectives, the focus on distinct targets and the development of a common agreement on objectives create value for the company.

Option pricing methods derived from the evaluation of stock options are explored for their applicability to R&D projects

While the augmented NPV approach is commonly accepted, option pricing methods derived from the evaluation of stock options are also explored for their applicability to R&D projects.[17–19] The reason is that R&D projects can be considered as options on future products, and it is concluded from financial option theory that discounting in option pricing models would better reflect the optionality of such projects. So far, there is no final consensus among scientists and practitioners about the validity and advantages of option pricing methods compared with augmented NPV. The discussion and comparison of both approaches need a separate article. There is evidence that the results of both approaches converge and lead to similar conclusions.[17,20,21] In the authors' opinion, augmented NPV is still the preferred choice for most applications. In any case, augmented NPV is built on generally known financial principles, while option pricing uses more abstract assumptions, in particular with respect to project risk, and would require specific education.

Results provided by option pricing models are usually comparable to results obtained by augmented NPV

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