A question based approach to drug development

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CHAPTER 1

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Drug development project management by a new question based approach and decision analysis support

Introduction

The value of knowledge

Peter is a clinical research manager at a pharmaceutical company and his current job is to set up a clinical development program for a new promising antipsychotic drug. His plan is to perform phase I studies in healthy volunteers (single ascending dose/multiple ascending dose/drug metabolism studies/food interaction), followed by phase II trials in well defined small groups of patients to select the optimal dose which he intends to use in the large phase III trials.

John just started working at the same company after having worked as an academic neurologist and he is unsure if the drug will penetrate the brain. Therefore, he has suggested adding a brain imaging study with positron emission tomography (PET) study immediately after the first study in man. This will require the development of a special radioactive labelled molecule and may delay the project by more than a year. John and Peter have discussed this with their manager. They have a short meeting about this during which the research director shows a spreadsheet (table 1).

TABLE 1 **Project valuation by Net Present Value (NPV)**

Peter's plan (xM$)										
Out	1	2	4	20	30	40	0	0	0	
In	0	0	0	0	0	0	100	100	300	
Balance	-1	-2	-4	-20	-30	-40	100	100	300	
John's plan (xM$)										
Out	1	2	2	4	20	30	40	0	0	0
In	0	0	0	0	0	0	0	100	100	300
Balance	-1	-2	-2	-4	-20	-30	-40	100	100	300
Net Present Value (NPV)										
Peter's plan (xM$)	241									
John's plan (xM$)	226									
Difference (xM$)	15									

"Sorry John but as you can see there is no chance we will do this. Delaying the project will not only cost us two million dollars extra, but worse, you reduce the value of our project by 15 million. I know that the board is unlikely to allocate enough priority to this project so we probably have to cancel

it altogether. Anyway, we will have to assess the efficacy of the new drug in the phase II studies in the patients. Also, John, please remember that we are a commercial company. Our job is to make money -not write interesting papers. With a planned yearly turnover of about 500 million dollars this is what I see as the cost of a year's delay!"
John feels there is something wrong with the logic of this reasoning and ponders two possible scenarios. Of course the drug may be developed according to Peter's plan, but what if the drug does not penetrate the blood brain barrier? In that case the first indication of this will only come in expensive phase II or III trials.

TABLE 2 **Recalculation of the plans for the scenario that the drug does not penetrate the brain.**

Peter's plan (xM$)										
Out	1	2	4	20	30	40	0	0	0	
In	0	0	0	0	0	0	0	0	0	
Balance	-1	-2	-4	-20	-30	-40	0	0	0	
John's plan (xM$)										
Out	1	2	2	4	0	0	0	0	0	0
In	0	0	0	0	0	0	0	0	0	0
Balance	-1	-2	-2	-4	0	0	0	0	0	0
Net Present Value (NPV)										
Peter's plan (xM$)	(74)									
John's plan (xM$)	(8)									
Difference (xM$)	(66)									

John wants to convince his boss that in the latter case, his development plan would have saved considerably more resources than Peter's. While the initial value of his plan was lower according to his boss's estimation, he feels the project valuation did not adequately value the contents of his program or the value of the early discontinuation of the development. He is not quite sure why the calculation of the Net Present Value of his plan does not seem to reflect exactly what he sees as value. He manages to get his manager's spreadsheet and recalculates it for the situation that the project is discontinued after Phase III for Peter's plan because the drug is not effective in schizophrenia. In John's plan the PET study may have given unequivocal evidence that the drug does not get into the brain and the project is stopped immediately after the PET study (Table 2). To his surprise this shows a very different picture. Now the value of both projects is negative because there is no income anymore but Peter's plan produces much more negative value

than his does! John goes back to the research director and presents this again. “John, my dear fellow, you seem to be making an academic exercise out of everything you do! I do not rate the probability that this happens very high. You would be best advised to just do what you are paid for- show that our new drugs work in patients.”

John is disappointed. His boss obviously judges the probability of certain scenarios differently, but why? It surely can’t be as black-and-white as this? How can he find a way to communicate with his colleagues about these matters? John leaves the office and wonders how he can express all these different facts so that his point does become clear -he has never been the type that gives up easily.

Problem with modern drug development

Every year 200.000 compounds are examined on potential medicinal properties worldwide. About twenty new drugs are introduced every year. This implies that one in ten thousand compounds make it through the drug development program. The discovery and development of new medicines is an expensive and time-consuming process. It takes an average of 12-15 years to discover and develop a new medicine. Most of that time is spent testing the drug to make sure it is safe. The average cost of bringing one new medicine to market in 1990 was estimated at $500 million. The Tufts University Center for the Study of Drug Development found that the time from synthesis of a new drug to marketing approval has increased over time. While in the 1960s the approximate time from synthesis to approval was about 8 years, this has increased to 14.2 years in the 1990s. Recent figures show that although pharmaceutical companies spend more on research and development of new drugs, the number of new compounds launched decreases (Figure 1). There is no denying that many of the diseases that fuelled the enormous explosion in profit and turnover of the pharmaceutical industry in the 1980’s and 90’s (like asthma and gastric ulcers) are now well controlled and this reduces the potential added value of any new treatment. Furthermore, the many diseases that remain inadequately treated are chronic with complex pathophysiology and difficult outcome measurements. Good examples are neuro-psychiatric diseases or cancer. Therefore, pharmaceutical companies need to rely on a few highly successful products to fund the high costs of innovative research and development (R&D). The data show

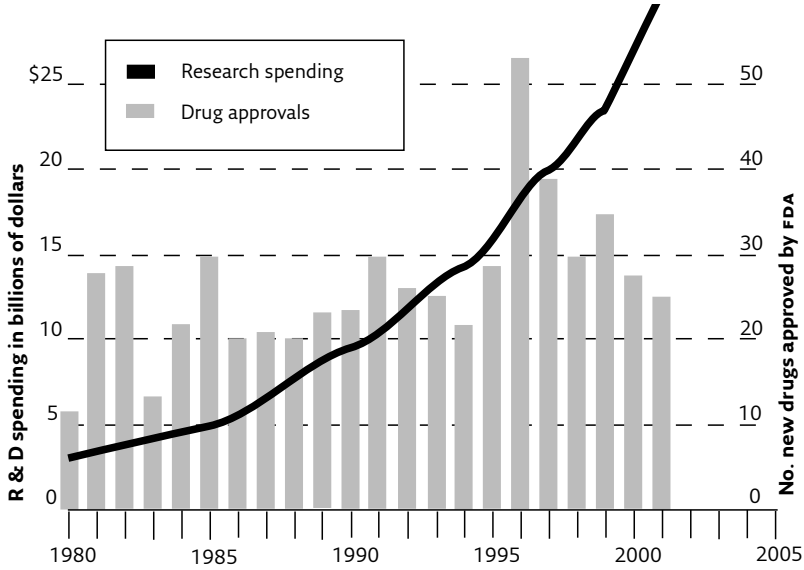
ref. 1

ref. 2

ref. 3

that it is increasingly difficult to develop new drugs for the treatment of the complex diseases that remain inadequately treated. To limit the costs of drug development it pays to discontinue failures as early as possible.

FIGURE 1 **Growing drug development costs and declining number of registrations of new drugs**



In order to cope with this changing perspective, several attempts are made to optimise the development of new drugs:

Target optimisation

Several individual approaches are introduced to optimise the process of identifying new lead compounds both in quantity and selectivity:

- **Computer aided drug design**

The use of computational techniques to design and optimise molecular targets has increased the number of new chemical entities (NCE's). Furthermore, the selectivity of the NCE's is enhanced by evaluating and optimising the binding affinity to selected targets *in situ*.

- **Combinatorial chemistry**

Combinatorial chemistry techniques (often automated using synthesis

robots) have facilitated and increased the number of synthesised NCE's with potential biological activity.

- **High throughput screening**

The increased number of synthesised compounds is easily screened using molecular biological techniques usually referred to as high throughput screening. This usually implies that several hundreds of related compounds can be simultaneously screened for activity at receptor level using fluorescent activation markers. Therefore, the most potent compounds at receptor level can be selected from the wide range of available compounds.

- **Genomics**

The availability of the human genome has generated a wealth of new possibilities for new drug targets. New insights to the origin of complex diseases are under investigation. Furthermore, gene chips are available to evaluate the effects of new drugs at DNA/RNA/protein production level providing more detailed knowledge on the mechanism of action of new and existing drugs.

There is no doubt that these approaches are producing many molecules that bind to biological targets. However, for these to be successful as medicines much more is needed. New drug targets do not necessarily mean that the relation of these to disease is well understood and realising this understanding may be very time consuming. An immediate payback of these techniques is therefore not expected. ref. 4

Process optimisation

Optimisation of the discovery of new drugs is complemented by optimisation of the development process.

- **Optimisation of resources**

Pharmaceutical companies have merged in an effort to increase the company's pipeline of new investigational drugs and to combine expertise on different indication areas as well as reduce overhead costs. This has largely failed from this point of view. The percentage of turnover spent on research and development has remained constant for companies before and after mergers. This gives no indication of any economy of scale. Clearly there may have been other advantages of the increased market share that are beyond the scope of this paper.

- **Rigorous selection of investigational new drugs**

Identifying and stopping development of drugs that will fail to reach registration as soon as possible once it has entered the clinical development phase is highly rewarding. For this reason, more and more effort is put in early selection of the compounds.

- **Inclusion of biomarkers for effects in an early phase**

Part of the early selection and cost reduction is the inclusion of biomarkers at an early stage and introduction of early proof of principle or proof of concept studies.

- **Project value estimation and portfolio analysis**

In order to select the most profitable project within a company's pipeline, each project is valuated in advance, usually using Net Present Value (NPV; see box 1) calculations. The highest NPV is achieved by projects with the highest estimated market value combined with the lowest development costs and shortest time to registration. Throughout the development process the milestones to monitor the project progress are usually defined by the classical development phases 1 (small healthy volunteer studies on safety, kinetics and tolerability), 2 (small patient population studies on mechanism of action and therapeutic window) and 3 (large multi centre trials to confirm efficacy and safety). A description of these clinical phases by the US Food and Drug Administration (FDA) is given in box 2.

Because Peter's program optimised many procedural aspects of the development including time and costs, his project had a high NPV as estimated by his boss. John assumed that the bottleneck for the potential antipsychotic could be the penetration in the brain and he proposed to spend additional time and money to get an early confirmation of the critical question. Subsequently, the NPV of his project was lower than Peter's but it was unclear to them how to value the early increase of critical knowledge. For some reason they communicated about procedural aspects but seemed to lack a device to communicate about the content of their project. Whilst the procedural aspects were covered by numbers any discussion about the probabilities of certain events occurring was done intuitively.

Improving the discovery or the process has not resolved the main problem of the apparent slack in drug innovation. One of the matters that has not been dealt with is the integration of both procedural and knowledge aspects of drug development. We therefore postulate a question-based approach to drug development that integrates the two into a comprehensive concept.

Question-based development (QBD)

During the classical phases 1 to 3 (and 4), a number of generic questions need to be answered (Figure 2). The detailed questions have to be determined on a case-by-case basis but the questions groups may give some structure to the list.

1 Does the biologically active compound/active metabolites get to the site of action?

This main generic question contains several issues that need to be determined such as absorption, distribution, metabolism and excretion of the drug. Not only the parent compound, but also any possible active metabolites should be included in answering this question. Additional items can be relevant for certain drugs such as ability to penetrate the blood-brain-barrier for CNS active drugs. Unexpected biologically active metabolites can be formed *in vivo*, or unexpected sites of action can be discovered, which should be incorporated in this main question as soon as observed.

2 Does the compound cause its intended pharmacological / functional effect(s)?

Answering this question includes the demonstration of the mechanism of action of the investigational drug. For example a new drug for hyperlipidemia will at least have to reduce the plasma cholesterol in a dose or plasma concentration dependent manner.

3 Does the compound have beneficial effects on the disease or its pathophysiology?

This question reflects the question traditionally answered in the classical phase 3 studies to establish the effects on the disease but also the alteration of other physiological systems resulting in clinical side-effects.

4 What is the therapeutic window of the new drug?

The therapeutic window of each investigational drug needs to be established in order to select the optimal dose that is clinically efficacious at tolerated levels. This question includes important sub-questions: Which dose regimen will keep the drug's concentration within the therapeutic window? What is the optimal dosing interval relative to the intended indication (chronicity of intended drug exposure)? Can controlled drug delivery improve the product's action? What is the forgiveness of the product (i.e. the difference between the product's post-dose duration of effective therapeutic action and the recommended interval between doses)?

ref. 5

ref. 6

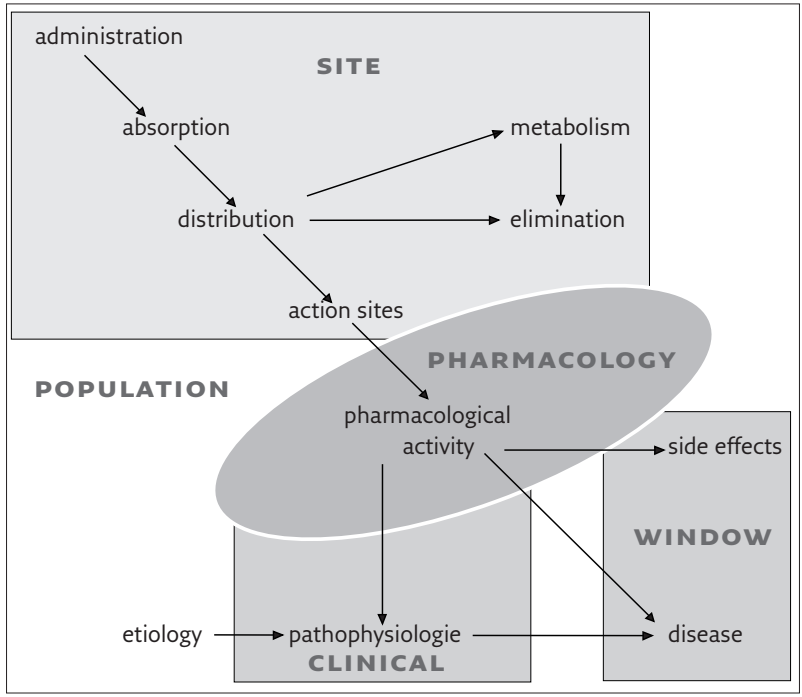
5 How do the sources of variability in drug response in the target population affect the development of the product?

The sources of variability in drug response have been defined as: Dose (formulations and compliance), Pharmacokinetics (absorption, distribution, metabolism and elimination), Pharmacodynamics (sensitivity, maximum response) and other (disease, other drugs, circadian rhythms). The main question should include: Are there any specific factors in the target population that may affect dosage? A general sub-question can be: is there any food-interaction with this compound? But also more drug/population specific questions can arise. The regular use of co medication within the

ref. 7-9

target population may require extra drug interaction studies. Ethnopharmacological issues and pharmacogenomics can play a key role in some development programs (*e.g.* for introduction of a 'western' drug in Japan).

FIGURE 2 **Schematic representation of the course of action of drugs (from administration to effects) and the questions from the question-based development plan**



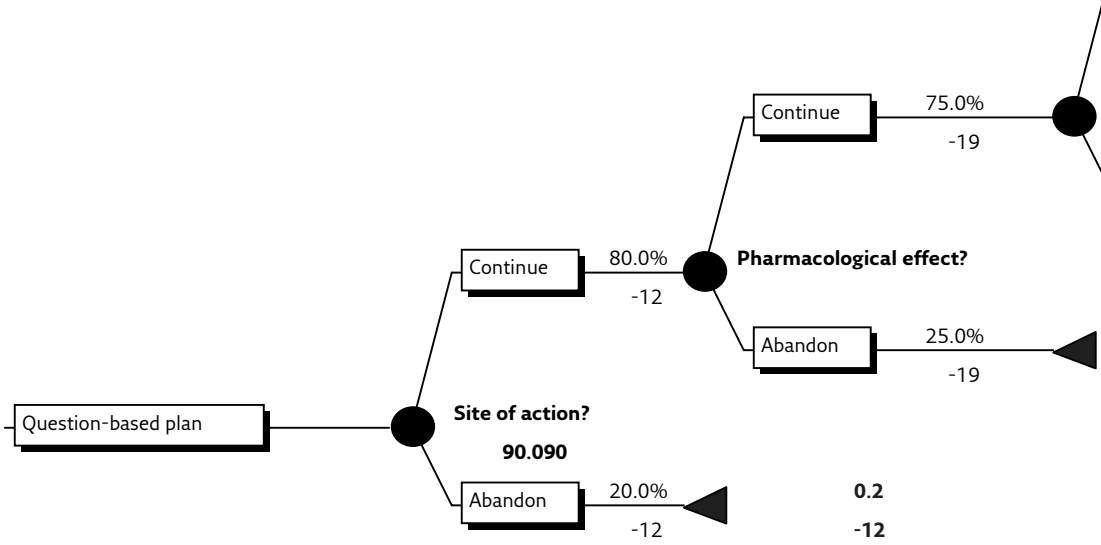
One question can be concealed in several studies and one study can provide partial answers to multiple questions. However, when a project is monitored by its progression through the traditional phases, little is learned about what questions are actually being answered. Managers will have to assume this is being done adequately. The first time the answers are sometimes critically examined is by the regulatory authority that has to give approval for marketing. Extreme disappointments and losses can occur in such cases. In 2002 the company Bristol Myers Squibb paid several billion dollars for a small biotech company Imclone with an interesting anticancer agent (Erbitux). A fee of 200 million dollars was paid when the dossier was sent

to the FDA who subsequently judged the data to be insufficient. The details will probably never be known but the questions lingers how experienced drug developers at BMS were able to miss something that was found after review of the dossier by the FDA.

The question-based approach is designed to make the central issue in drug development projects explicit rather than implicit. This central issue can be described concisely as "Are all the relevant questions asked AND answered adequately?" If so, a regulatory authority can confidently give market authorisation. During the development period, managers can monitor the progress of the study by the questions that are answered and the length of the remaining list. Obviously, it remains important to answer these questions as rapidly and as cheaply as possible, but the tools for doing so should be in place in any sensible company.

QBD assumes that the costs of an answer and the probability an answer can be given adequately can be estimated. These probabilities and costs can be estimated using either expert opinions or historical data. Subsequent sensitivity analysis can reveal the relative impact of the estimations on the project value. Each set of probabilities and costs (combined with market value) will have its own optimal priority sequence. Therefore, early evaluation

FIGURE 3 **Question-based drug development plan**

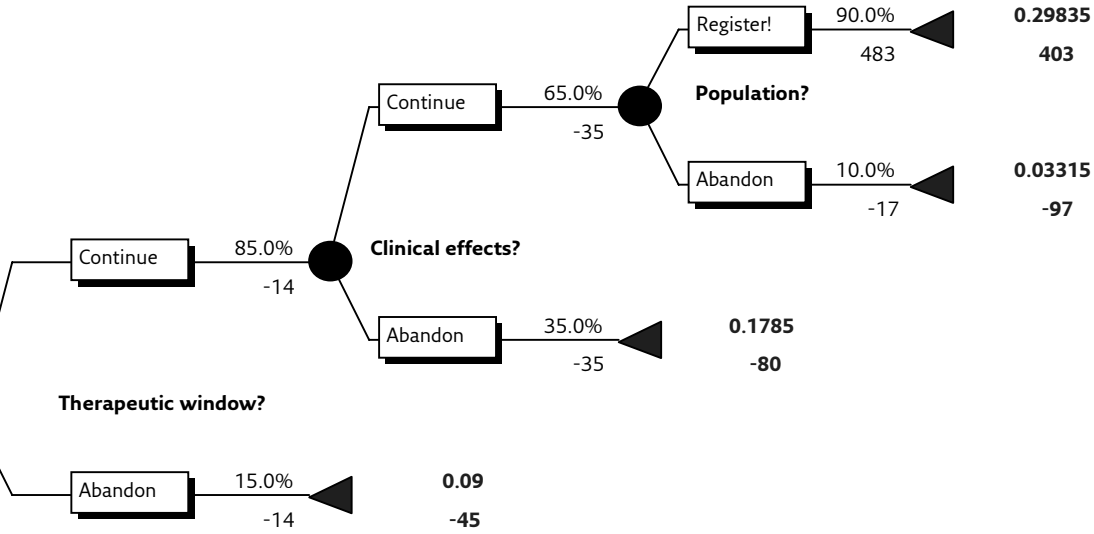


studies on the most critical questions are highly rewarding, since these prevent expenditure on projects that are unlikely to produce a positive cash flow. NPV analysis just indicates that such evaluation studies only cost time and money. NPV calculation inadequately values the increases in knowledge.

ref. 10

The option-based theory takes such probabilities of success into account. However, this method is rarely used and if so, it uses the classical phases of drug development as decision points (or knots in the project's decision tree). These phase definitions are not relevant as drug development targets but are merely classifications based on the type and number of patients involved in such studies.

We therefore propose a question-based approach that uses decision points that are relevant to the development of knowledge in the drug development



process (the five standard questions). The question-based approach now moves one closer to an adequate reflection of true risks and values of the uncertainties that are faced during the development of a new drug.

Additionally, the question-based approach can demonstrate how the project value varies with increased knowledge generated by early evaluation studies. The unique combination of probabilities on successfully answering the question in combination with the costs (and market value) determines

the optimal development strategy that varies for each drug. Furthermore, it displays the bottlenecks within the development and can contribute substantially to the early discontinuation of failures. The estimation of the market value of the new drug can be less accurate in this question-based approach as long as the market value far outweighs the costs. As the probability of successfully answering the questions is determined both by the compound's potential and the availability of methods to demonstrate effects, the question-based approach incorporates the value of both knowledge about methodology and additional early evaluation studies contrary to conventional NPV calculations.

If John and Peter's boss had used the question-based approach to develop the antipsychotic drug, he would have estimated the probabilities and costs of answering the questions. He would have wanted the input from his fellow project team member's (including pre-clinical scientists as well as John and Peter) opinion on the compounds potential and the availability of adequate methods to successfully answer the questions. Together, they might have reached consensus that the 'site of action' question for the potential anti-psychotic had the lowest probability of success and therefore, this question would have required the highest priority in the program. The addition of John's suggested PET study combined with the 'traditional' phase I studies would have adequately answered the 'site of action' question at the earliest possible stage. The question-based approach to drug development is especially valuable for stopping development of drugs that have a high probability of failing by identifying the critical issues that will lead to the discontinuation and dealing with these first. Early discussions about probabilities are also an excellent device to promote communication about critical issues within the project team and to higher management.

The decision analysis tree shown in figure 3 now shows Peter's plan with the probabilities as estimated by the team. The input parameters for the development plan are shown in table 3. The team has decided that the overall probability the compound will make it to registration is comparable to the historical probability of a drugs making it through the clinical phases; *i.e.*, about 30%. They used the cost and payoff estimates from the NPV calculations: total development costs will be M$ 97 and the payoff will be M$ 500.

Decision analysis revealed that the estimated project value taken these success probabilities into account would be M$ 90.1. According to the original NPV analysis, addition of the PET study according to John's

suggestion would increase the overall costs with M$ 2. A lively discussion begins in the team how the input parameters will change if the PET study is performed. One team member argues that the probability that too low a dose will be selected for further development is substantially decreased if the PET study is performed. The team agrees with the assumption that with this study a dose can be found that shows minimum receptor occupancy.

TABLE 3 **Input parameters for Peter's development program**

Parameter	Value
Success action site	80%
Success pharmacological effect	75%
Success clinical efficacy	65%
Success therapeutic window	85%
Success population	90%
Costs action site	12 M$
Costs Pharmacological effect	19 M$
Costs Clinical effect	35 M$
Costs Clinical window	14 M$
Costs Population	17 M$
Estimated marketvalue	500 M$

According to the literature, lower than 90% occupancy can not have any clinical effect. This consideration would increase the probability that clinical effects will be observed with the selected dose and the successful defining of the therapeutic window will also be enhanced because the lower limit is determined. The team does not want to be too optimistic towards management so they decide to increase the estimated probabilities of success on both the 'clinical' and the 'window' question both with only 1%. The additional costs of the PET study are divided amongst the 'clinical' (M$ 36) and 'window' (M$ 15) questions. The project value is recalculated and instead of the loss of M$ 15 according to the NPV analysis, the estimated value is increased with M$ 2.6 to M$ 92.7!!

John decides to investigate how much more costs can be introduced in Peter's plan if the success probabilities are affected more than the estimated 1%. He calculates the project value for a series of different success probability combinations. He varies both the 'clinical' and the 'window' question up to ± 10% of the base values. This two-way sensitivity analysis is displayed in table 4. John realises that his gut feeling that Peter runs a higher risk to lose relatively large amounts compared to his plan is confirmed by this analysis.

John and Peter needed some time to explain their question based plan and the decision analysis that demonstrated that an early PET study actually had a high probability to be very cost effective. However, management agreed in the end. It was agreed to add a question-based Gantt chart to the traditional project and regularly review the progress in answering questions as well as the conventional progress in the studies.

TABLE 4 **Break-even table for success probabilities 'clinical' and 'window'; the bold project value is the expected value for 1% increase in both probabilities**

	Success probability 'window'										
Success probability 'clinical'	0.77	0.79	0.81	0.83	0.84	0.86	0.88	0.89	0.91	0.93	0.95
0.59	67	69	71	73	76	79	81	84	87	89	92
0.61	70	72	74	76	79	81	84	87	90	92	95
0.62	72	74	77	79	81	84	87	90	93	95	98
0.63	75	77	79	82	84	87	90	93	96	98	101
0.65	78	80	82	85	87	90	93	96	99	102	105
0.66	80	83	85	88	90	**93**	96	99	102	105	108
0.67	83	85	88	90	93	96	99	102	105	108	111
0.69	86	88	90	93	96	99	101	105	108	111	114
0.70	88	91	93	96	99	102	104	107	111	114	117
0.71	91	93	96	99	102	104	107	110	114	117	120
0.73	94	96	99	102	105	107	110	113	117	120	123

BOX 1 NET PRESENT VALUE CALCULATION

The Net Present Value (NPV) of a project is calculated by adding the present value of all future cash flows and subtracting the initial investments. The calculation of the present value is performed by discounting the future cash flows with a percentage, which reflects the required return of investment of the project according to the following formula:

$$NPV = \sum_{t=o}^{n} \frac{CF(t)}{(1+i)^t}$$

Where
NPV= Net Present Value; CF(t) = Cash flow in period t (including investments), incoming +, outgoing −; t = Period; n = Number of periods; i = Required return of investment (or discount factor)

The NPV assumes an incremental cash flow. Therefore, the NPV calculation compares the situation where the project is performed and the situation that results if the project is cancelled. If the NPV of a project is positive, the project adds value to the company and is therefore worthwhile.

NPV calculation requires the *a priori* determination of the required return of investment. This factor correlates with the risk associated with the investment in the project. The higher the risk of the investment, the higher the return of investment should be. Usually, the discount factor is determined using the Weighted Average Cost of Capital:

$$WACC = K_d(1-T_c)\left[\frac{MVD}{TDE}\right] + K_e \frac{MVE}{TDE}$$

Where
WACC = Weighted Average Cost of Capital; Kd = Interest rate; Ke = Treasury rate; Tc = Tax return; MVD = Market Value of Debt; MVE = Market Value of Equity; TDE = Total Debt and Equity = MVD + MVE

BOX 2 PHASES IN CLINICAL DRUG DEVELOPMENT

PHASE I

Research using small groups of healthy volunteers. Traditionally, this phase mainly focuses on if the human body tolerates the new drug and on finding a dose where the level of tolerance is acceptable. In general, this phase takes about 1 to 2 years. The centre for drug evaluation and research of the United States Food and Drug Administration (FDA) states:

"*Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug, but is generally in the range of twenty to eighty.*"

PHASE II

Research on a group of patients where the first proof for efficacy is established. More characteristics of the NCE are determined and a safe and well-tolerated dose is determined where the drug is efficacious. According to the FDA:
"*Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.*"

PHASE III

The potential new drug is tested on thousands of patients in multi-centre research projects to investigate the side effects of the drug at a set dose in more detail. Furthermore, the efficacy of the drug at the determined dose is compared to existing medication. Further research is conducted to investigate possible side effects after long-term treatment and development of the drug for different indications is investigated. The FDA describes:
"*Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labelling. Phase 3 studies usually include several hundred to several thousand people.*"

PHASE IV

The registered drug is monitored closely to examine the occurrence of unexpected side-effects and interactions with other drugs.

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Outline of this thesis

As shown in the previous case study, changing the development plan from phase/time oriented to question based can improve the insights on the information that needs to be obtained and will help display the priorities within the program. In conventional phase-based drug development, timing is not the most important issue, as long as studies are performed rapidly. In this thesis, it is shown that the order in which studies are performed has a significant impact on the efficiency and quality of the drug development process. The impact of this novel approach can best be demonstrated by calculation of the financial consequences of resolving the right questions at the right time, during the development of new compounds. This calculation is based on the real-option theory, applied to drug development questions. Simple decision analyses suffice to determine the best sequence of research projects, and detailed pharmaco-economic models are unnecessary for this purpose. The thesis also provides some examples of research projects that were performed at different stages of drug development, with widely different consequences for the values of the projects concerned.

This thesis consists of four main sections.

SECTION 1 *Literature evaluation* describes some examples of evaluating existing biomarkers for clinical effects in healthy volunteers as helpful tools for early phase drug development. A structural procedure was adopted to evaluate the methods used in healthy volunteer trials using antipsychotics (Chapter 2) and benzodiazepines (Chapter 3). The use of REM sleep reduction as a frequently used method to evaluate the effects of antidepressants is reviewed in Chapter 4.

SECTION 2 *Developing a new formulation* describes four clinical studies with rilmenidine -a centrally acting antihypertensive agent- that investigate and define the optimal characteristics of sustained release rilmenidine formulations. Chapter 5 investigates the *in vivo* properties of a sustained release formulation in healthy volunteers. Furthermore, these *in vivo* pharmacokinetic characteristics are related to the *in vitro* sustained release properties. Chapter 6 defines the pharmacokinetic/pharmacodynamic relationship between rilmenidine concentrations and the development of side effects in healthy volunteers. In Chapter 7, the pharmacokinetic / pharmacodynamic relationship between rilmenidine concentrations and the reduction of blood pressure is investigated in mild to moderate hypertensive patients. Finally, in Chapter 8 the effects of multiple doses of sustained release formulations are investigated in mild to moderate hypertensive patients.

SECTION 3 *Bridging the gap to Japan* exemplifies two ways of comparing Japanese and Caucasian subjects with the aim of reliably extrapolating clinical data from Caucasian subjects to Japanese subjects. Chapter 9 describes an interethnic comparative study between Japanese and Caucasian volunteers. A Japanese study on the pharmacokinetic/pharmacodynamic relationship of nitrazepam is repeated in Caucasian subjects matched for gender, age and body size and the results are subsequently compared. Chapter 10 describes a simultaneously performed bridging study on a new oral contraceptive agent where the single dose and steady-state pharmacokinetics are compared between Caucasian female subjects and Japanese female subjects.

SECTION 4 *Market advantage* shows that early in the drug development program a small study can be performed to investigate potential advantages of newly developed agents over existing drugs. Chapter 11 describes a study in healthy volunteers to compare two doses of a potential anxiolytic drug with lorazepam and placebo to investigate the central nervous system effects of the new agent.

Each section is concluded with a value estimation, which discusses the impact of the presented studies on the drug development program using the question-based approach.