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## A question based approach to drug development

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# CHAPTER 12

# Summary and Conclusions

# Introduction

ref. 1 The 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 safety of the drug. 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 first synthesis to approval was about 8 years, this time period has increased to 14.2 years in the 1990s. Most of this increase in time is due to the prolonged period from first administration to humans to submission for registration, which increased from 3.1 to 8.6 years.

ref. 3 The exact costs of drug development today are difficult to determine. Over \$500 million is supposedly spent to introduce one single new drug on the market. About 30% of these costs (\$150 million) are spent on the clinical development phases I to III. Therefore, stopping as soon as possible the development of drugs that will fail to reach registration is highly rewarding. Growing research & development (R&D) expenditures have fuelled the development of hundreds of new medicines over the past half-century by the pharmaceutical industry. As illustrated before, drug development is both high-cost and high-risk. It was, for instance, estimated that in the period between 1980 and 1984 only three of every 10 NCE's had returns higher than average after-tax R&D costs. Many attempts have been made to optimise the development of new medicines, both by improving the drug target and the process of development.

ref. 4

# Target optimisation

Computer aided drug design has made it possible to identify many compounds that adequately bind or fit onto the target site. The synthesis of new biologically active compounds has been facilitated by the use of combinatorial chemistry. The most active compound on receptor level is selected from the wide range of new compounds by comparing hundreds of compounds at once using high throughput screening. By sequencing the human genome, many new potential targets for new drugs have been identified. Unfortunately, the relationship between a modification of a certain biological target and the improvement of a clinical endpoint is often unknown, particularly for multifactorial diseases. There are probably 100's of genes associated

with the potential of a breast cancer to metastasise but it remains unknown which one(s) or which combination to block yet. Developing an inhibitor for each target is prohibitively expensive, so biological knowledge will have to precede chemical synthesis.

## Process optimisation

The cost of development and the increased number of lead compounds have made adequate selection of compounds to enter the clinical phase crucial. Mergers and take-overs of pharmaceutical companies to form bigger companies with larger pipelines reflect attempts of procedural optimisation. The obvious goal is to have more investigational compounds so that more drugs will be successful and spread the risk of failure. Because the selection of compounds has become so important, more efforts are aimed at early discontinuation of failures (*i.e.* compounds that will not reach registration). Therefore, there is a growing pressure on the drug development process to enhance the relevance of studies at all stages. Traditionally, phase 1 studies were mainly concerned with kinetics and tolerability of a new compound in healthy volunteers, but efforts are now made to include potential biomarkers of clinical endpoints.

In order to compare and select the compounds that will enter the clinical phase of the drug development process, the Net Present Value (NPV) is often used. NPV is commonly used because of its ability to discount present and future cash flows and to provide an estimate of the total (financial) value of a project. NPV uses a discount rate to convert a stream of future cash flows to a single value today. In the calculation of a project's NPV, a comparison is made between the situations that arise if the project is continued or abandoned. NPVs greater than zero indicate the amount the organisation will earn in excess of traditional financial investment of the outgoing cash flow. The NPV can then be used to compare different projects using the same factors. The value of future cash flows is predominantly dependent on the factor time (spending money as late as possible and generating revenues as early as possible). Therefore, the most influential parameters for NPV calculations of a drug development project are costs of development (as low as possible), revenues (as high as possible) and time to introduction on the market (as early as possible).

ref. 5-6  
The difficulty of development of useful treatments is not solved by the described target -and process optimisation efforts. A structured approach

that combines and optimises both knowledge and procedural aspects of drug development may improve success rates and/or reduce some of the expensive failures of development.

## Classic development phases

Classically, the clinical development program of a drug is divided in four phases:

- 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. Furthermore, it examines how the drug enters and leaves the human body. In general, this phase takes about 1 to 2 years.
- 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.
- 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.
- Phase IV: The registered drug is monitored closely to examine the occurrence of unexpected side-effects and interactions with other drugs.

The different phases of the research and development process are represented in figure 1. The description of these phases is typically process oriented and contains very little information about which scientific aspects are actually covered during the development.

## Generic question groups

During these phases a number of generic questions are generally answered. Posing these questions throughout the development of a drug is in agreement with the learn-confirm view described by Sheiner. The main generic question groups are:

ref. 7

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

Related issues: Absorption, route of administration, bioavailability, distribution, tissue distribution, accumulation, action site penetration, metabolism, active metabolites, metabolic routes, excretion: hepatic/renal, clearance, half-life

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

Related issues: Effects related to mechanism of action, additional effects of primary pharmacological activity, effects of secondary pharmacological activity, other, undesirable effects

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

Related issues: Effects on relevant physiological systems, effects on disease, undesirable clinical effects

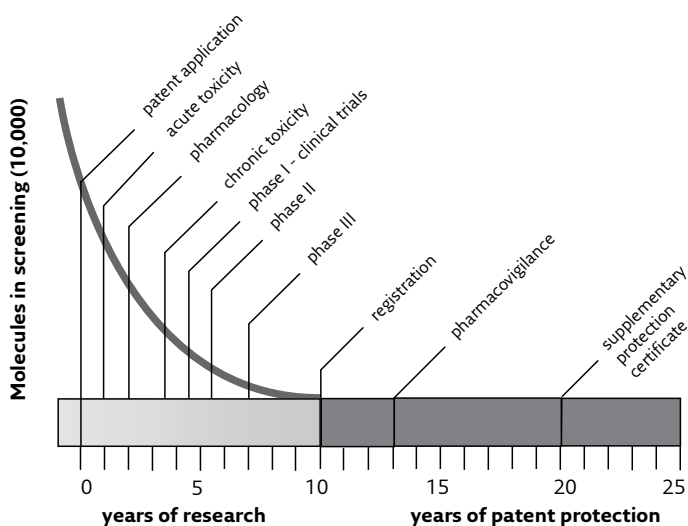
- What is the therapeutic window of the new drug?

Relevant issues: Clinical effects at tolerated dose, dose regimens/intervals, controlled drug delivery, forgiveness

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

Relevant issues: Compliance, pharmacogenomics, ethnic differences, concomitant medication, variability in pharmacokinetics, pharmacodynamics and disease state

**FIGURE 1** Pharmaceutical research and development process for a new product (<http://www.fda.gov/cder/>)





Each of these questions has a probability to be successfully answered but answering these questions will introduce development costs. The set of probabilities and costs varies from drug to drug and is therefore unique. For one drug it can be very difficult to successfully answer the 'site' question whereas it can be relatively easy for another compound. The unique set of probabilities and costs defines the optimal development strategy for each compound. Addressing a question with low probability of success at an early phase can be highly rewarding. NPV analysis merely shows that these type of additional studies only introduce additional costs and development time and the NPV of the project will decrease. Therefore, the NPV of development projects does not adequately reflect the value of additional knowledge on a compound, which requires a different value estimation method. The option-based theory takes into consideration the fact that projects can also be discontinued at various stages of the development program. The early discontinuation of drugs that will be unsuccessful is desirable and the value of early evaluation studies on relevant questions can be incorporated in the option-based theory. However, the option-based method is rarely used and is often defined using the classical phase I-III description of the process as decision knots in the decision tree. These phases are not relevant as targets in the development process but merely a classification based on the type of study and the number of patients involved in the trial.

This thesis introduces a question-based approach to drug development which uses decision knots that are relevant for the development of new drugs: generic questions that are really answered throughout the development program. The resulting question-based decision tree reflects the true risks and uncertainties that are faced in the development of an individual drug. Furthermore, the question-based approach shows how the project value can increase by performing an additional early phase evaluation study that helps to adequately answer a question later on. These studies can help in preventing unsuccessful compounds to enter late stages of development after substantial costs have been incurred. The early discontinuation can substantially reduce the costs of drug development. By defining the costs and probabilities of success and constructing the decision tree for a new compound, the bottleneck in the development of each individual drug will be identified. In four sections, several examples are presented to illustrate the use and impact of the question-based development plan.

# Value of research on biomarkers

In Section 1, three methodological reviews on potential biomarkers for the effects of drugs in healthy volunteers are presented. The proposed generic questions can be answered in several studies (e.g. the FTIH can provide an indication of 'pharmacology' and 'clinical'). To adequately answer questions, appropriate methodology to show effects is needed. For some questions/drugs this selection of the appropriate methodology is easy: e.g. 'site' or 'pharmacology' for a peripherally acting antihypertensive agent (plasma levels of the drug and blood pressure, respectively). But for drugs indicated for diseases such as depression, schizophrenia and anxiety this selection of the appropriate methodology is more difficult. The probability of successfully answering the question is therefore linked to the available methodology. Increased knowledge about the specificity and selectivity of the available methodology allows better selection of methods in clinical trials, and therefore, the probability of successfully answering the question will grow. The added value can be obtained by an increased probability of success but also on an increased probability a failure will be discontinued early (reduced costs). So knowledge of methodology (and research on methodology) has intrinsic value which should be included in the project value of a new drug.

NPV shows that additional research costs money (including time) and therefore, the NPV will drop if research on biomarkers is included in the project value of a drug. However, the question-based approach assumes the method factor to be incorporated in the probability factor of the compounds potential to successfully answer the relevant question. The reviews presented in section 1 all address the available methods for answering the 'pharmacology' and 'clinical' questions.

Currently, no validated biomarkers for the effects of antipsychotics, benzodiazepines or antidepressants in healthy volunteers are available, but a useful marker should meet the following requirements:

- 1 a clear, consistent response across studies (from different groups) and drugs
- 2 a clear response of the biomarker to a therapeutic dose of the drug
- 3 a dose (concentration)-response relationship
- 4 a plausible relationship between the biomarker, the pharmacology of the drug and the pathogenesis of the disease.

If these basic requirements are used as a filter on all described methodology in healthy volunteers, most methods are not very useful biomarkers. Chapter 2 describes that only prolactin response to antipsychotic agents fulfils the

requirements of a useful biomarker. The same goes for saccadic peak velocity as biomarker for the effects of benzodiazepines in healthy volunteers, as described in Chapter 3. Chapter 4 shows that REM sleep characteristics are of limited value as biomarkers for antidepressant effects in healthy volunteers, but this observation can be caused by inadequate modelling of the complex structure of human sleep. Sensitivity analyses on the probability of success on 'pharmacology' versus project value according to the question-based development approach allows construction of a 'break-even' table. This table shows how much project value is gained by increasing the method factor for each percent. The question-based development approach using historical data input (probabilities and costs) shows that every % increase in success probability of the 'pharmacology' question (by increased knowledge on the available methods) causes an increase in project value of M€ 0.8. A similar analysis of the 'clinical' question shows an increase in project value of M€ 1.4 for each % increase in success probability. Furthermore, the probability a method will be selected that will not show an effect at a therapeutically relevant dose of an efficacious drug will be reduced thereby preventing useless studies and the use of volunteers/resources.

## The value of timing additional studies

Section 2 showed that with a relatively small number of volunteers the question "Can a new formulation improve the therapeutic window and clinical effects of an existing drug?" could be answered. Using blood pressure and the most sensitive marker for the side effect of sedation (saccadic peak velocity), it was possible to identify the optimal therapeutic window of a drug. Furthermore, it was possible to correlate the *in vivo* with the *in vitro* dissolution of the new formulation. Combined, these studies helped in designing a sustained release formulation for an existing drug with adequate clinical effects at tolerated levels. Because the drug has been on the market for quite some time, the development of the original formulation apparently did not optimally answer these questions. Now additional studies were performed at a post-registration stage. The followed strategy was apparently to bring the original product to the market as soon as possible and use additional market-experience to consider a different (hopefully patentable) formulation. Additional useful information was obtained from market experience. This approach has also been adopted in the nifedipine case, where after introduction of the original product, an improved formulation was successfully developed based on the discovery of a novel pharmacodynamic property of the drug. The improved product after the launch of the

original product is sometimes referred to as a 2nd-cycle product. Another possible strategy could have been early inclusion of additional studies to evaluate the effects of a different formulation. The inclusion of these studies at an early stage in the original development of rilmenidine would have allowed the introduction of the sustained release formulation for rilmenidine and thereby reducing the additional costs of having to introduce a new formulation. The NPV of such a hypothetical development plan would probably have been lower than the one actually used, but the result would be a formulation that would meet a larger market demand and the revenues could therefore have been higher. These studies increased the knowledge on rilmenidine which would not be adequately valued using NPV, in contrast with the question-based approach. The rating of the success probabilities would yield a suggested policy to examine the 'window' and 'clinical' questions early in the development.

## Added value of bridging studies

Two comparative studies between Japanese and Caucasian subjects are presented in Section 3. The introduction of new drugs in Japan is increasingly interesting for western pharmaceutical companies. Japan has a large population and the availability of western drugs is rare. The Japanese registration authorities often require repetition of most clinical trials in Japanese subjects before registration. However, in some cases, a comparative trial can show that the complete repetition of all the clinical trials is not necessary. The 'population' question should nevertheless be adequately answered. If there is a difference in ethnopharmacological factors, additional trials in the Japanese population are required. Therefore, early comparative studies between Caucasians and Japanese have intrinsic value to the drug development program. The added value can be caused by two options: one option is that the comparative studies show that there are no differences in drug response that affect dose. Similar drug responses in both groups would allow extrapolation of the western data to the Japanese population and hence prevent additional trials in Japan. Another option would be the timing of these comparative studies. If the probability the drug response is similar is high, the QBD tree shows that one should decide to answer the 'population' question late in development (there are more important questions to ask). But especially if there is a real probability the drug response will be different between the ethnic groups, an early evaluation study can add substantially to the project value of the new drug. The example in Chapter 10 of the potential oral contraceptive illustrates that it is important to take all

questions into account when constructing the drug development decision tree. Even if one identifies the ‘population’ question as tangible, the other questions can have more significant impact on the optimal development strategy. In the presented case, the probability the drug would prove to have an improved side-effect profile would have to be estimated very low. As a consequence, the drug was discontinued after the comparative study presented in this thesis had been completed. Adequate estimation of the probabilities of success using the QBD-approach would have saved at least the presented comparative trial. The construction of a decision tree for the oral contraceptive would have revealed that the ‘clinical’ question far outweighs the ‘population’ question.

## The value of determining critical questions early

In Section 4, a study in the development of a potential new drug for the treatment of generalised anxiety disorder (GAD) is presented. The development of a selective GABA-a partial agonist could have a therapeutic advantage over existing anxiolytics. The main issue for these kinds of new drugs is that the proposed mechanism of action indeed shows a differentiation of the effects. Also, the drug or active metabolites must reach the site of action (*i.e.* it must pass the blood-brain-barrier). Therefore, the two most important questions for the novel drug are ‘pharmacology’ and ‘site’. In the classic NPV approach, performance of an additional cross-over study to determine the pharmacodynamic effects on sedation, body stability and memory compared to the existing market leader introduces extra development costs and maybe time. However, because of the early evaluation, the study showed indications that there are *in vivo* differentiation of effects and a less sedative dose can be selected to examine the efficacy in patients. The maximum dose is crucial because it is the core of the market advantage over the existing drugs. Therewith, the study attempts to prevent late failure because of relative over dosage. The ‘site’ question is not fully answered but the effects observed in the presented study are indicative for central penetration.

## Conclusions

The use of NPV analysis in drug development does not adequately reflect the additional value of knowledge. Similar to other efforts, NPV analysis is

an attempt to deal with the uncertainties and risks of drug development in a procedural approach. A question-based approach to drug development seems more rational and better incorporates the alteration of success probabilities. Furthermore, the question-based approach has implications for the execution of the drug development project and the selection of new biologically active compounds. It is beyond the scope of this thesis to present a universal model for drug selection and development. Based on several examples this thesis illustrates that the combination of success probabilities and accompanying costs to answer the questions are a unique data set that can vary with different compounds. Even if the overall probability of success and the overall costs are the same, these unique sets dictate an optimal development strategy. The sequence of relevant questions should serve as a priority list in the development of new drugs throughout the program. Regular updates of all probabilities and costs will optimally direct the development process. Another advantage of the question-based approach is that experts of different company departments all involved in the development of new drugs discuss and agree on the chances and threats in the development of new drugs.

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