Optimization and Simulation in Drug Development - Review and Analysis

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Keywords: Pharmaceutical R&D, Drug Discovery and Development, Modelling and simulation, Clinical Trial Simulation Portfolio optimization

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Abstract

We give a review of pharmaceutical R&D and mathematical simulation and optimization methods used to support decision making within the pharmaceutical development process.

The complex nature of drug development is pointed out through a description of the various phases of the pharmaceutical development process. A part of the paper is dedicated to the use of simulation techniques to support clinical trials. The paper ends with a section describing portfolio modelling methods in the context of the pharmaceutical industry.

1 Introduction

The present paper is the result of the initial research in the general part of the research project *Computer Supported Drug Development* at IMM-DTU. Here, we are currently investigating the potential for applying optimization models and methods from Operations Research to the pharmaceutical development process. A part of this task has been to analyse the current pharmaceutical development process and related modelling and simulation techniques used for decision support.

The basic observation driving the project is that the current process of discovering and developing a drug is extremely complex, time consuming and costly. Furthermore, drug development projects are high risk projects in the sense that a project may be halted in almost any of the development stages, if results from tests show unforeseen complications or if adequate experimental results are not provided to support the approval of the drug by the official authorities. Note here that the latter situation does not necessarily indicate that adequate results cannot be provided, merely that the performed sequence of experiments has failed to produce these. Unfortunately, this situation sometimes occurs in the most costly part of the experimental phase, Phase III of the clinical trials.

An obvious question is therefore how to increase the efficiency of the discovery and development process and how to decrease the failure risk. Here, improvements in all levels of the process should be considered from the very basic components of subprocesses to the overall process structure. Also, it becomes interesting to view the discovery and development of single drugs as elements of the business process of a biotech company.

Starting from the detailed level, a number of the subprocesses in drug design shows potential for the use of mathematical models, e.g. the process of identifying lead candidates for a specific drug. Applications are here depending on a detailed knowledge of the chemical processes in the cells, a research area usually termed system biology or bioinformatics. Here, optimization methods like dynamic programming are in extensive use, and the potential for application of more complex methods are certainly present. Also the detailed PK/PD models described in the current paper belongs to this level of detail.

One the less detailed one may study the possibility to enhance the efficiency of the complete process as a whole. One possibility to decrease the risk of unsuccessful experiments is to use simulation as a tool to predict whether the outcome of a planned series of experiments is likely to satisfy the goals for the experiment. If simulation models and methods can be developed for all experimental stages of a project, these may also be used in the evaluation of the expected revenue of the drug development seen in a long term perspective.

Portfolio optimization is a well know tool in the financial sector, however, project portfolio optimization is less well understood that the optimization of portfolios of financial instruments. The ability to evaluate the risk of projects at different stages is or paramount importance to be able to develop realistic portfolio optimization models for industries with high risk projects as e.g. the biotech industry. It should also be mentioned that the multi-criteria nature of project portfolio optimization adds a level of complexity to the problem.

The paper is organised as follows: Section 2 and 3 sets the scene with respect to the pharmaceutical industry and modelling and simulation, and Section 4 describes the different elements of the current discovery and developments process in detail. Also, potential future changes in the current process are described. Section 5 describes portfolio optimization in the context of the pharmaceutical industry, and Section 6 sums up our findings.

2 Pharmaceutical products

2.1 Pharmaceutical R&D

The pharmaceutical industry relies on extensive research and development (R&D) to bring a new drug from idea to market launch. On average $802 million and 10-12 years are spent prior to marketing [2].

These figures are not unlike expenses and time horizons faced by other R&D intensive industries such as e.g. the aerospace or automobile industry. What separates pharmaceutical R&D from traditional R&D is the extreme element of risk inherent in the pharmaceutical development process. In most R&D intensive industries it is possible to assess the technological barrier associated with successfully completing the development of a product quite early in the development process. Uncertainty regarding the product is then due to market related issues such as lack of consumer interest etc. Within the pharmaceutical industry, however, the distance from idea to marketed product is much larger, as drugs are designed to interact with far from fully understood mechanisms of the human body. Thus, once the idea for a new drug has been conceived, it remains very uncertain whether there exists a molecule capable of manipulating the underlying physiological mechanisms of the disease and doing this without causing serious side effects to the drug user.

The life cycle of a pharmaceutical product is divided into a long R&D phase, applying for approval for marketing, launching the drug in the market, and a long-term sales phase. Patent applications are usually filed early in the development process, which along with a typical 20 year period of patent coverage, leaves pharmaceutical companies with a relatively short period of time to cover the expenses paid during R&D. Moreover, revenues generated by successful drugs must also cover losses imposed by unsuccessful R&D projects.

Each year pharmaceutical companies in the United States spend $30 billion on pharmaceutical R&D [10]. The R&D costs imposed by the large number of projects which fail during development must be covered by the revenues generated by a few drugs which reach the market. A rather small group of drugs are responsible for the majority of the total sales, as only 3 out of 10 marketed drugs produce revenues that match or exceed average R&D costs [10]. Among this group of profitable drugs, the so-called blockbusters stand out. Blockbusters are drugs which $ 1 billion in sales by year two of launch and are clearly destined to achieve peak sales of several $ billion. According to [7] 66 blockbusters occupied 45 % of the total pharmaceutical market, which in 2002 totalled $ 203.6 billion and $ 90.6 billion in the United States and Europe, respectively [6].

However, only large pharmaceutical companies have the resources to fund the development and marketing of potential blockbusters. The key objective is to effectively utilise huge marketing and sales investments to capture maximum market share as quickly as possible. In addition, a blockbuster must address an unmet medical need, and must target a large population size. Examples of blockbusters include Prozac from Eli Lily, whose sales in the United States totalled $ 2.6 billion in 1998 [7].

Even though smaller pharmaceutical companies cannot afford the marketing and sales efforts required for a drug to obtain blockbuster status, they too often rely on a few big selling drugs to generate the majority of the sales revenues. Examples include Cipramil from H. Lundbeck A/S whose sales totalled DKr. 3.4 billion in 2001.

During the last three decades the annual R&D costs spent by the pharmaceutical industry have increased 12 times in inflation adjusted terms [3], whereas the rate of new drugs reaching the market has merely doubled in the same period. Consequently, the cost of developing a new drug has increased dramatically. In inflation adjusted dollars, the cost of researching, developing and introducing a new drug was $ 138 million in 1975, $ 318 million in 1987, and $ 802 million in 2000 [10].

There are several reasons for the large difference between the growth rates of R&D expenditures and the rate of approved drugs. Within the early stages of the development process, the focus on more complex diseases has in turn lead to the use of more complex scientific tools and disease targets (targets are the underlying physiological disease mechanisms which are manipulated by the drug). E.g., potential drug candidates for degenerative diseases require more time to study than drugs for simpler diseases and acute illnesses. Within the later stages of the development process, the increase in R&D costs is caused by the increasingly complex structure of clinical trials. Pharmaceutical companies are required to provide complex and statistically significant clinical data about their products, which has become increasingly expensive with the need for more complex clinical data. Furthermore, the use of more complicated treatments and the associated increased complexity of clinical procedures and drug delivery systems (drug delivery systems are manmade systems with the purpose of delivering a drug or another chemical directly into a cellular target, such as a via a manmade vesicle called a liposome).

Despite the huge efforts put into the pharmaceutical development process, drugs are usually easy to replicate, which has lead to the emergence of many generic products. Thus, a drug only represents its true value while it is still covered by a patent. Once the patent expires, the sales typically drop dramatically. According to [7] a drug might experience to have lost 60 % of its peak sales 12 month after generic entry and 70 % 18 month later. In this respect, the situation of the pharmaceutical industry differs from many other R&D intensive industries such as e.g. the aerospace industry, where products are very difficult and expensive to copy, and industries, where the brand is very important.

In summary, the development of pharmaceutical products is an extremely difficult and risky task, comprising the following key challenges:

- To point out an unmet or not sufficiently met medical need, which given a suitable marketed drug would generate sufficient revenues to justify the preceding R&D investment.
- To develop products which pass all phases of the development process successfully, and obtain approval for marketing from the regulatory authorities.
- To develop products in sufficiently short time to allow for patent coverage, which has a sufficient duration to generate enough revenues to cover expenses imposed by the development of the drug and, additionally, expenses from failed development projects.

2.2 Types of drugs and treatments

Drugs function through complex biological and biochemical interaction between the molecular entities of the drug and *targets* in the patient, which typically are proteins related to the molecular mechanisms of the disease or disorder being treated. Depending on the objective of treatment and the understanding of the underlying molecular mechanisms of the disease, different targets and drug designs may be used for the same disease.

The ideal type of treatment may be characterized as follows: For each patient the disease type should be identified exactly among the often many subtypes of a particular disease resulting in similar symptoms. Moreover, the exact disease state should be identified among the different states a disease progresses. The drug which subsequently is administered to the patient should halt or reverse the progression of the disease rather than merely ameliorate the disease symptoms. The choice of treatment should take into account that patients with different genetic make-up may respond differently to the same treatment. A phenomenon which often results in lack of efficacy and/or serious side effect in large parts of the patient population. Thus, in order to predict the potential benefit or side effects associated with the treatment, the assignment of treatment should therefore include advanced techniques, such as diagnostic methods based on biomarkers, based on genetic/biomolecular traits of the patient.

However, treatments often do not meet the requirements put forward above. Different types of treatments reflect various levels of understanding of the mechanisms through which diseases work, and the way drugs and targets interact.

Traditional treatments typically come in a one-size-fits-all form and target a very broad patient group. They are often taken orally by the patient herself/himself without the presence of a specialist and generally treat chronic conditions by ameliorating the symptoms as distinct from changing the progress of the disease. This category of drugs are typically based on chemical entities and have produced some of the most profitable blockbusters of the pharmaceutical industry.

One-size-fits-all treatments are usually based on limited knowledge of the molecular mechanisms through which the disease works. Consequently, many diseases which traditionally have been considered as if they were the same disease are in fact different diseases within a particular disease family (or collection of related diseases). Similarly, the same treatment have often been assigned to the various disease states through which a disease progresses. Thus, one-size-fits-all treatments attempt to treat conditions which superficially seem the same identically, despite important differences in the underlying molecular mechanisms of disease subtypes. In addition, these treatments neglect the variation in treatment responses caused by differences in the genetic make-up of patients. Consequently, most drugs only work for between 40 and 60 % of the patients for whom they are prescribed. Moreover, drugs which work well for some patients cause intolerable side effects in others.

In order to eliminate some of the shortcomings of one-size-fits-all treatments, high density treatments are used to treat clinically defined subpopulations. These treatments are typically aimed at specific disease states and albeit they generally treat chronic conditions through alleviating the symptoms, they sometimes modify the progression of the disease. Due to the generally higher complexity of high density treatments compared to one-size-fits-all treatments, they are often administered by specialists.

Emerging technologies such as genomics and proteomics are expected to facilitate the development of a class of drugs, denoted targeted treatments, which will overcome the short-comings of one-size-fits-all and high density treatments with regard to lack of efficacy and/or serious side effects in large parts of the patient population. Targeted treatment solutions are based on knowledge of how drugs and diseases function at a molecular level. They will typically consist of biological entities, designed specifically to interact with targets validated through a detailed understanding of the disease pathology on a molecular level. Moreover, targeted treatments will comprise tests which distinguish between patients with different reactions to a given drug, due to the difference in genetic make-up.

In the future, a gene-based therapy is expected to deliver treatments to otherwise untreatable diseases. The basic principle of gene-therapy is to transfer DNA into the cells of the patient. Once inside the cells, the genetic material should then start to code for proteins which constitute the actual treatment. However, no commercial gene-based therapies are currently available.

In summary, the pharmaceutical industry has relied on just a single product type, one-size-fits-all treatments. In the future, multiple product types will be equally important. The importance of the conventional mass-market blockbuster will decrease. The importance of high density drugs for specific defined populations will increase. Knowledge of how diseases and drugs function at a molecular level will change treatments and it will be possible to assign the right treatment to each individual patient.

3 Optimization and Simulation

3.1 Mathematical Models

A *mathematical model* for a decision or a decision process is a description of a limited part of reality. The tool for the description is "mathematics", and the purpose is to get information regarding the real world through calculations, usually by means of a computer.

When building a model, care has to be taken that the model is sufficiently detailed that the outcome of using the model for decison making is meaningful for the problem considered. From this point of view, the model should be as detailed as possible. However, there is a trade off between detail and computing resources: The more detailed a model is, the harder it is to solve. The ideal model is therefore as detailed as possible, given that the necessary computations in the decision making process are feasible within the time frame of the process.

Model building is a difficult task, and it is made even more complex by the fact that real-life constraints are often "soft" constraints: When a delivery has a deadline, a delivery plan exceeding the deadline is not necessary infeasible, although the level of infeasibility of the plan is increasing with increasing delay. The models used in practice have different ways of attacking the soft-constraint problem, e.g. to include the minimization of constraint violation as a goal in the model.

Models may be of various different types:

- differential equations
- difference equations
- simulation models
- optimization models
- descriptive models

Models used for decision support are often optimization models or simulation models.

In figure 1, the model building process is illustrated.

3.2 Simulation

Simulation is the imitation of the operation of a real-world process or system over time. Simulation involves the generation of an artificial history of the system, and the observation of that artificial history to draw inferences concerning the operating characteristics of the real system that is represented. Simulation is used to describe and analyze the behavior of a system, ask "what if" questions about the real system, and aid in the design of real systems. Both existing and conceptual systems can be modeled with simulation.

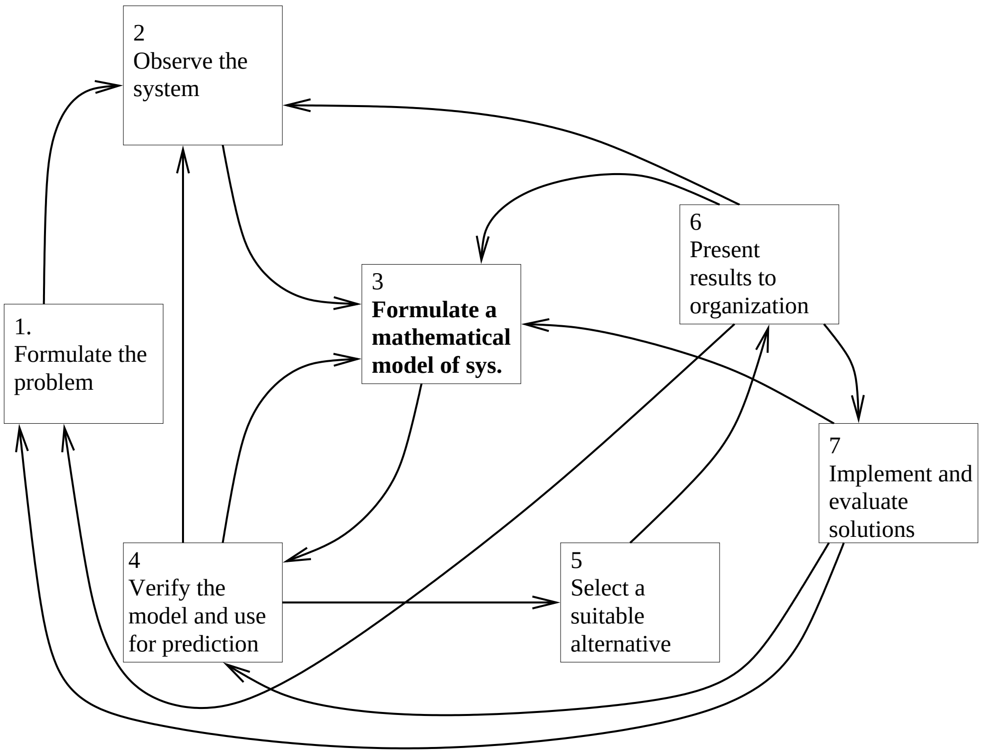


Figure 1. The OR modelling process - from [14].

Put differently, the term "simulation'" is used to describe a number of different activities based on software, which allows to investigate the performance and effects of a system without taking this into production. Simulation may be deterministic assuming that the future is completely known, or stochastic, where events in the future appear according to pre-defined probabilities.

The results from simulations are hence of diffent types ranging from consequence evaluation for a specific event in a specific system context over estimations of expected consequences of a particular action on an event to measures of average performance of a system over a longer time period with respect to events all following probability distributions.

In on-line simulation, simulation is used as a tool for decision makers to evaluate the effect of a potential here-and-now decision. Off-line simulation on the other hand enables analysis of strategies and tools to be applied in the decision process. The on-line situation is often envisaged as deterministic simulation, whereas off-line simulation is stochastic.

3.3 Optimization

A mathematical optimization model is a model expressed in terms of variables and mathematical expressions as “equal to”and “less than or equal to”. Such a model consists of

- A set of *variables* indicating the possible actions of the decision maker.

- An objective function giving the preferences of the decision maker
- A set of *constraints* in terms of equations and inequalities describing the feasible solutions for the problem at hand

The underlying idea is that by expressing the decision problem in terms of mathematical expressions it is possible to design and implement general software, which for any mathematical optimization model is able to solve the model and thereby indicate the best among the feasible solutions. Several types of optimization models exist:

- Linear Programming models
- Non-linear models
- Discrete models

Each model has its own advantages and disadvantages. Again, the trade-off is between the expressiveness of the model and the computational power necessary to solve it.

A solver is a software tool, which determines the values of the decision variables based on the actual problem data. The solver may be *exact* finding an *optimal* setting of the variables - corresponding to an optimal decision - or *heuristic* finding a *good* solution satisfying the constraints of the problem. Generally, very efficient commersial solvers exist for models of the general types mentioned above. However, it is often either necessary or more efficient to implement a tailored solver for the problem at hand.

Further information on mathematical modelling, optimization models, and solution methods can be found in [4, 9]

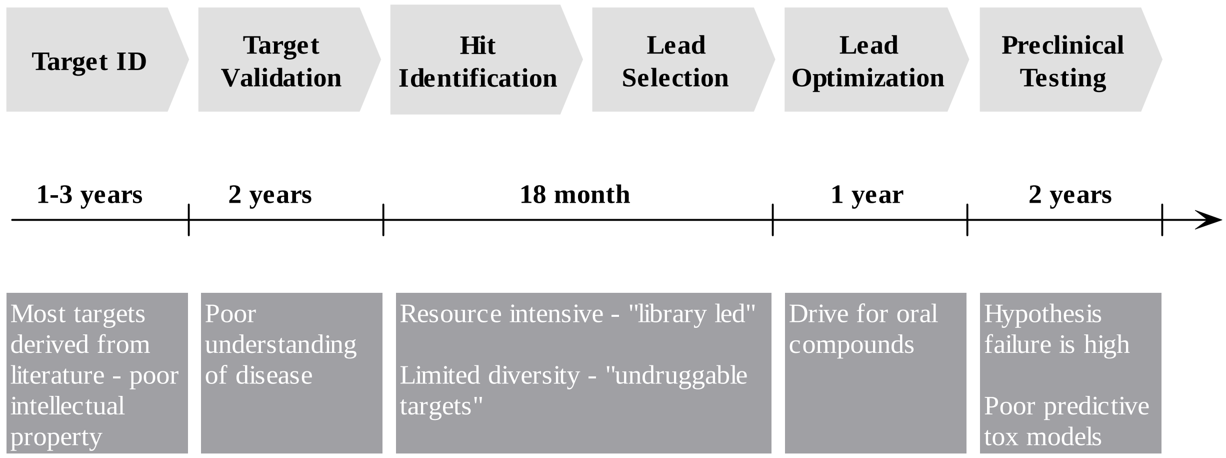


Figure 2. The current discovery process

4 Drug Discovery and Development

4.1 Overview

In this section the current and future structures of the drug discovery and development processes are discussed. The context is based on a report [13] published by IBM Business Consulting Services on the future of pharmaceutical development. The report addresses the expected changes in the discovery and development processes spurred by a shift in drug product types and emerging technologies such as genomics and in silico modelling and simulation.

The development of pharmaceutical products is traditionally divided into a discovery phase comprising nonclinical activities, and a development phase comprising clinical activities. In Figures 2 and 3 (adapted from [13]) the discovery and development processes are illustrated.

Both processes are sequential and divided into clearly distinct phases. Upon completion of each phase the *confidence* held in the drug candidate may be estimated. Figure 4 illustrates this concept, where the percentage-numbers on the vertical axis reflects the probability of bringing the drug candidate successfully through the remaining stages of discovery and development.

The current discovery process is time consuming and requires on average 6.5 years from target identification to preclinical testing. Furthermore, if a compound is required to be taken orally, the lead optimization stage is prolonged and additional time is added to the process. The different phases seen in Figures 2 and 3 are either exploratory of confirmatory in nature. E.g. the initial phase of identifying targets related to a disease is exploratory, whereas the following phase of validating targets is confirmatory and often leads to abandonment of projects. Similarly, exploratory activities take place at the lead optimization phase, which involves suggesting improvements of the chemical/biological entity based on computational techniques, in vitro studies, measurements of binding affinity etc. The

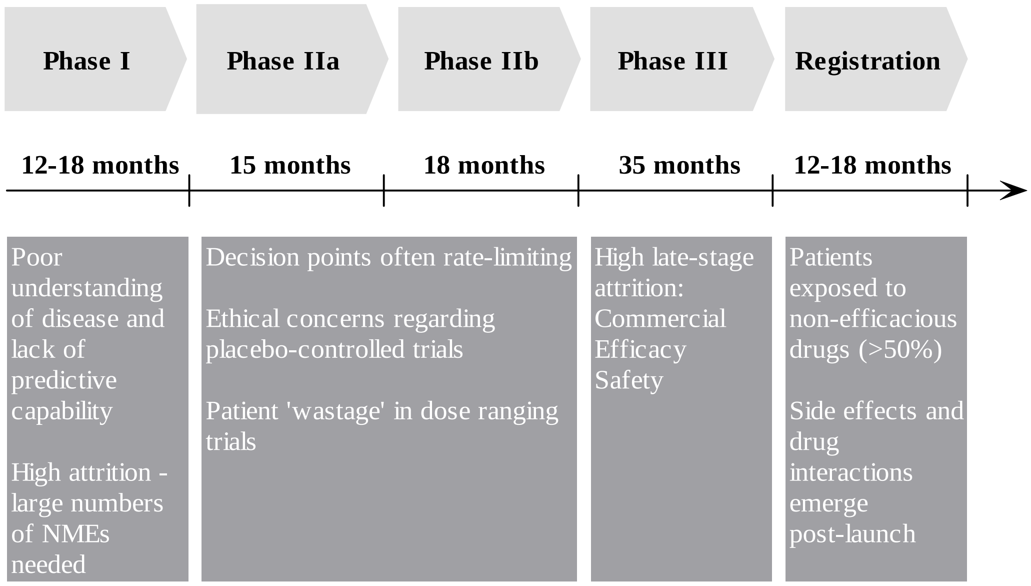


Figure 3. The current development process

molecular design is then put to a test in preclinical testing, where animals are used to detect potential toxic effects. In the development process the exploratory activities evolve around the phase I and IIa trials, whose purpose is to provide a range of safe doses to be used in confirmatory trials in phase IIb and III.

The largest share of R&D costs lies in the development process (see Figure 3), which according to IBM Business Consulting Services is expensive and inefficient. In particular, only 11 resp. 55 % of all drug candidates entering phase 1 and 3 respectively will eventually reach the market.

To eliminate the inefficiency of the current approach, IBM Business Consulting Services envisions a total transformation of the discovery and development processes. At the core of this transformation lies the redefinition of many diseases on a molecular level, which will in turn facilitate target validation. Lack of target validation is one of the biggest reasons why drugs do not work in man. The pharmaceutical industry must turn increasingly to biologics to find molecules to hit the right targets, as conventional chemistry will not generate enough variation. The new discovery process, see Figure 5, uses a disease-centric, biological approach to discovery and involves the following stages:

1. Identify the targeted disease and the objective of treatment, which could be either to amelioarate the symptoms associated with the disease or to halt/reverse the progress of the disease.
2. Identify the disease pathology and the underlying molecular mechanisms of the disease.
3. Identify targets using genome-based techniques.

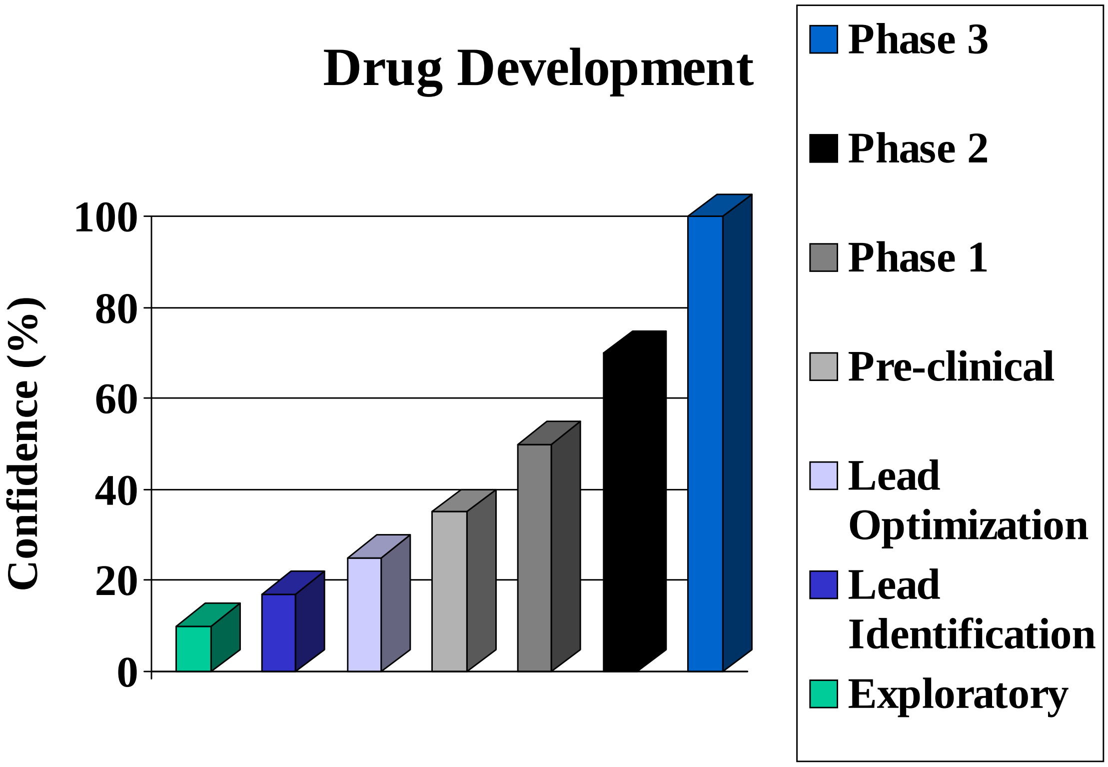


Figure 4. Confidence in a new drug candidate during the different stages of the discovery and development processes

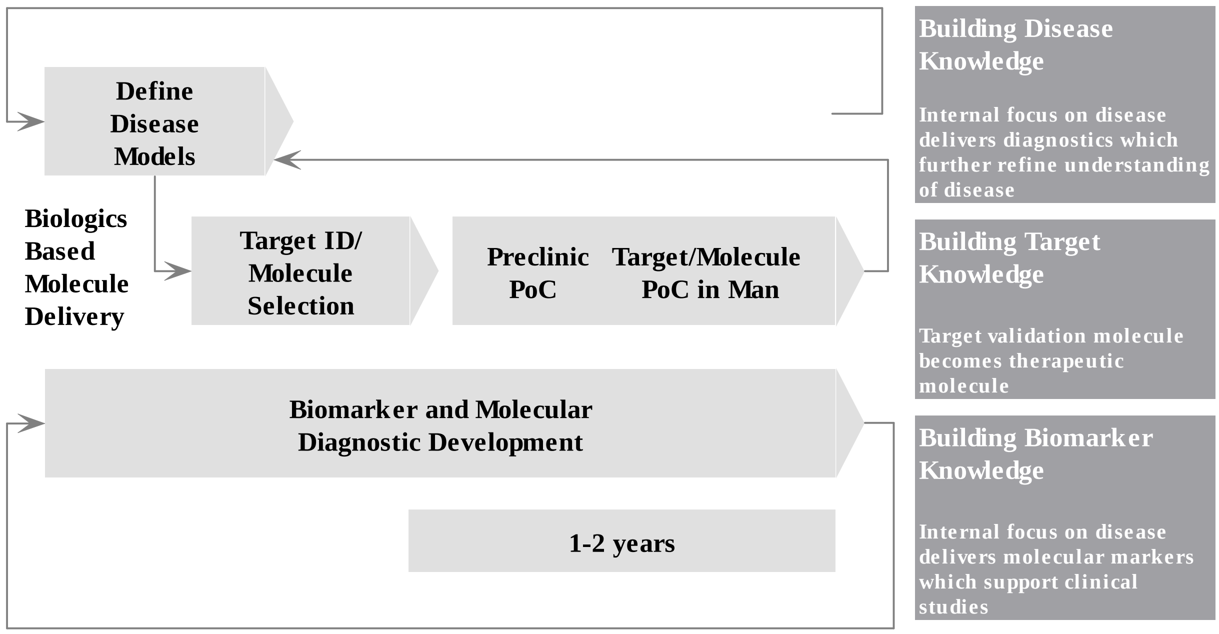


Figure 5. The discovery process of the future

4. Validate targets using biological molecules designed to interact with the targets. Simultaneously develop diagnostics based on molecular markers.

5. Use molecular markers to establish Proof of Concept (PoC) in man during the last part of discovery.

According to IBM Business Consulting Services the new approach has the potential to dramatically shorten the time from target identification to PoC in man to around 2 years from the substantially longer time horizon indicated in Figures 2 and 3. In addition, the risk of negative results from animal toxicity studies should decrease due to biological molecules generally carrying a lower toxic load than chemical entities.

The development process of the future is expected to undergo just as fundamental changes as the discovery process; Figure 6 illustrates the expected changes. In particular, the boundaries between the traditional phases of development will erode and part of the process will be replaced altogether. These changes will in part take place due to increasing use of modelling and simulation. Benefits of employing in silico techniques include a reduction in the number of clinical trials needed, as well as better trial designs. In particular, IBM Business Consulting Services expect modelling and simulation techniques to play a large role in conducting *adaptive trials*. Whereas the current method of clinical testing is static and phase-oriented, the traditional distinction between the various phases are likely to disappear in the future, and adaptive design principles will be employed. The fundamental idea is to use information acquired during one part of the trial to alter the course of the same trial, without compromising its statistical validity. Adaptive trials have already been conducted by several companies; Eli Lilly has used adaptive design principles in phase I cancer trials, and Pfizer has used adaptive dose-ranging trials.

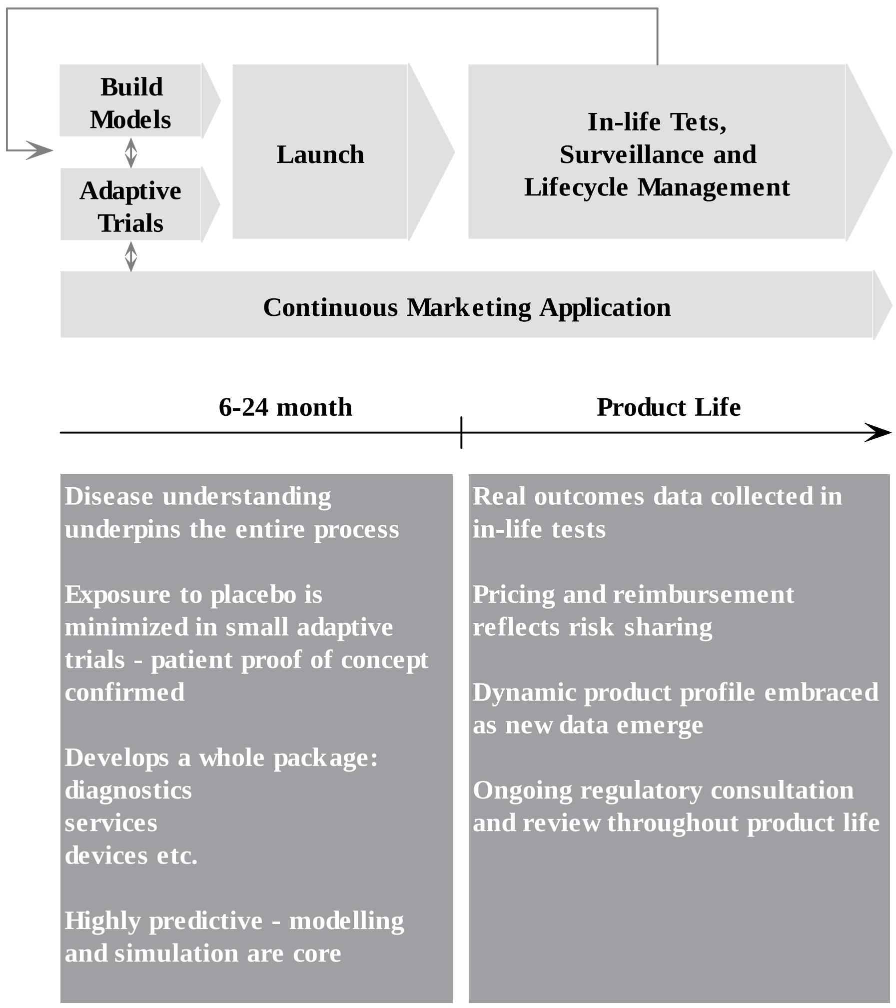


Figure 6. The development process of the future

In summary, the traditional approach to drug discovery and development is sequential, non-iterative and is carried out according to a plan-execute-evaluate principle. The approach of the future, however, is iterative, adaptive and is carried out according to a plan-execute-evaluate-replan-execute principle.

4.2 Nonclinical activities

The nonclinical activities are *the discovery phase* and *toxicity studies* which are discussed in the following sections.

4.2.1 Discovery

The discovery process comprises two overall activities; i) the identification of a drug target which is the physiological mechanisms through which a drug works, and ii) the design and refinement of molecules which will interact with the target. The various steps/procedures which are carried out in order to identify targets and design molecules, are depicted in Figure 7. These activities are described in more detail below.

Objective of treatment/knowledge of disease. This step involves considerations on portfolio level concerning company key areas of business and research expertise. The objective of treatment depends on the disease state targeted for treatment and whether the progression of the underlying disease mechanisms should be halted or reversed, or the symptoms associated with the disease should be removed.

Target discovery/target validation. Based on knowledge of the physiological mechanisms of a disease and the objective of treatment, researchers must identify a *target* whose link to the underlying disease mechanisms can be demonstrated. Drug targets were once found by chance, but today more detailed knowledge of the human genome allows for faster and more focused identification of targets. Valid targets include receptors (proteins), whose physiological action may be inhibited by binding to a *ligand*. Ligands are molecules that bind to receptors and thereby prevents the receptor from taking part in biochemical mechanisms related to a disease. Potential ligands to be used in a drug are called candidates and experiments involving estimation of binding affinity between the receptor and candidates are called screenings.

Assays. An assay is defined as a chemical or biological test that turns positive when a ligand interacts with a receptor. Often the test is some form of colorimetric assay where an indicator turns a specific color when complementary ligands bind to a receptor. The use of of fluorescently labelled reagents allows rapid optical screening of large collections of compounds. Microtitre plates enable small quantities of compound to be tested.

Screening. Once an assay has been defined, high-throughput techniques allow screening of hundreds of thousands of compounds in a matter of days to weeks. Often the starting point for the screening process is the corporate database of molecules, based on well established information on these compounds. An alternative strategy is to employ Structure-Activity Relationships (SAR). Using this approach, small “building block” molecules are identified that bind to a target. The individual molecules are subsequently assembled into larger molecules exhibiting equal or higher binding affinity than the product of the individual binding constants.

The outcome of the screening process should be the discovery of a small number of molecules, denoted *lead candidates*, binding to the target (receptor molecule). Often the lead candidates are weakly binding ligands, and the following steps in the flowchart focus on strenthening the binding affinity by altering the molecular structure of the lead candidates.

Combinatorial chemistry. This is a powerful technique employed by chemists to refine a lead candidate by synthesizing thousands of alternative molecular structures based on the original compound. Initially, a scaffold is defined as the part of the molecular structure of the compound remaining constant. Subsequently, the subsite groups of the original compound, which constitute the potential sites for derivatization, are reacted with combinatorial libraries. Thus, a multitude of new compounds are generated, from which high-throughput screening should identify new optimized lead candidates exhibiting higer binding affinity.

3D model of receptor/ligand complex. Knowledge about the receptor structure and receptor-ligand interactions may be obtained either computationally by employing homology models, or experimentally by employing x-ray crystallography or NMR.

Structure based design. This approach is often denoted rational drug design and employs knowledge of the 3D structure of the receptor/ligand complex to optimize the lead candidates. Using 3D molecular modelling software, regions of the ligand that fit poorly into the receptor target may be identified from the 3D model of the receptor/ligand complex and subsequently chemical changes may be suggested to improve binding. The computational optimization is followed by experimental estimation of the binding affinity, typically yielding an iterative process of modelling and experimental activities. The use of computer modeling to refine structures has become standard procedure in modern drug design.

Once one or a few lead candidates remain, the therapeutic effect and potential side effects of the molecules should be investigated. For ethical reasons, preliminary investigations of efficacy and toxicity are not carried out in humans and instead animals studies are conducted prior to human drug exposure in clinical trials.

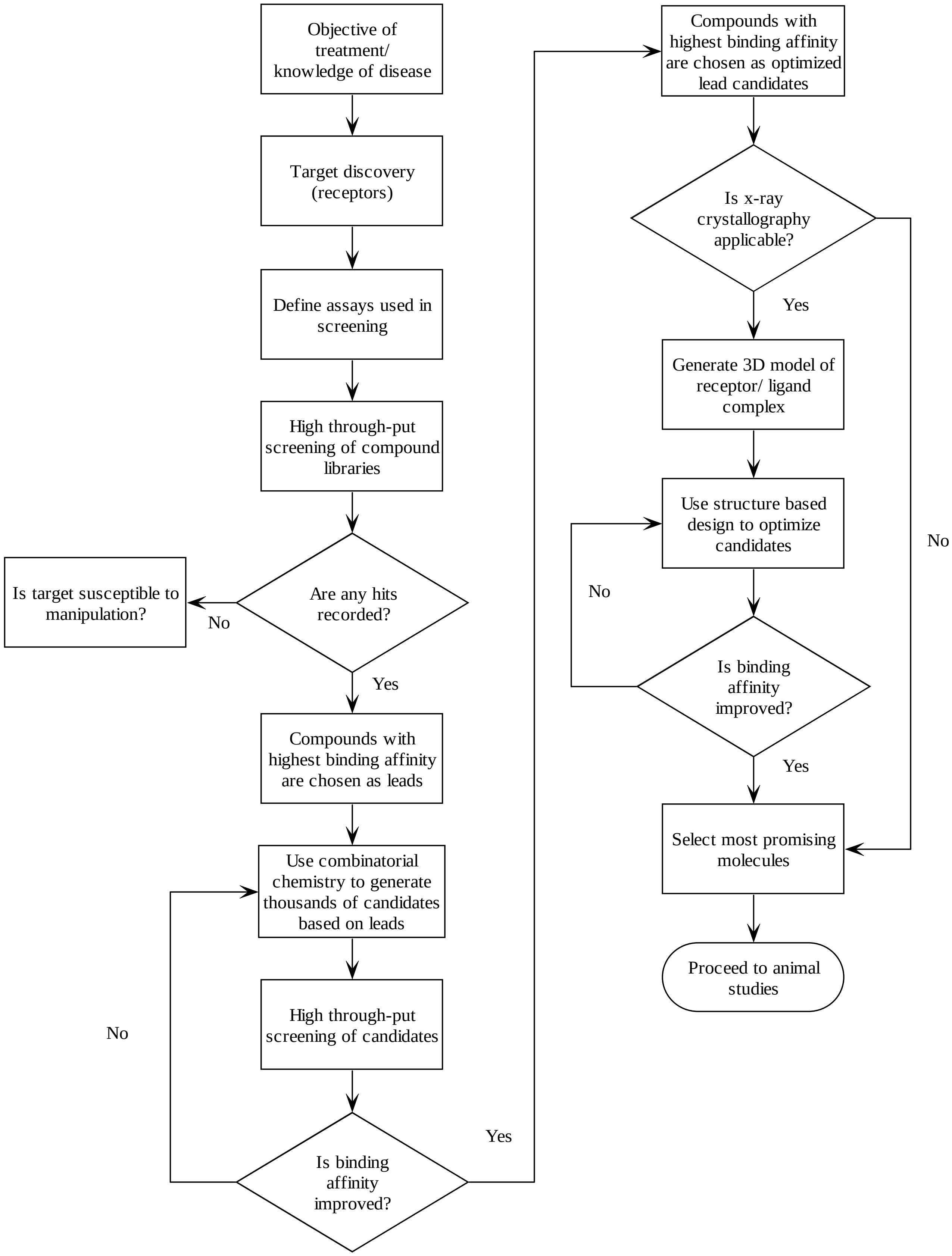


Figure 7. The Discovery Phase

4.2.2 Toxicity studies

In order for a new drug to obtain approval for marketing, the drug must be demonstrated to be efficacious and not to possess any serious side effects. The demonstration of a *safe profile* commences in socalled *toxicity studies* prior to human exposure in clinical trials. These studies are mainly systematic investigations into potential side effects of drug intake in animals, as very often animal studies provide reliable information regarding possible consequences of human drug exposure. Despite the predictive efforts of animal studies, side effects in humans may, however, show up during the clinical phases. Even during the final phase 3 trials, rare side effects may show up due to the large number of patients enrolled in these trials.

Toxicity studies are influenced by guidelines and regulations issued by i.e. FDA [1] and ICH [8]. The regulatory authorities require toxicity studies to support the clinical phases, and in particular, a number of short-term studies have to be carried out before the initiation of first-in-man studies. For drug candidates which succesfully pass the short-term toxicity studies, a likely range of safe clinical drug doses should have been established. Furthermore, the studies should provide indications of the potential consequences if these doses are exeeded.

Another type of toxicity studies of longer duration are allowed to run in parallel with the clinical phases, and are designed to investigate the long-term effects of drug use. The short term studies which comprise various in vitro tests and animal studies are described below in the section *Toxicity studies supporting clinical trials.* Experimental procedures are visualized in the flowcharts in Figures 8, 9, 10, 11 and 12.

During toxicity studies many drug candidates are rejected due to observation of toxic effects in animals causing concern about the expected clinical dose. The high failure rates may potentially be reduced if the chemical entities in drug candidates are screened for toxicity early in the discovery process using in vitro methods. Preferably, the toxicological properties of a new drug candidate should be considered already at the lead optimization stage, where molecule/target binding properties are also optimized. At this early stage, the cost of changing the molecular structure of a drug, or rejecting a drug candidate altogether, is low compared to stopping a development project, which has already entered toxicity testing or even the clinical phases. The methods of in vitro testing are described below in the section *In vitro cytotoxicity testing.*

4.2.3 Toxicity studies supporting clinical trials

Prior to the initiation of first-in-man Phase I trials, a basic package of data on the toxicological properties of drug candidates must be collected. The toxicological properties may be characterized in terms of *hazard* and *risk*, where hazard refers to the potential of the compound to cause damage to the body. The risk, on the other hand, refers to the probability of hazard under the prescribed conditions of treatment. The package of toxicity studies comprises (Adapted from [5]):

- Safety pharmacology - indication of adverse pharmacologically mediated actions on central nervous, cardiovacular and respiratory systems.

- Pharmacokinetics - prelimerary studies on absorbtion, distribution, metabolism and excretion (ADME).
- Single-dose (Acute) toxicity - two species by two routes of administration. One is usually intravenous to ensure systemic exposure and the other is by the proposed clinical route. Usually an evaluation of the Maximum Repeatable Dose (MRD) and possibly local irritancy.
- Repeat-dose toxicity - rodent and non-rodent species are required. The duration of the test depends on the duration of clinical exposure but many companies conduct two 14-day studies before going into man. Studies should be done using the proposed clinical route.
- Reproductive toxicology, usually embryo/fetal development studies in two species, are required in Europe and Japan if women of child-bearing potential are in cluded. Not required in the US for some early trials.
- Mutagenicity - *in vitro* tests for mutagenicity and chromosome damage.

The various steps involved in the safety pharmacology, single-dose and repeat dose studies are depicted in Figures 8, 9, 10, 11 and 12. Comments on the figures are given below.

Safety pharmacology. In vivo safety pharmacology experiments should be designed to define the dose-response relationship of the observed adverse effects. Usually the experiments are performed as single-dose experiments. The sample size, which is the number of animals participating in the study, should be chosen large enough to allow meaningful statistical interpretation of the experimental data. Appropriate negative and positive control groups should be included. The expected clinical route of administration should be used when possible. Exposure to the chemical entities contained in the drug and their major metabolites should be similar to or greater than what is observed in humans. However, as the drug has not yet been used clinically at this stage, the level of metabolites in humans must be estimated by considering similar drugs or through specific in vitro experiments.

Single-dose (Acute) toxicity. The single-dose studies are divided into preliminary and definitive studies. The preliminary studies are performed in order to provide an estimate of the Maximum Non-Lethal Dosage (MNLD) for use in definitive studies. Definitive studies are performed to evaluate effects that may result from acute exposure to the MNLD and predict effects of overdosage in humans. Single-dose studies are performed in two species, usually rat and mouse, and by two routes of administration; intravenous to ensure systemic exposure, and through the proposed clinical route. In both types of single-dose studies the, observation periods include clinical observations and measurements of the body weight. As appears from the single-dose preliminary flowchart, animals are terminated following the seven day observation period, upon which they undergo a full macroscopic examination and any unusual abnomalities are examined microscopically. At this point, preliminary information on target organ toxicity is obtained. Further information is added by performing full macroscopic and microscopic examinations following the definitive single-dose studies.

Repeat-dose toxicity. Similar to the single-dose studies, the repeat-dose studies are also divided into preliminary and definitive studies. The purpose of the preliminary repeat-dose study is to establish the maximum repeatable dose (MRD), which is then used in the definitive study. The flowchart depicts an escalating-dose MRD, which is the typical type of MRD-study, even though fixed-dose MRD studies also exist. The aim of both studies is to determine a profile of toxic effects and to provide estimates of pharmacokinetic parameters. The toxic profile is established by clinical observations, measurement of body weight, pulse rate in dogs, haematology, clinical chemistry, urine analysis, plasma drug concentration, macroscopic and microscopic post mortem examinations, ophthalmoscopy, electrocardiography, organ weights, and in some laboratories, hearing tests. The pharmacokinetic parameters are determined by measuring the time to reach (T_{max}) the maximum plasma concentration (C_{max}) and to provide an indication of exposure by the area under the plasma time concentration curve (AUC), the plasma elimination half-life ($T1/2$) and the minimum plasma concentration (C_{min}) after single and repeat doses. Before any measurements of pharmacokinetic parameters can be made, however, a suitable assy has to be developed.

4.2.4 In vitro toxicity testing

Potential toxic effects of a drug may be considered already at the lead optimization stage where the drug/target interaction is improved through refinement of the molecular structure of the lead candidates. Testing for toxicity at this stage involves the screening of a large number of molecules generated through combinatorial chemistry. Thus, the thoughput capacity of any test becomes an important issue, and in this respect animal tests are too slow and cumbersome.

To meet the requirement of high-throughput capacity, toxicity assays have been developed, where tests are carried out by exposing cultured cell lines to small quantities of a compound. In vitro toxicity testing is a rapid, standardized, sensitive and inexpensive way of determining whether a compound contains significant quantities of biologically harmful extractables. The high sensitivity of the tests is due to the isolation of the test cells in cultures and the absence of protective mechnisms that assist cells within the body.

A positive result in an in vitro toxicity assay is an early warning sign that a compound contains one or more substances, which in turn could lead to toxic responses in subsequent animal studies or clinical trials. A negative result indicates that a material is free of harmful substances. However, it cannot be considered evidence that a material can be considered biocampatible. It is simply a first step.

The primary targets of drugs are the cells in the liver, kidney, central nervous system, skin and lungs. Cell lines from these organs are cultivated, and a suitable assay is devised to investigate toxicity. Depending on the number of compounds to be screened, different experimental techniques may be employed.

Automatic techniques. The company Cellomics is developing assays in cultured cell lines of liver and kidney origin from different species. The company has developed the Multiparameter Cytotoxicity 1 Assay for simultaneously determining the toxic effects of compounds on different cellular properties such as the nuclear morphology/size, cell membrane permeability, lysosomal physiology and cell loss. Another assay from this company is the Cell Viability Assay for rapid quantitation of the percentage of live and dead cells in the analyzed population. Both assays image cells in 96-well plates in Cellomics ArrayScan

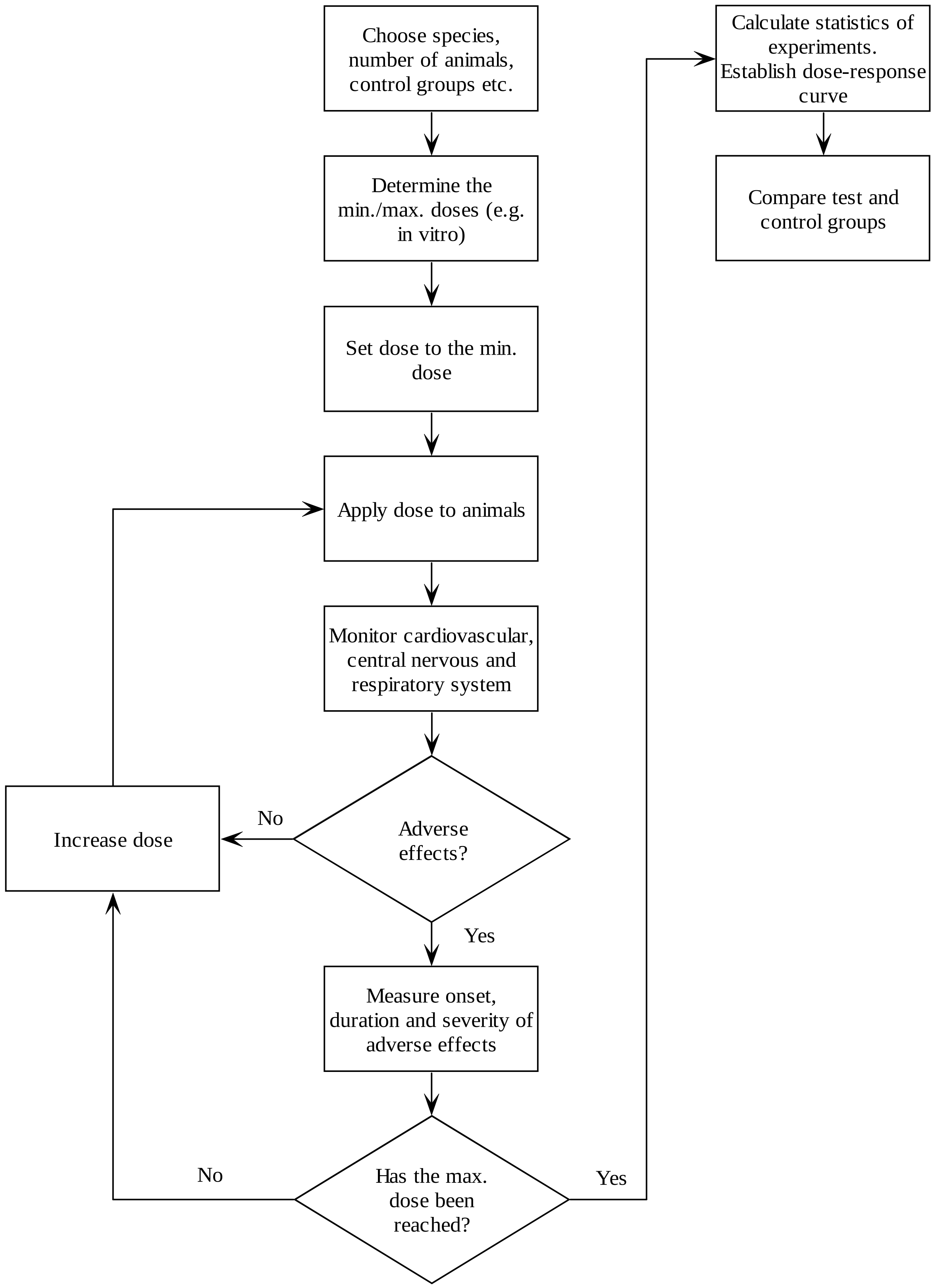


Figure 8. Safety Pharmacology

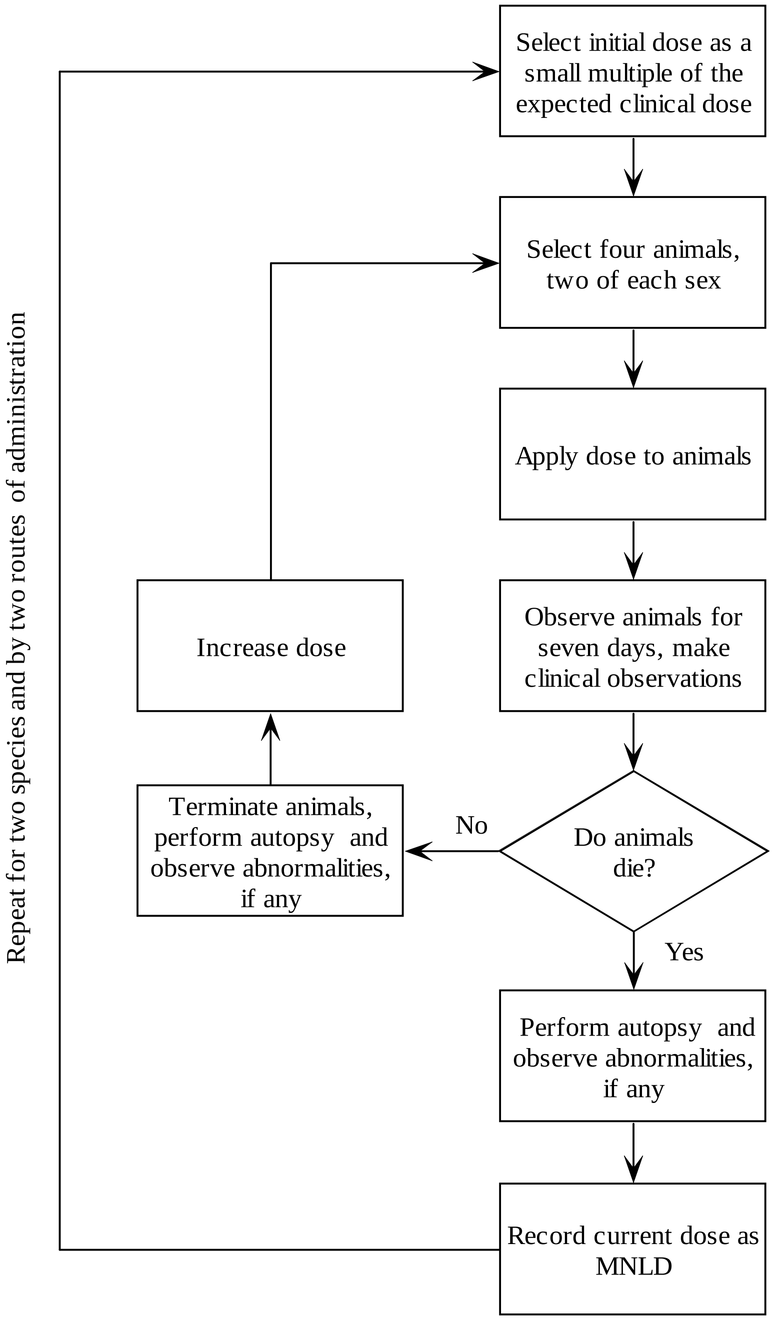


Figure 9. Acute Toxicity (single dose)

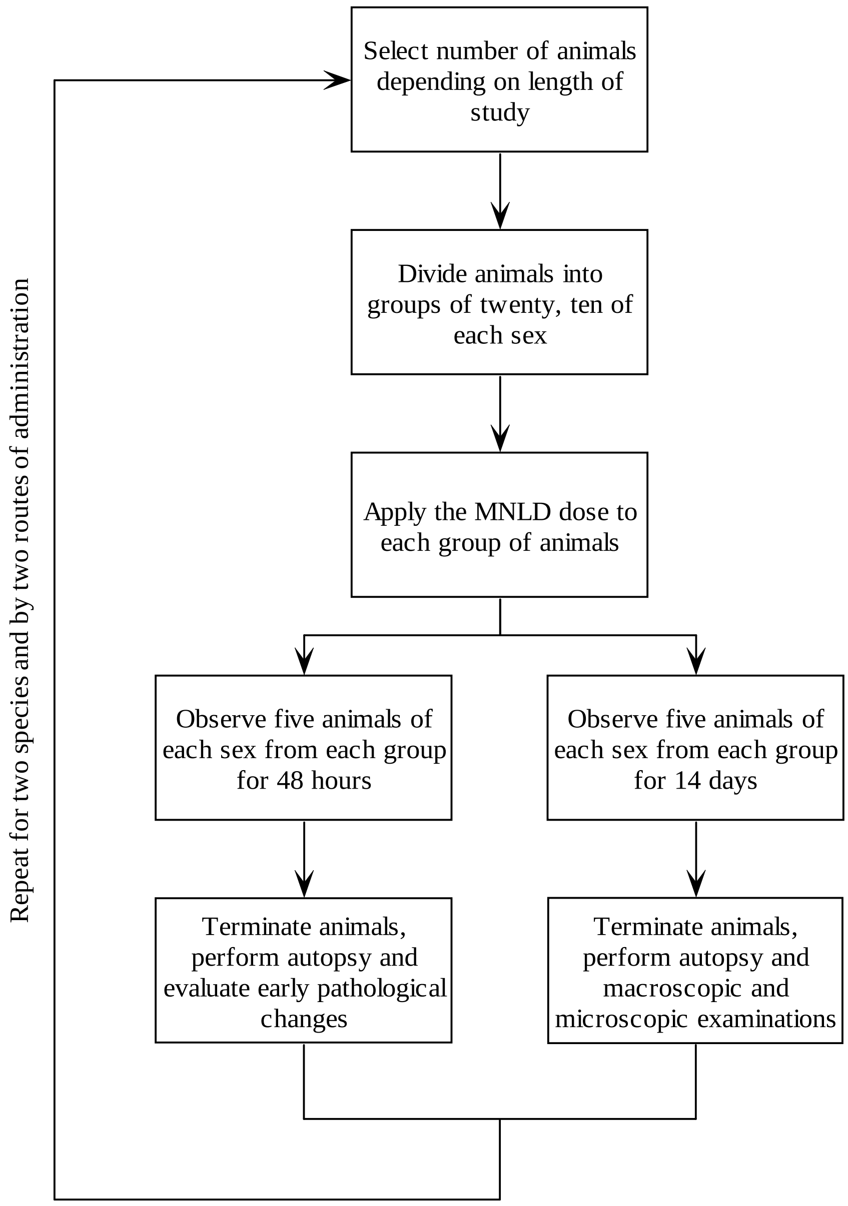


Figure 10. Acute Toxicity (single dose)

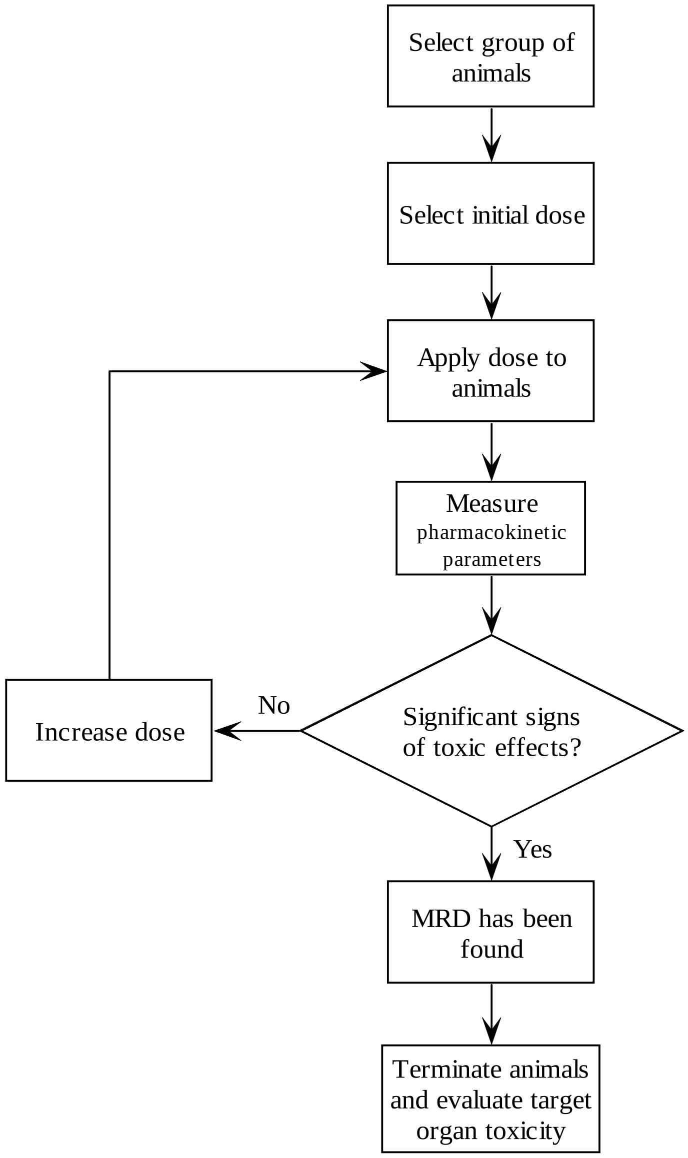


Figure 11. MRD

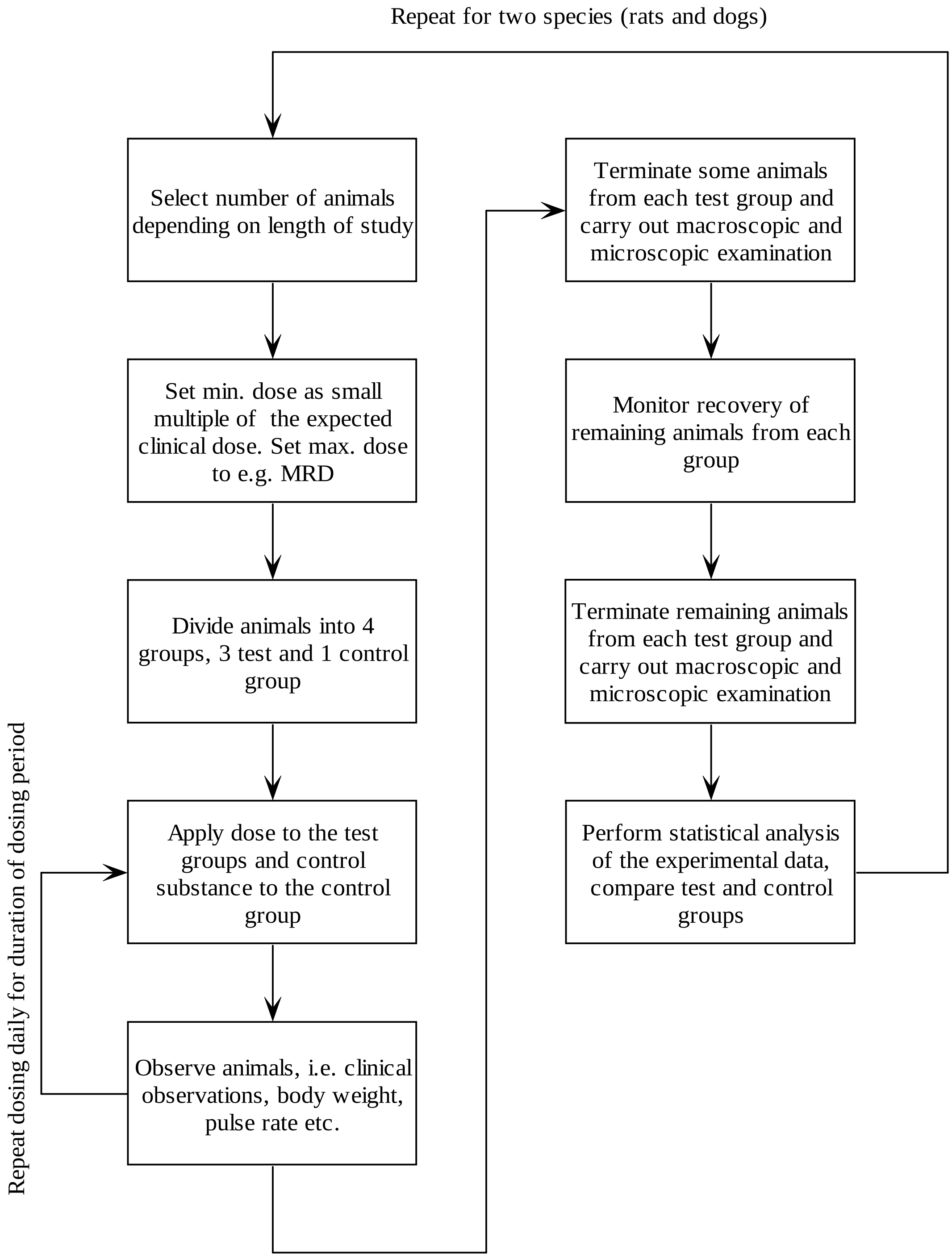


Figure 12. Repeated dosing

High Content Screening (HCS) System, and the images are analyzed rapidly by a dedicated image processing method providing high content information about the effects of compounds on the various cellular targets at the individual cell level.

Manual techniques. Laboratory technicians culture mammalian cells, which are typically of mouse or rat origin, in flasks using nutrient culture media. In standard cytotoxicity test methods, cell monolayers are grown to near confluence in flasks and are subsequently exposed to test or control compounds. The cells are stored in an incubator, and are periodically removed for microscopic examination at designated times. Observations are performed for visible signs of toxicity in response to the test and control compounds, such as change in the size or appearance of cellular components. If the properties of the cells, exposed to the test compound, vary from the control cells at a statistically significant level, the presence of toxic effects have been established.

4.3 Clinical trials

Once a drug has completed animal toxicity studies succesfully, humans are exposed to the drug in a series of experiments called clinical trials. The activities carried out during the clinical development process may be divided into two main categories; i) exploratory trials whose aim is to establish a range of (safe) doses to be used in subsequent confirmatory trials, ii) confirmatory trials investigating whether a hypothesis regarding a drug candidate is true. The purpose of confirmatory trials is to either make go/no go decisions regarding the continuation of development or to provide the information to the regulatory authorities required to obtain permission for marketing.

4.3.1 Classification of clinical trials

Traditionally the clinical development process is divided into three distinct phases, phase I, II and III:

Phase I At this point the drug candidate is tested in man for the first time. Usually the testing takes place in a small number (tens) of healthy volunteers, but patients may be used at times. The objective of the trial is to assess tolerability, preliminary safety, pharmacokinetics, and pharmacodynamics if possible. In particular, a range of doses which do not result in toxic effects has to be established. This phase lasts an average of six month to one year.

Phase IIa Based on the range of safe doses found in the preceeding phase I, the drug candidate is tested in a small number (10-200) of patients suffering from the targeted disease. The pharmacokinetics and pharmacodynamics are assessed, and preliminary estimates of efficacy and safety are made. Potential surrogate endpoints (see below) are validated. Surrogate endpoints are endpoints different from the therapeutic effect itself. E.g. changes in physiological parameters which are indirectly connected to the therapeutic effect. Such indirect links must be verified at this stage. During this phase, a range of doses to be used in the subsequent phase IIb and III trials should be found.

Phase IIb Based on the knowledge obtained from the preceeding Phase IIa trial, a larger scale trial (several hundred patients) is carried out to formally asses the dose-response relationship. The clinical responses to the treatment should establish Proof of Concept (PoC). PoC is the demonstration of efficacy and safety in a limited patient population compared to the number of patients used in phase III.

Phase III These trials aim at establishing efficacy and safety in a large number of patients (hundreds to thousands of patients) through socalled *controlled* measurements of clinical responses. Controlled trials compares the effect of a new drug with existing similar treatments or placebo in the event of no comparable drugs. Based on the outcome of this phase, the regulatory authorities evaluate the efficacy and safety of a drug, and eventually decides for or against issuing approval for marketing.

4.3.2 Evaluating the outcome of a trial

Prior to initiating a clinical trial an endpoint or several endpoints, stating the objective of the trial, must be defined. For phase I trials whose objective includes assessing tolerability and preliminary safety, the trial endpoint is a range of safe dose to be used in subsequent trials. For Phase II and III trials, aiming at demonstrating efficacy and safety, the endpoint could be the direct demonstration of therapeutic effect (e.g. pain relief or decrease in blood pressure) in a sufficiently high number of patients. Alternatively, surrogate endpoints may be employed. Surrogate endpoints must represent a plausible link to the therapeutic effect mediated through a surrogate marker, and must hold a high predictive value for the therapeutic effect. As stated above, surrogate endpoints should be validated in phase II. However, strong evidence for the link between the surrogate endpoint and the therapeutic effect is best found in Phase III, when a sufficient number of study subjects have achieved a therapeutic response that can retrospectively be correlated with the change in the surrogate marker. Thus, surrogate endpoints are most valuable for follow up on drugs, when the link between the therapeutic effect and changes in the surrogate marker has formally been established.

4.3.3 Basic design principles

One of the most important aspects to take into account when designing a trial is how to avoid bias, which is the introduction of a systematic error or series of errors that distort the obtained data, and which may affect statistical analysis of the clinical trial data. During the design and execution phases of the trial, bias may occur in the selective sampling of subjects for the trial, in allocating the treatments, and in measurements relating to the trial endpoint. Aspects of clinical trial design that are introduced to avoid bias include randomization of treatments and blinded designs. The concepts of randomization and blinding are described below.

Another important aspect of clinical trials is to evalute the effect of the drug being investigated in comparison to existing treatments. For Phase I trials, however, whose aim is not to demonstrate efficacy but to establish a range of safe doses, comparator treatments are not included. When estimating the efficacy of a drug in Phase II and III trials, the inclusion of comparator treatments allows discrimination of outcomes caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease etc. The comparator medicine, which acts as a “bench mark” is in practice the most widely prescribed medicine. If there is no accepted standard therapy in common use, however, placebo treatment may be used. A new treatment may be compared to a comparator treatment on three different levels; i) demonstrate equivalence of the two treatments, ii) demonstrate superiority of the new treatment, and iii) demonstrate non-inferiority of the new treatment.

Non-inferiority trials are more common than equivalence trials in Phase III, and demonstrate, if succesfully, that a new treatment is no less effective than an existing treatment.

4.3.4 Randomization

Controlled randomized trials, which compares two or more types of treatment, are viewed as the state-of-the-art technology for clinical evaluation of drugs. In all controlled trials (trials including comparator treatments) the population of the control groups, to whom the comparator medicine is administered, must be as similar as possible to the group receiving the drug being investigated. Therefore, all patient groups participating in the trial are assembled according to certain inclusion/exclusion criteria regarding patient covariates such as age, sex, race, weight, previous medical history, previous and current medication, status of major organ function.

The purpose of randomization is to generate comparable groups of patients who share certain characteristics, in order to facilitate statistical evaluation of the trial results. The use of randomization can prevent subjective assignment of patients to treatment groups, and consists of:

1. Random selection of a representative sample from the targeted patient population.
2. Random assignment of patients to different treatment groups, which are required to be comparable with regard to e.g. the distribution of covariates (sex, body weight, age etc.) or the disease stage.

When recruiting patients from an inhomogeneous patient population, stratified sampling may be employed to obtain groups of homogeneous subpopulations with respect to certain covariates. The idea is to sample patients according to some prescribed patient characteristics. The patients are divided into groups denoted strata, where the variability of patients within each strate is chosen to be small compared to the between-strata variability. Having divided the patient population into strata, the patients may be assigned to different treatment groups such that the distribution of treatments with respect to important covariates is balanced. This in turn ensures that the statistical evaluation of the treatment effect possesses the optimal precision.

4.3.5 Parallel designs

In trials using parallel designs, a number of patient groups corresponding to the number of treatments are established using randomization procedures, followed by administration of one type of treatment to each group. Two different types of parallel designs exist:

- Group comparison
- Matched pairs parallel design.

The simplest type of group comparison is the two-group parallel design, which compares two treatments, e.g. an active treatment group and a control group.
Before patients enter a clinical trial, a run-in (or lead-in) period of placebo, no active

treatment etc. is usually employed prior to randomization. The advantages of including a run-in period prior to the active treatment include:

1. It acts as a washout period to remove effects of previous therapy
2. It can be used to obtain baseline data and to evaluate if patients fulfill study entry criteria.
3. It can be used as a training period for patients, investigators, and their staff.
4. It helps in identifying placebo responders.
5. It provides useful information regarding patient compliance
6. It can be used to estimate and compare the magnitude of possible placebo effects between groups.

4.3.6 Use of blinding in trials

The concept of blinding a trial is to block the identity of treatments to the patients alone or to the patients and other parties involved in the trial. Blinding is used to prevent bias caused by subjective judgement in evaluating the effect of treatment, processing data, performing statistical analysis, due to knowledge of the identity of treatments.

The four different types of blinding employed in clinical trials correspond to the amount of knowledge of the assigned treatments, which is being held by each of the three parties involved in a trial. The three different parties involved in a trial are the patients, the study center or investigator, and the sponsor (usually the company aiming at obtaining regulatory approval of a drug). The four types of blinding comprise:

Open-label Both the patient, investigator and the sponsor know to which treatment group the patient is assigned.

Single-blinding The patient is unaware of the treatment he or she is receiving (e.g. active treatment or placebo), whereas the investigator and sponsor are informed.

Double-blinding Neither the patient, nor the investigator know to which treatment group the patient is assigned (e.g. active treatment or placebo), whereas the sponsor is informed.

Triple-blinding An extension of the double blinding concept, in which the sponsor monitoring the trial is also deprived of knowledge of the type of treatments being assigned to the patients.

Open-label studies are generally not recommended for comparative clinical trials due to the risk of bias in evaluating patients. Especially subjective endpoints such as the assessment of the pain level associated with a disease are subject to bias. But even objective endpoints such as blood pressure levels may be associated with bias.

4.4 Modelling and simulation in discovery and development

The potential for using modelling and simulation in drug discovery and development is huge, however, the actual use is limited. In the following, we focus entirely on *Clinical Trial Simulation* - the area, in which there is a long tradtion for using mathematical model and software in the process development process.

4.4.1 Clinical Trial Simulation

The aim of this section is to illustrate the use of simulation to support decision making during the clinical development process. Below some general remarks regarding Clinical Trial Simulation (CTS) are given, followed by two cases of applying simulation to phase I and III trials, respectively.

A general overview of CTS is provided in Figure 13. As appears CTS is rather complex and builds on a number techniques/technologies. In particular, an effort must be made to establish a PK/PD model prior to initiating simulations.

The fundamental idea of CTS is to investigate whether a given trial design suffices to meet the trial endpoint by carrying out virtual trials, given knowledge about the trial population, trial execution and the effect of the drug in question. This fundamental ability to predict trial outcomes opens up for a broad variety of possible applications. These applications include

1. CTS may be used to investigate aspects of either exploratory or confirmatory types of trials. The endpoint of an exploratory trial could e.g. be the Maximum Tolerated Dose in healthy volunteers (first-in-man, phase I), whereas confirmatory type of trials typically aim at demonstrating efficacy and safety in patients. Examples of confirmatory types of trials include the proof-of-concept (POC) in Phase II, and Phase III trials aiming at demonstrating efficacy and safety in a large number of patients for the benefit of obtaining regulatory approval.

2. For a given model of the drug, different trial designs may be compared regarding e.g. cost and chance of meeting the trial endpoint (see point 3 below). Similarly, for a given trial design, the sensitivity of the trial endpoint to changes in the model of the drug may be explored (see point 4 below). Also operational issues relating to variability in executing the trial may be analyzed employing CTS (see point 5 below).

3. Altering the study design (protocol). For a given drug model, CTS allows for comparison of different choices of protocol variables including the number of centers, center sizes, inclusion criteria, exclusion criteria, study type, treatments, randomization procedures, observations, dose escalation schedules etc. One such application of comparing study designs involves determining the composition of the trial population which maximizes the chances of meeting the trial endpoint.

4. Altering the drug model (PK/PD). For a given study design, the PK/PD model governing the effect of the drug on patients/volunteers may be perturbed in order to

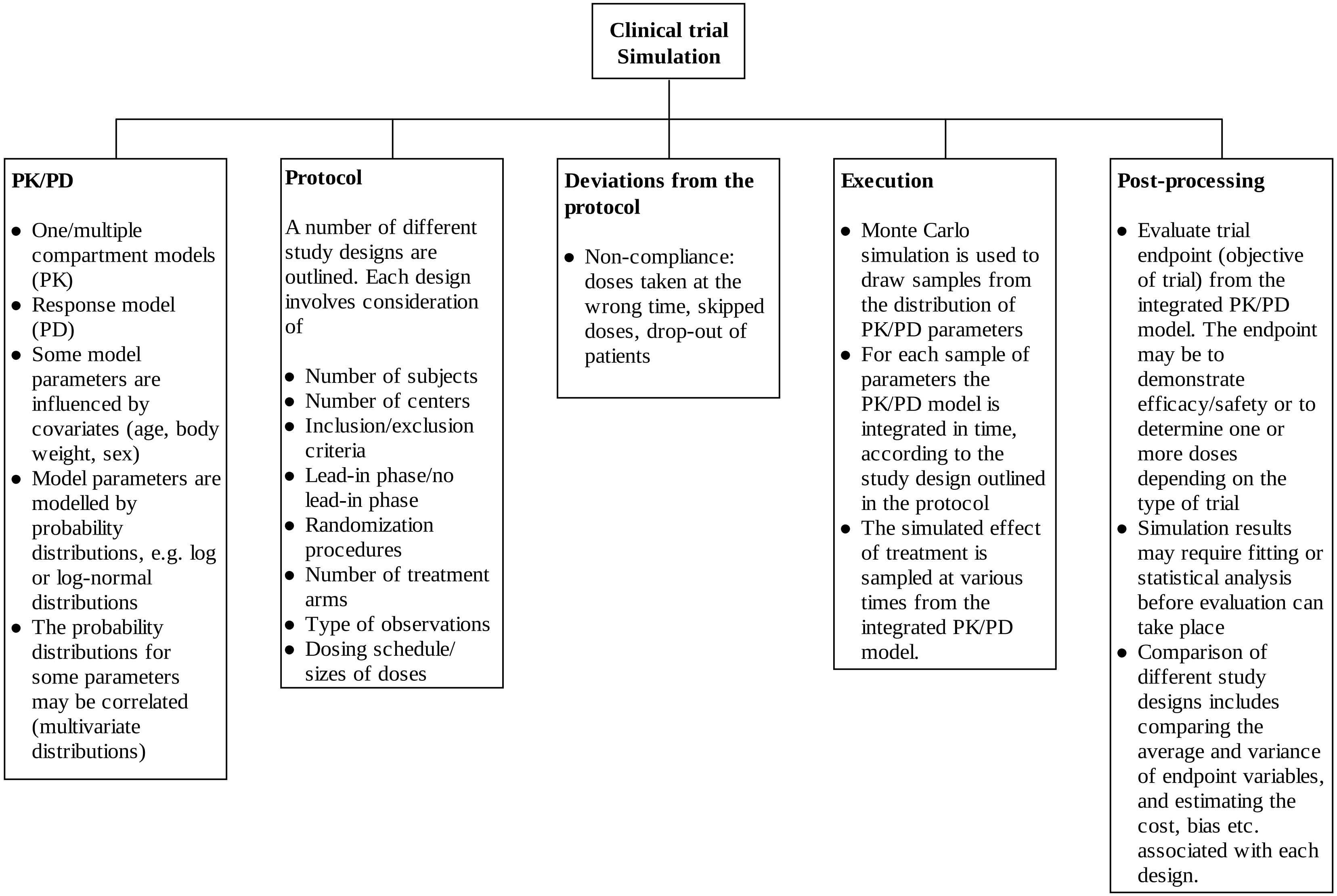


Figure 13. Overview of different elements of Clinical Trial Simulation

investigate the sensitivity of the trial outcome to changes in the structure/parameters of the drug model. E.g. if the trial outcome varies significantly with small changes in the PK/PD model, further investigations into the PK/PD properties of the drug may be required before initiating CTS.

5. Execution of the trial. Executing clinical trials are associated with varying degrees of uncertainty relating to patient behaviour, differences between study centers etc. Important aspects of patient behaviour include drop-out rates, compliance to treatment, drug holidays. The effect of these various sources of variability on the trial outcome may be investigated through CTS.

4.4.2 Using CTS in a Maximum Tolerated Dose study

In the example of CTS discussed below, simulation is applied to a Maximum Tolerated Dose (MTD) study, where healthy volunteers are exposed to increasingly larger doses until Dose Limiting Toxicity (DLT) occurs. The MTD study belongs to the phase I category of clinical trials, the primary objective being to determine a safe dose or a range of safe doses for further studies of therapeutic activity. Below the following steps needed to arrive at simulated estimates for the MTD are discussed:

- Establishing a PK/PD model, including determination of the basic model structure and obtaining probability distributions for selected model parameters.
- Determining a number of different trial designs to be explored by simulation.
- Using stochastic methods to simulate the probability distribution of possible drug responses in the trial population for different treatment regimes.
- Post-processing of the simulation results, including comparison of different trial designs.

4.4.3 Establishing the PK/PD model

Initially a short-term safety trial is conducted to collect PK data, and to monitor physiological changes associated with the pharmaco-dynamic properties of the drug. The parcitipating subjects are observed to have decreased white blood cell (WBC) counts. A population PK/PD model linking the concentration and the WBC is built based on the trial data. The PK model is a one-compartment population model with absorbtion, and the PD model is an indirect response model for the suppression of WBC formation. As an indicator of toxic responses in study subjects, the WBC is translated into one of the four values in the CTEP's Common Toxicity Criteria, with Dose Limiting Toxicity being defined as grade 4 toxicity. The parameters in the PK/PD model are described by probability distributions to simulate the inherent variation across the trial population.

4.4.4 Study design

The overall structure of the experimental scheme for determing the MTD is depicted in Figure 14, whereas further details of evaluating toxic responses are illustrated in Figure 15.

Before starting the experiment the initial dose must be set to a level belived to be safe in humans, e.g. one third of the LD10 in mice (the one-tenth of the lethal dose for mice). Once the initial dose has been set, the trial commences by applying the dose to a cohort of CSIZE0 subjects, who are then monitored for Dose Limiting Toxicity (DLT). The treatment of the cancer disease considered in the present case calls for repeated dosing at each dose level. The treatment schedule could e.g. consist of three cycles, with each cycle consisting of two weeks of dosing and one week without dosing (see below for alternative treatment schedules used in the simulation part of the study). Depending on the number of subjects experiencing DLT, different actions may be taken. In particular, if DELIM0 toxic responses are observed, the current dose is applied to an additional CSIZE1-CSIZE0 subjects, bringing the total number of subjects to CSIZE1. If the total number of toxic responses among the CSIZE1 subjects is less than DELIM1, the dose is increased to the next level, and the dosing procedure is repeated for new subjects. The dose escalation scheme terminates once the pre-determined tolerance level for the allowed number of toxic responses is reached for the current cohort of patients, and the immediate prior dose level is then declared as the temporary MTD. The dose escalation phase may be followed by a confirmation phase, during which the tentative MTD is further tested in a confirmation cohort of patients. Factors to take into consideration when evaluating MTD studies include:

- Precision of the estimated MTD, which is of central interest in phase I trials
- Issues relating to the cost of the study, including the number of patients/volunteers and the duration of the study.

4.4.5 Simulating the trial

The foundation of CTS are PK/PD models, which predict the effect of treatment, taking into account the variability in drug response by employing probability distributions to describe stochastic effects influencing the model parameters. Using these models it is possible to investigate the trial outcome for multiple scenarios of the trial design, in order to identify a dosing strategy with an acceptable safety profile. In the present case, different variations of the MTD scheme in Figure 15 are created by varying CSIZE0, CSIZE1, DELIM0 and DELIM1, and employing different procedures for dose escalation. When evaluating the outcome of the simulations, the following questions are relevant:

- Which dose escalation scheme appears to be superior?
- Which trial design has the least bias?
- Which trial design uses the least patients/volunteers?

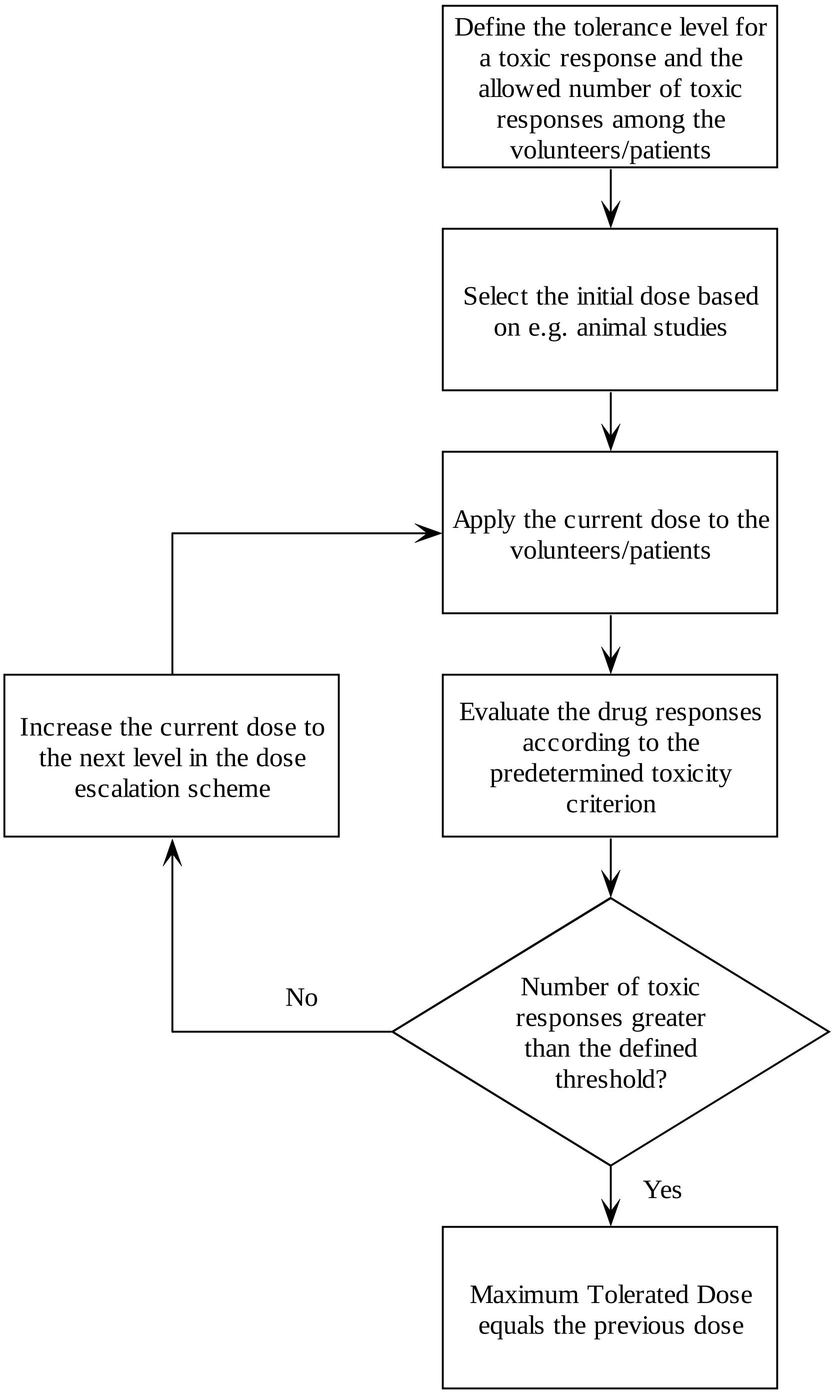


Figure 14. Scheme for determining the Maximum Tolerated Dose

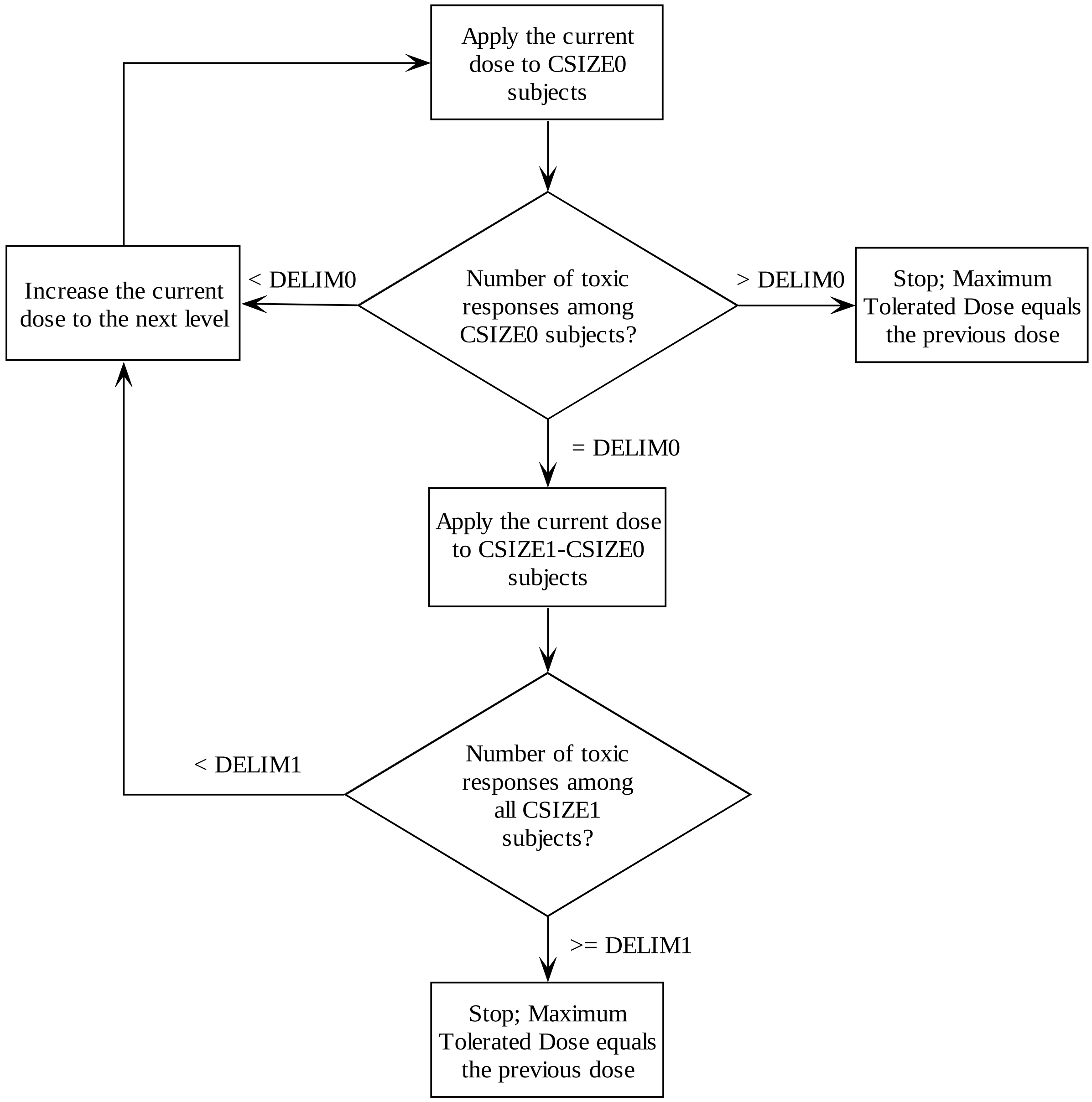


Figure 15. Scheme for determining the Maximum Tolerated Dose

- Which trial design is the most aggressive?
- How much value is added by including a confirmation phase following the basic MTD scheme seen in Figure 15?

Monte Carlo (MC) simulation techniques are employed to perform the actual simulation. Before integrating the PK/PD model, yielding the temporal variation of the WBC and the hence the degree of toxicity, the treatment schedule must be established. In the present case two different treatment schedules are compared:

1. 2 weeks on 1 week off (1 cycle of treatment) regimen with 100-800 mg for three cycles
2. 1 week on 2 weeks off (1 cycle of treatment) regimen with 100-800 mg for three cycles

4000 study subjects are used in the CTS, which is separated into one simulation for each of the doses in the MTD dose escalation scheme and for each of the treatment types listed above. For each subject, MC techniques are used to randomly sample a set of parameters from the distributions modelling the PK/PD parameters. Subsequently, the PK/PD model is integrated according to one of the treatment schedules using the particular set of model parameters, yielding values for the WBC count and the corresponding toxicity grade. Once the integration has been repeated for parameters sampled for all 4000 study subjects, the percentage of subjects experiencing Dose Limiting Toxicity at each dose level may be calculated . See Figure 16 for a more detailed explanation of the various steps involved in the simulation.

4.4.6 Post-processing

The simulation yielded the percentage of subjects experiencing DLT at each dose level, which in turn may be used to calculate the average of the MTD and the average number of subjects needed to arrive at the MTD according to the MTD scheme. Thus, different variants of the MTD scheme may be compared.

4.4.7 Using Clinical Trial Simulation (CTS) to predict the outcome of a Phase III trial

The present case story discusses the application of Clinical Trial Simulation (CTS) to a Phase 3 study of an antischizophrenic agent.

4.4.8 Drug model

Prior to initiating the simulation of the Phase 3 trial, the effect of the agent on virtual patients enrolled in the simulation study had to be established through the construction of a population PK/PD model. The data needed to establish the PK and PD properties of the agent were provided by the phase 1 and 2 trials, which designs are illustrated in Figure 17 and 18. The two trials were characterized by the following features (see below for explanation of terms specific to clinical trials):

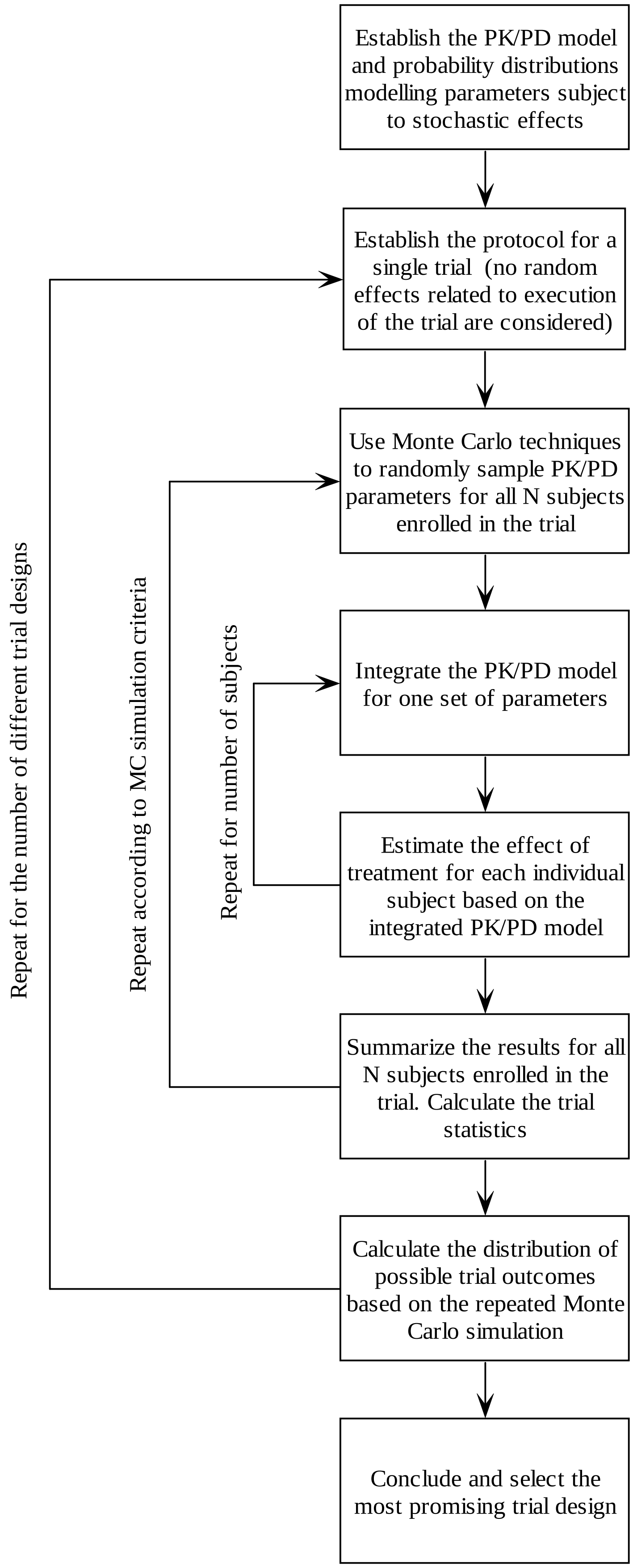


Figure 16. Flowchart illustrating the process of Clinical Trial Simulation

- **Phase I trial**. An open, multiple, ascending-dose trial in patients with schizophrenia.
- **Phase II trial**. A multicenter, double-blinded, placebo-controlled, paralleled comparison of low-dose (0 to 250 mg/d) and high-dose (0 to 750 mg/d) regimens of quetiapine in the treatment of hospitalized patients. To measure the clinical effect of the agent, the Brief Psychiatric Rating Scale (BPRS) was employed.

The phase I and II trials yielded 780 plasma concentrations and 1913 BPRS records from a total of 295 subjects. The concentrations from the two trials were combined and analyzed by use of the nonlinear mixed effects modelling program NONMEM to establish a population PK/PD model. The interindividual and intraindividual variability of the pharmacokinetic and pharmacodynamic parameters were modelled by either normal or log-normal distributions. The resulting pharmacokinetic part of the model reads

$$\mathrm{C_p} = \frac{\mathrm{k_a\,dose\,F}}{\mathrm{V\,(CL/V - k_a)}}\left(\mathrm{e}^{-\mathrm{k_a\,time}} - \mathrm{e}^{\frac{\mathrm{CL}}{\mathrm{V}}\,\mathrm{time}}\right), \qquad (1)$$

where $\mathrm{C_p}$ is the plasma drug concentration, $\mathrm{k_a}$ is the absorption rate constant, CL is the clearance, V is the volume of distribution, and F is the bioavailability. The pharmacodynamic part of the model reads

$$\mathrm{BPRS} = \mathrm{baseline\,BPRS} + \mathrm{drift} \times \mathrm{time} - \frac{\mathrm{E_{max}C}}{\mathrm{EC_{50}} + \mathrm{C}}, \qquad (2)$$

where $\mathrm{E_{max}}$ is the maximum effect (shift in BPRS score from the baseline) that can be attained as a result of exposure to drug concentrations, $\mathrm{EC_{50}}$ is the drug concentration producing 50 % of the maximum effect, and drift is the slope reflecting the time course of disease progress and placebo response. The covariates age, body weight and sex were tested for correlation with the PK/PD parameters but since no significant relationship was found, no covariates were included in the parameter estimates.

4.4.9 Simulation

The overall design of the phase III trial, which outcome is to be predicted by simulation, is illustrated in Figure 19, and is characterized by the following features:

- **Phase III trial**. A multicenter, double-blind, placebo-controlled, randomized, parallel, multiple fixed-dose comparison of quetiapine in the treatment of hospitalized subjects with acute exacerbation of chronic or subchronic schizophrenia. The trial comprises a 6-week fixed dose treatment (0, 75, 150, 300, 600, 750 mg/d) after a 1-week lead-in period. Patients with a 20 % or greater decrease in BPRS in the lead-in week are considered placebo responders and are excluded from the trial. Also patients with a BPRS score less than 27 at trial entry are excluded.

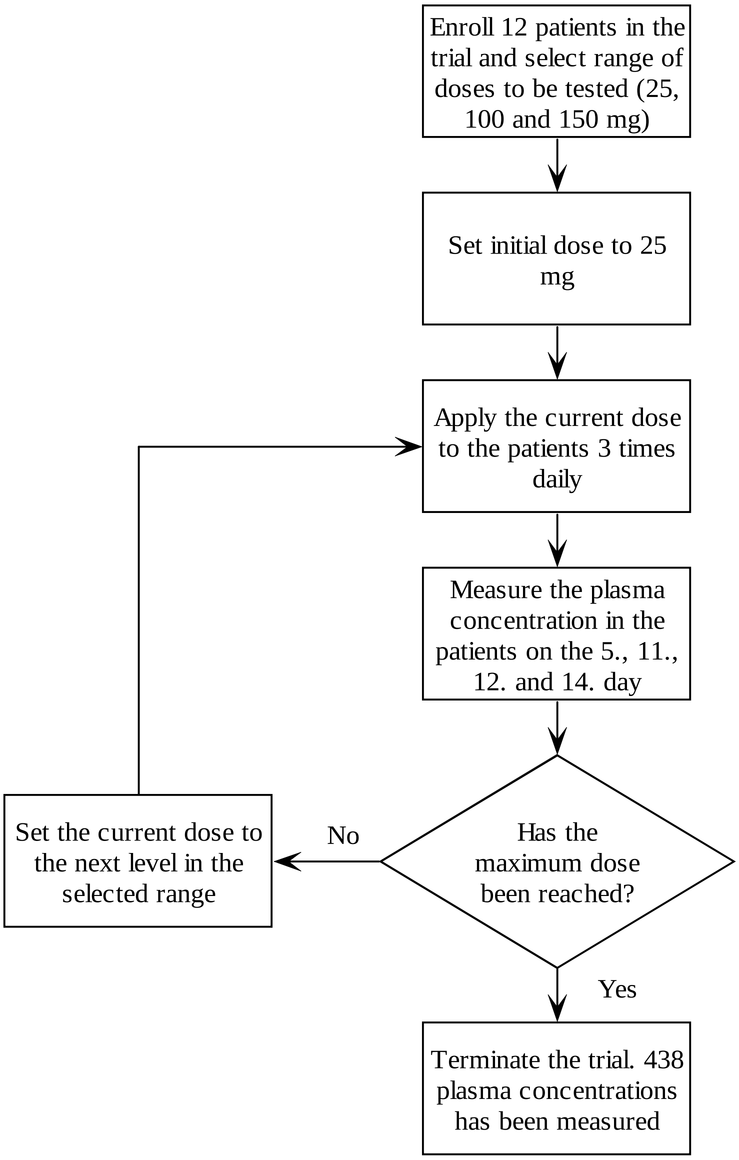


Figure 17. Flowchart illustrating the design of the phase I trial

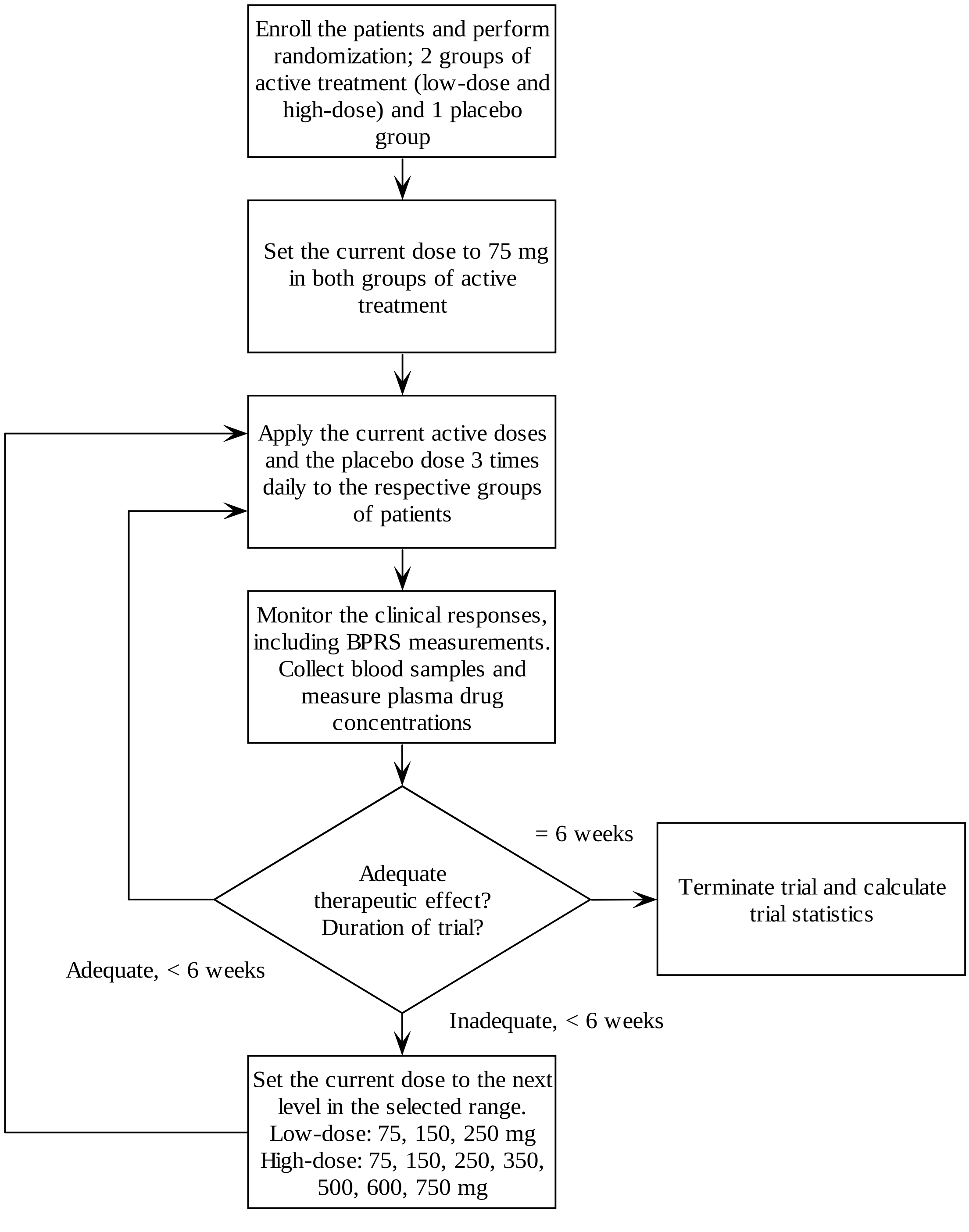


Figure 18. Flowchart illustrating the design of the phase II trial

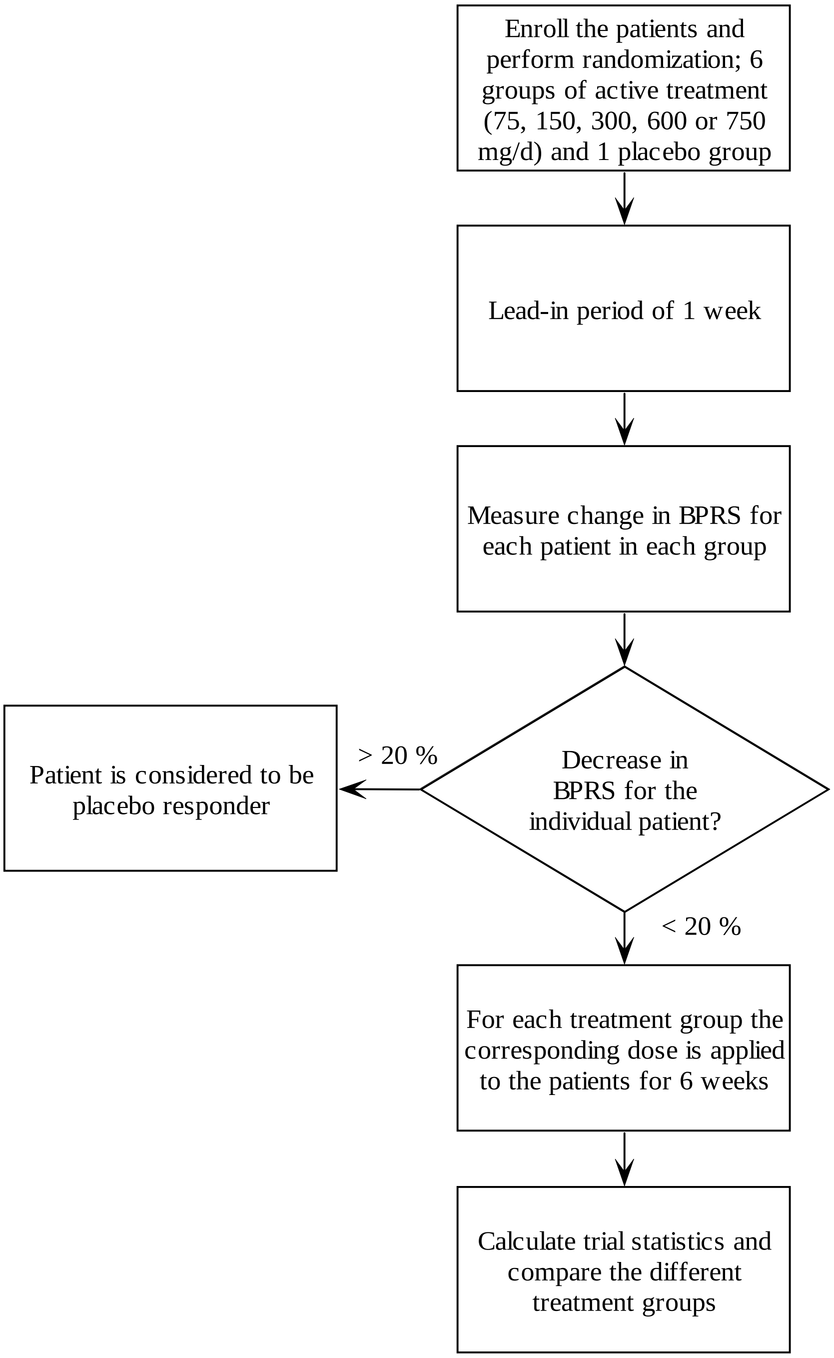


Figure 19. Flowchart illustrating the design of the phase III trial

The different phases and decision structures involved in the simulation of the phase III trial are illustrated in Figure 20 and 21. The upper flowchart in Figure 20 depicts the overall structure of the simulation, which can be summarized as:

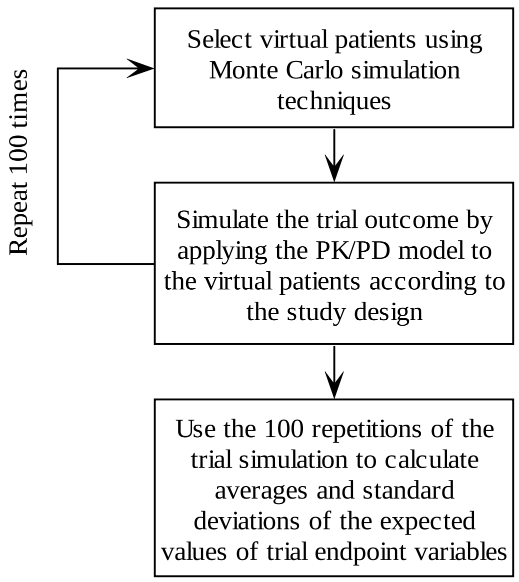
1. Select virtual patients randomly for each treatment group, given certain inclusion/exclusion criteria.
2. Carry out the simulation of the trial for all virtual patients in all treatment groups, yielding predictions of the values of trial endpoint variables.
3. Repeat the two previous steps 100 times.
4. Calculate the trial statistics, based on the 100 replications of the simulation.

The lower flowchart in Figure 20 illustrates the selection of virtual patients, including checks for placebo response and allowed values of baseline BPRS. The placebo lead-in period of 1 week is modelled by merely equating the plasma drug concentration, C_p, in Eqs. 1 and 2 to 0. Then for a given value of baseline BPRS larger than 27 (required at trial entry), the allowed range of the drift parameter is found by requiring the right-hand side of Eq. 2 to drop no more than 20 % during 1 week for $C_p = 0$.

The flowchart in Figure 21 depicts the stages involved in one replication of the actual simulation, which is carried out following the selection of virtual patients. The simulation is characterized by the following features:

- **Drop-out model**. From the phase II trial data, a patient drop-out pattern has appeared. To reproduce this pattern, a random drop-out algorithm is employed to select the duration of participation for each patient, reflecting drop-out rates of 70 % and 60 % for the placebo and 75 mg doses, respectively, and 50 % for the rest of the doses. If a virtual patient drops out before week 6, the last measurement of BPRS is used as data from week 6 when interpreting the trial outcome (last observation carried forward procedure).
- **Titration period**. The simulation commences with a 2 week titration period, during which the dose is increased step-wise until the maximum dose is reached (one of the fixed-dose levels: 75, 150, 300, 600 or 750 mg/d).
- **Adherence/missing observation**. It is assumed that the measurement of BPRS levels in the patients is neither affected by non-adherence to the treatment nor missing observations, due to the trial taking place in a hospitalized setting.
- **Results**. Each replication of the simulation yields the predicted change in BPRS from the baseline for all 50 patients in each treatment group. This set of values of change in BPRS is used to compare the different active treatment groups and the active and placebo treatment groups. For each pair of treatment groups the power to detect a difference is calculated. Upon completing the 100 replications of the simulation, the mean and standard deviation of the power to detect a difference between each pair of different treatment groups are calculated.

Based on the predictions of the power values to detect differences between the various treatment groups, important decisions regarding the real life phase III trial can be made.



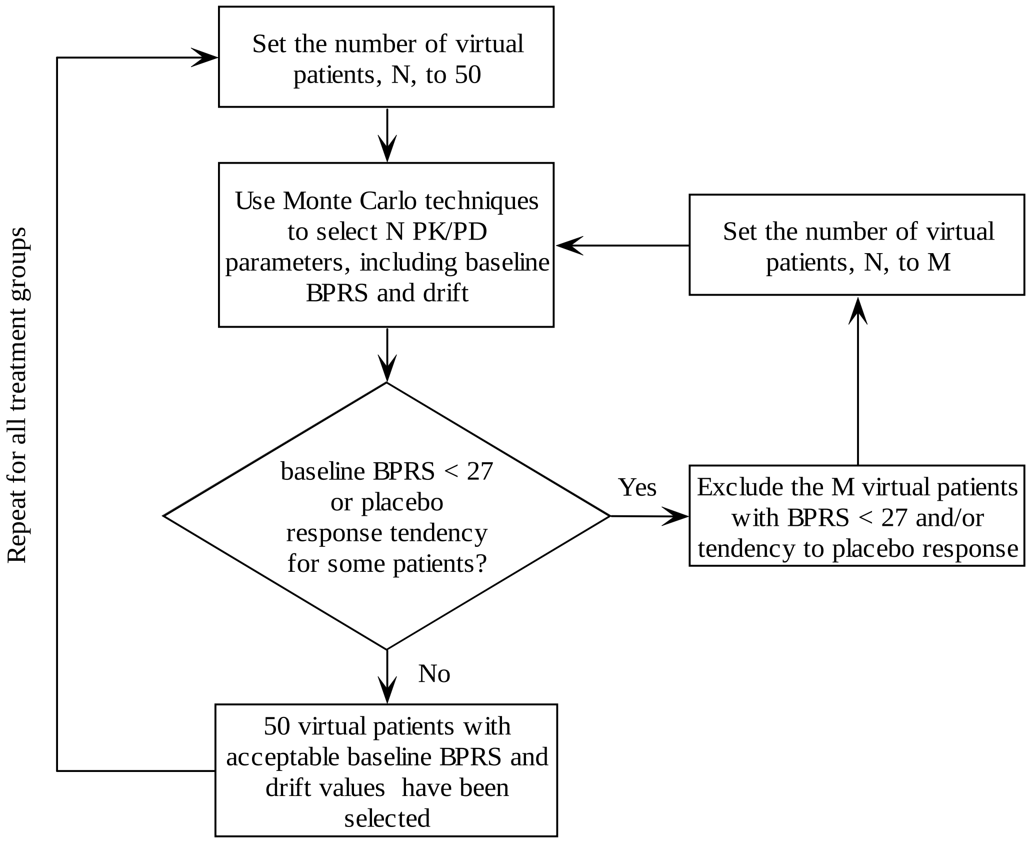


Figure 20. Top: Schematic overview of the simulation process. Bottom: Illustration of the process of selecting virtual patients.

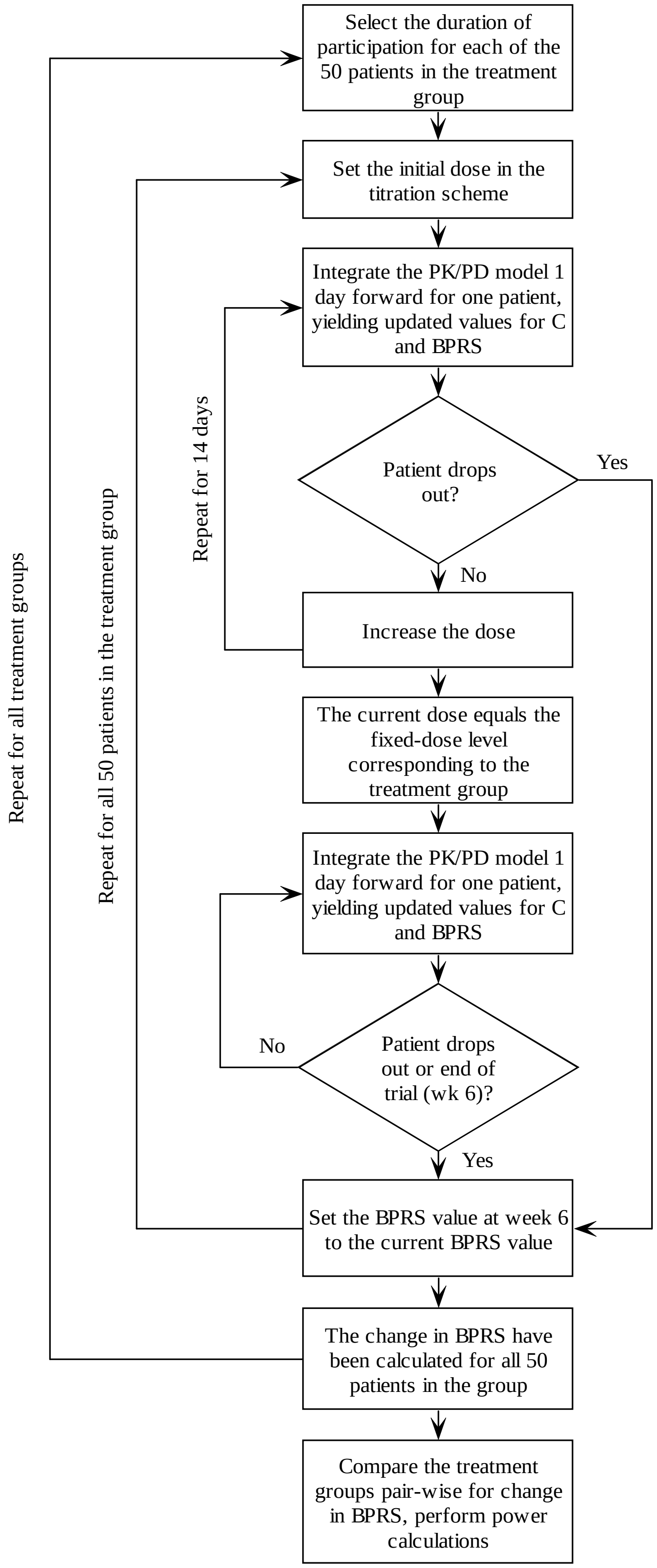


Figure 21. Flowchart illustrating the process of Clinical Trial Simulation

5 Portfolio management

Pharmaceutical companies fund R&D projects at various stages of the development process. Due to the large fraction of projects which are abandoned at some point during development, the majority of projects are nonclinical research projects, whereas relatively few projects have entered clinical development.

A typical medium sized pharmaceutical company funds 20-40 projects, whereas the largest pharmaceutical companies fund more than 100 projects. When managing the R&D activities of a pharmaceutical company, it is useful to consider the set of R&D projects as a *portfolio*.

The term portfolio originates from finance and defines a collection of bonds, stocks or financial instruments. Financial portfolios are similar to pharmaceutical R&D project portfolios in that the assets in both types of portfolios are subject to risks; financial securities may loose their value due to unfavorable market conditions while the development of a new drug risks experiencing technical failure.

A pharmaceutical R&D portfolio typically contains projects with different characteristics; e.g. early-stage projects associated with great uncertainty, late-stage projects associated with less uncertainty, projects which are on the same stage of the development process, but which are characterized by different risk attributes.

5.1 Portfolio modelling

Within pharmaceutical R&D the term *portfolio modelling* refers to using modelling and simulation to manage and/or valuate a portfolio of R&D projects. Key features of portfolio modelling include:

- To assist decision makers in creating, managing, terminating and funding projects according to criteria for acceptable risks and desirable returns.
- To determine whether the size and structure a R&D portfolio is in accordance with the number and types of drugs which are planned to be marketed in the future. E.g., is the R&D portfolio capable of delivering replacements for a number of already marketed drugs before patent expiration.
- To estimate the probability of obtaining a given revenue in a given number of years. Are the expected future revenues large enough to sustain desired future R&D activities?

Prior to applying portfolio modelling, the risks, costs and potential returns associated with the various projects in the R&D portfolio must be estimated. Herein lies one of the largest challenges of portfolio modelling. Traditionally historical industry averages have been used to assess the risk associated with R&D projects. However, new technologies such as Clinical Trial Simulation (CTS) promise to deliver more accurate risk assessment.

5.2 Existing methods

Below two methods for modelling portfolios are reviewed. The classic Net Present Value (NPV) approach to project valuation is briefly described and the shortcomings of this method in regard to pharmaceutical R&D are discussed. Subsequently, a new method based on the valuation of options from finance is described. This method which is called Real Options Valuation (ROV) has recently been presented in the literature.

In very general terms, both the NPV and ROV methods model R&D portfolios by using a financial metric to valuate the set of projects in a portfolio. Subsequently, the optimum portfolio is found by determining the values of a set of decision variables relating to portfolio management which maximise the value of the portfolio.

5.3 Calculating the Net Present Value of research projects

For each project in a portfolio, all future revenues generated by the commercialization of the project must be estimated and discounted into its present day value. Also, all present and future R&D investments in the project must be estimated and discounted into their present day equivalents. The NPV of a project is then the discounted revenues subtracted the discounted R&D investments.

The discount rate must reflect the risks associated with a project. Undertaking high-risk research projects is equivalent to investing in high-risk bonds with the return rate r_{high}, whereas undertaking low-risk research projects is equivalent to investing in low-risk bonds with the return rate r_{low}. Thus, future revenues generated by low- and high-risk projects should be discounted by the rates, r_{low} and r_{high}, respectively, in order to yield their present day equivalents.

The application of the NPV approach to pharmaceutical R&D is limited by the use of a constant discount rate to calculate the present day equivalents of future cash flows and R&D investments. This is due to the NPV approach assuming that the risk associated with a research project is constant through all phases of development. On the contrary, the discount rate should change in order to reflect the change in risk levels as more information becomes available.

The scope of the NPV approach may be extended to account for changing risk levels of R&D projects by incorporating Decision Tree Analysis (DTA) into the valuation of research projects. Within the framework of DTA all possible future directions a research project can follow are considered, including the possibility of project abandonment. NPV estimates for each possible project outcome may be obtained by moving backwards through the tree, while discounting future cash flows and R&D investments into their present day equivalents. The discount rate used at a certain point in the decision tree should reflect the risk level of the particular state of the project at that time.

5.4 Real Options Valuation (ROV)

In order to overcome the limitations of the extended NPV approach (DTA), the idea of applying Real Options Valuation (ROV) to pharmaceutical R&D has been proposed [12, 11]. The underlying idea of ROV is to recognize that R&D activities include the option value of future opportunities to alter the course of a project as more information becomes available. If a project has passed some stages of the development process successfully, the company has the option of proceeding with the remaining stages of the process, or to abandon the project due to unfavorable market conditions (competitor drugs etc.), internal budgetary limitations, the existence of related projects with more promising technical and economic profiles etc. Hence R&D projects are considered as real options.

In very general terms the ROV method uses a single financial metric, derived from options pricing, to valuate the projects in a R&D project portfolio. Given estimates of risk of technical failure and estimates of the volatility in the commercialization values of projects, the method finds the optimum portfolio by maximizing a financial metric under various constraints imposed by limited resources etc.

Below the ROV method is described in more detail. Upon completion of each phase of the pharmaceutical development process, a decision to either abandon a project or continue with further development is made based on the available information. Future investments are made only if preceding R&D is deemed promising.

Within the framework of the ROV approach each sequential R&D investment is analogous to a financial *call option*. A call option is the right to buy a financial asset at a future date at a predetermined price. The price in the option contract is known as the strike price and to obtain the option a premium is paid. If the price of the underlying security on the expiration date exceeds the strike price, the option is exercised by paying the strike price and obtaining the underlying security in return. Otherwise, the call option is allowed to expire because the holder is under no obligation to buy the security.

When translating the concept of financial call options into the framework of pharmaceutical development, a R&D investment at a given stage of the development process may be viewed as the premium paid for a real option. Given the paid premium, a project is brought one phase further through the development process. Consequently, a pharmaceutical company acquires the future right to invest in R&D at later stages of the development process and eventually to commercialize. The strike price is the sum of all future R&D costs following the payment of the premium. The value of a R&D project, corresponding to the value of a financial asset, is the discounted value of the estimated future cash flow produced by the project following product launch. The real option is only exercised (investment in further R&D or commercialization) if preceding R&D has been successful.

Methods for calculating the value of financial options exist. Within the ROV framework these method are then, with appropriate extensions, applied to the valuation of pharmaceutical R&D projects. Given a number of R&D projects at various stages of development, budget constraints, required future investments in each project, expected future sales revenues generated by each project given success in R&D, and estimates of the probabilities of clinical success, the ROV algorithm selects a subset of the projects which maximizes the ROV of the portfolio.

6 Summary and conclusion

6.1 Summary

Pharmaceutical development is a very expensive and highly risk intensive activity. For a single drug, on average \$ 802 million and 10-12 years are spent prior to marketing.

In an attempt to limit potential losses, the pharmaceutical development process is separated into distinct phases, with the completion of each phase being followed by a decision to either abandon the given R&D project or to continue with development.

The development of a new drug starts with the identification of a *target* which is a physiological parameter linked to the underlying molecular mechanisms of a disease. Next, the search for a molecule which will interact with the target begins; usually a number of such molecules (denoted *hits*) are found and subsequently subjected to an iterative process of refinement and modification until a few molecules (denoted *lead candidates*) remain. The lead candidates are then tested in animals in an attempt to discover potential toxic side effects of drug intake. The toxicity studies precede the clinical development process which aims at demonstrating efficacy and safety in man.

Despite the use of a sequential development process, incorporating carefully positioned go/no go decision points to eliminate non-promising projects, the cost of developing a new drug has increased dramatically during the last decades.

Emerging technologies based on modelling and simulation are, however, promising with respect to increasing the efficiency of the pharmaceutical development process. Applied to the very expensive clinical part of the development process, Clinical Trial Simulation (CTS) brings a predictive element into the conduct of clinical trials. In particular, CTS enables decision makers to assess the probability of meeting a trial endpoint and/or to optimize trial designs.

Portfolio modelling is a mathematical optimization technique used to assist decision makers in managing the large number of projects pursued by pharmaceutical companies.

Recently a portfolio modelling method based on Real Options Valuations has been introduced. This method uses a financial metric, derived from the pricing of financial options, to valuate pharmaceutical R&D project portfolios. Portfolio optimization is then carried out by determining the portfolio attributes which maximize the portfolio valuation.

6.2 Conclusion

Based on our survey of the pharmaceutical discovery and development process, we identify a number of areas which may particularly benefit from application of mathematical optimization techniques. Application of optimization techniques to various R&D subprocesses has the potential to increase the efficiency and decrease the cost of the discovery and development process as a whole.

When restricting ourselves to the areas of clinical development and R&d project management, we believe the most promising areas for further research to be:

- R&D project portfolio management.
- Simulation and optimization as part of the integrated drug discovery and development process of the next decade.
- Modification of clinical trial simulation techniques to account for the expected structural changes in the discovery and development process as e.g., the expected shift towards more adaptive trials, or the use of informations from "genomics" in clinical trial simulations.

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