DDT Vol. 6, No. 15 August 2001

Modelling and simulation in clinical drug development

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Pharmaceutical companies are under greater pressure than ever before to improve the R&D process[1]. There is a growing need to increase productivity in R&D, and to use technologies that can both increase and more efficiently facilitate the flow of products through the development pipeline. This article describes how the twin processes of modelling and simulation are being used to improve the efficiency of the clinical drug-development process, and consequently how these methodologies have delivered significant benefits in the drive to save time, money (and additionally assisted in ensuring an 'optimal quality' drug label) in the development of novel therapeutic agents.

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▼ Pharmaceutical and biotechnology companies have invested substantial resources in new technologies, such as genomics, HTS and combinatorial chemistry, to accelerate and improve the drug discovery process. While new technologies have been developed to expand the number of new drug candidates, the clinical development process continues not only to be lengthy and relatively unpredictable but also increasingly costly. The bottleneck in drug development has clearly shifted from discovery to the clinical development process. The total cost of clinical development per new molecular entity (NME) is increasing steadily as a result of an increase in the number of trials performed during the development cycle, an increase in the number of patients required in trials, an increase in the number and cost of procedures performed on the patient during trials and the increasing cost of data management, data analysis and Good Clinical Practice (GCP) monitoring of trials. At the same time that the development costs are increasing, the window of market exclusivity for novel therapeutic products has dramatically decreased, which has resulted in decreased revenue per product. Pharmaceutical companies are beginning to acknowledge that future revenue growth depends more than ever on bringing innovative and competitive drugs to market more quickly, at lower costs and with more competitive drug labels.

There is a growing awareness that a process change is needed to improve the efficiency of the drug development process. To date, most efforts have focused on improving the execution of the current clinical development process (e.g. using information technology platforms such as electronic data capture, and electronic case-report forms among others), rather than on fundamentally changing the process. Although clearly of benefit in capturing and analyzing data more efficiently, these technologies fail to change the development paradigm, and simply improve a single step in the process. There is an increased need for rational decision-making with respect to go/no-go decisions, clinical trial design, dose and endpoint selection and the positioning of a product in the market place based on its commercial advantages.

Anyone who has flown across the Atlantic in the last five years has probably flown on a Boeing 777. The 777 is the first of a new breed – an aeroplane that was totally researched, developed and put into mass production using the technique of computer simulation. Although simulation is a methodology that has been used extensively in several engineering-based industries, particularly the automotive and aerospace industries, the use of this technique is only now beginning to filter through into the mainstream pharmaceutical sector[2–4].

The use of computer-assisted trial design (CATD), whereby mathematical models of drug action and disease state and progression

1359-6446/01/$ – see front matter PII: S1359-6446(01)01855-4

are developed, and subsequently inputted into a sophisticated computer-software program that can simulate the clinical trial process, provides a quantum leap in the rational development of drugs. This technology, using knowledge-based quantitative analysis, is a significant addition to the more traditional empirically based methodologies, which have been the mainstay of clinical drug development over the past 30 years. The intended end benefits of these improvements are informed risk management, faster and/or less expensive development programmes, and more competitive drug labels.

Traditional paradigm in clinical drug development

The established and accepted approach in the development of novel therapeutic products has been based on an empirical, linear model. Knowledge accumulated from the preclinical arena (i.e. *in vitro* and *in vivo* animal pharmacology and toxicology) is used to enable the drug to be administered to humans with minimal risk. Early Phase I studies in humans look at the safety, tolerability and pharmacokinetic profiling of the NME and, using intermediate markers such as surrogate markers, aim to establish a probable dose range. Phase II studies test the dose range hypothesis, and Phase III studies aim to demonstrate efficacy in a statistically robust manner. Although rarely challenged, this approach relies on empirical decision-making, that is, decisions made in a semi-qualitative and semi-quantitative manner, based upon a limited series of study outputs. It fails to fully quantitatively assess the likelihood of success and risk associated with particular decisions, and can lead to suboptimal development strategies.

Planning and modifying clinical trials and programmes relies on a progressive accumulation of in-house and literature data and a synthesis of that data into useful information. The overall drug development programme is planned by a diverse group of individuals who form the global project team. Although this project team is charged with integrating the process of drug development, the level of input from any one discipline varies over the course of development. Information scientists are involved throughout the R&D process in providing the organization with the tools and services to obtain, process and manage internal as well as external information resources to support the established R&D process. However, in a desire to aid comprehension and to ensure brevity, each component of the process is often reduced to a summary. During this process, much knowledge that could be of subsequent use in designing further clinical studies becomes effectively lost or is not optimally used. Analysis of information provided within project teams focuses on elucidating descriptive facts and testing hypotheses. Power calculations and bias analysis form the backbone of the statistical plan. However, clinical teams can miss opportunities to more fully use the richness of data sources that are available. The sample size calculation for a particular study looks at point estimates and degrees of variability of the measured efficacy variable at specific doses to calculate the number of subjects to be included in a particular trial (to a particular statistical power), the magnitude of drug-effect on the disease state and the anticipated difference in effect between treatment arms. In reality, however, this is only half the story.

A novel paradigm using quantitative analysis

The costs of conducting Phase II and III clinical trials constitute a significant proportion of the development costs for any NME. Because of the pressures on R&D productivity, we are moving into an era where failure of a drug in Phase III trials is increasingly being viewed as commercially unacceptable. As a means of improving decision-making in product development, the technique of CATD can be implemented at various stages throughout the process to maximize the likelihood of success for those compounds entering Phase III. CATD can be used to test various 'what if' scenarios that are related to both drug and disease characteristics as well as trial design. By using this technique, the development team can predict and evaluate a range of potential results any given trial might generate before the dosing of a single patient in a clinical study (Fig. 1).

During the drug development cycle several important decisions have to be made about the development strategy of the novel compound. The project team can independently make some of these decisions based on certain assumptions, whereas senior management is often involved in others (Fig. 2). CATD is a tool for the project team and senior management to help to optimize the chain of decision-making required to bring candidate drugs to market (see Fig. 2). CATD improves the drug development decision-making process in several ways:

- Provides a quantitative assessment of current information.
- Evaluates alternative treatment strategies and assumptions, and quantifies uncertainties in predictions.
- Evaluates alternative trial and development strategies.
- Supports the evaluation of the development strategy from a financial value perspective.
- Enhances communication between the project team and senior management, as well as outside the company with regulatory agencies and investigators.

An integral component of the CATD process is the requirement to develop a model of drug action and disease response that brings together both current knowledge (on

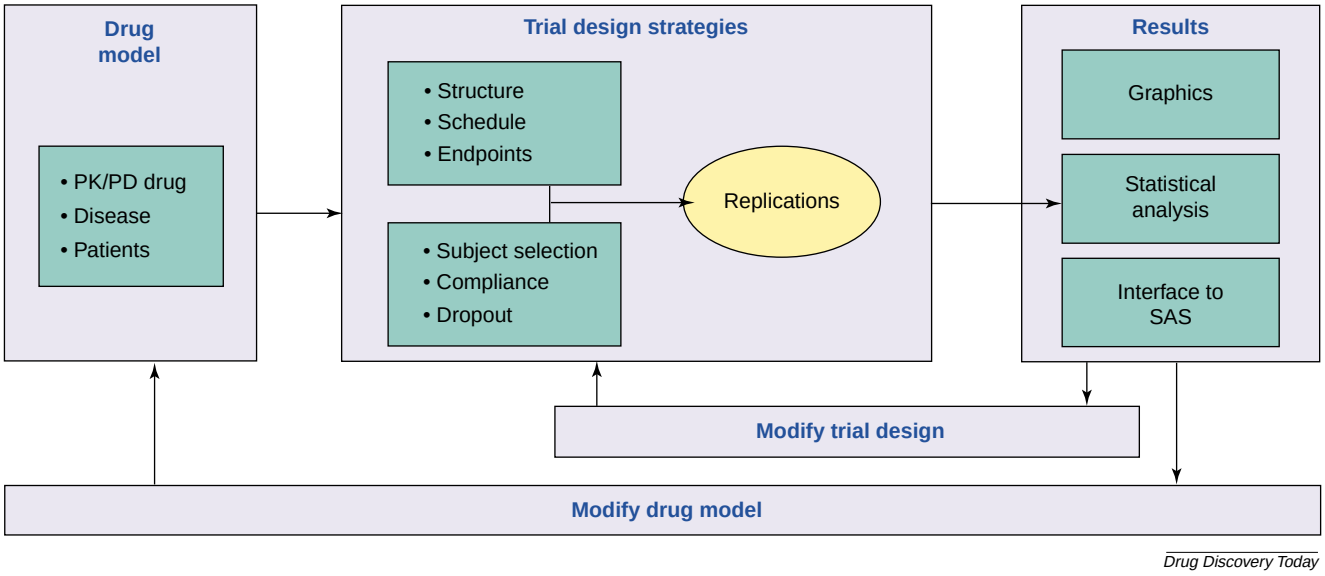

Figure 1. Computed-assisted trial design (CATD) can be used to predict and evaluate a range of results for a proposed clinical trial before administration of the drug to patients. A drug model is developed that describes the pharmacokinetic and pharmacodynamic (PK/PD) characteristics of the drug, the disease state and the patient population. This model is inputted into functions that describe the proposed study design and a series of study replications are generated using trial simulation software.

the drug and disease state) and any assumptions required to investigate the various 'what if' scenarios. The drug and disease model characterizes the relationship between drug dosing and clinical outcome (which might include beneficial effects, adverse drug-effects or a combination of both) in an individual patient within a specific patient population. Included in the drug and disease model are the dependence of the drug action on the specific patient characteristics (e.g. severity of the disease at study entry), operational variability (both patient compliance and dropout) and biological variability (both inter- and intra-patient variability). Drug and disease models are continually developing tools that are based on completed preclinical and clinical studies, and other information available in the public domain, for example, literature data on drugs with similar mechanisms of action or drugs with similar indications. In effect, the drug and disease model becomes a knowledge repository for a specific drug in its given indication, as well as for back-up compounds. Typical components of this model might include:

- Pharmacokinetic (PK) models for parent drug and active metabolites.
- Pharmacodynamic (PD) models for surrogate and clinical endpoints (as well as side effects) characterizing the interaction between disease progression, placebo effect and drug effect.
- Covariate models relating patient characteristics to the PK and PD model parameters.
- Models to capture inter- and intra-patient variability in PK and PD parameters.
- Models to capture patient compliance and dropout.
- Models to capture uncertainty.

The components to be used within any specific drug and disease model depend upon the drug, development stage and therapeutic area, the nature of the disease that is altered by the drug and the aim of the simulations. Specific questions that can be addressed by CATD can include[5]:

- Is the current design adequate and efficient to meet the objectives of the trial?
- Can the trial design be modified to provide more information with minimal risk and additional cost?
- What are the optimal treatment schedules to be used in Phase II and Phase III?
- What design characteristics have the greatest impact on trial outcome?
- What characteristics of the drug and patients have the largest impact on variability in response and what is the optimal way to manage the variability in the design of the trial?
- How will a change in the eligibility criteria affect outcome?
- Should the dose be adjusted in patient subpopulations?
- What will be the Phase II metric on which the dose for Phase III will be selected?
- What is the likelihood of success in Phase III?

On the basis of the outcome of these questions, the clinical trial structure, treatment schedule, eligibility criteria, clinical endpoints, compliance and dropout assumptions might be reviewed. Using software products such as the Pharsight Trial Simulator (Pharsight Corporation, Mountain View, CA, USA), multiple 'virtual' clinical trials can be simulated using virtual patient populations, and the range of potential trial results or outcomes can be reviewed and the likelihood of success can be evaluated. This process can be repeated as often as necessary to analyze the various parameters that could impact upon the potential outcome of the clinical trial.

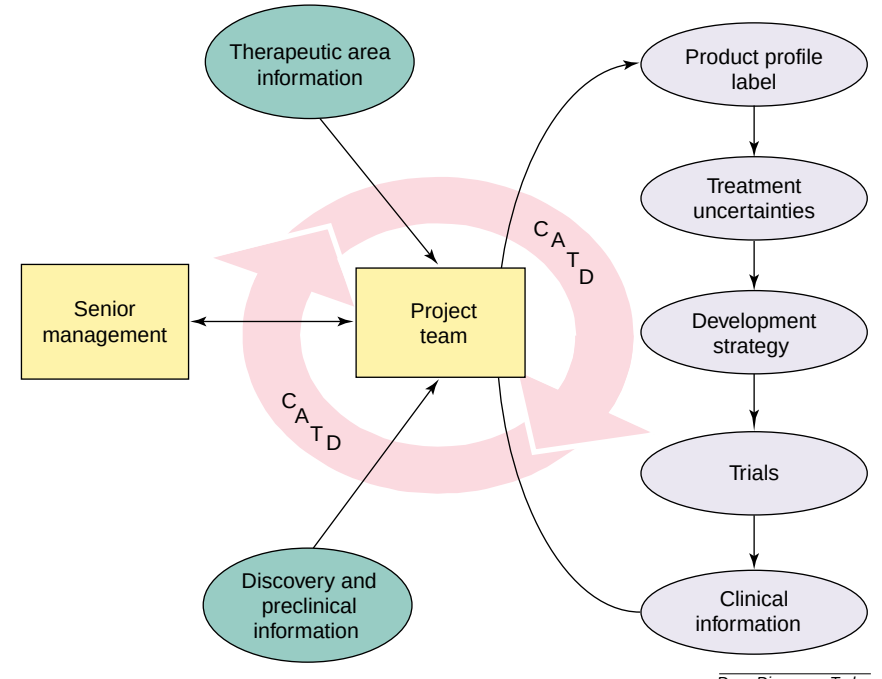

Figure 2. Computer-assisted trial design (CATD) is a tool for the project team and senior management that can help to optimize the chain of decision-making required to bring candidate drugs to market. The project team drive the development strategy for any given candidate drug, using CATD methodologies to assist in decision-making processes throughout the development cycle.

CATD in practice – some examples of the decision tree

A typical question asked by a pharmaceutical company in early product development is: 'Should we proceed immediately to a Phase II dose ranging in patients on the basis of preclinical potency data and Phase I PK data?' The dilemma of this strategy is that it might be necessary to plan an extensive dose ranging trial (with a wide range of doses or more treatment arms) because of the uncertainty in the scaling of the relative potency and efficacy from animals to humans. Alternatively, should the uncertainty be reduced by completing a dose-finding study using a biomarker before embarking on the dose-ranging trial in patients? Clearly, such a strategy would only be valuable if the biomarker trial provided additional information on the probable active range of doses compared with the preclinical data. Another alternative would be to elucidate all dose finding on the basis of the biomarker and move directly to confirmatory Phase III trials without doing extensive dose-finding in patients. Such a strategy might be valuable if there is almost no uncertainty in the scaling of the relative potency determined from the biomarker to the clinical endpoint, and biomarker trials are substantially cheaper and quicker than patient trials.

Early in development, the drug and disease models are primarily used to validate the product profile and identify the uncertainty in the dosing strategy required to achieve the product profile. Depending on the outcome of this evaluation several key decisions will be made:

- The analysis might show that enough is known on the potential clinical behaviour of the compound and that, consequently, extensive dose-finding in the actual patient population can be minimized and the switch to confirmatory Phase III trials can be made. The value to the company is a substantial reduction in the number of Phase II studies to be conducted during the development programme.
- The analysis might show that the intended product profile is unlikely to be realized on the basis of the available data and an adjustment of targets needs to be made (or even development terminated). The value to the company is to shift attrition to earlier in the development cycle and to develop realistic targets.
- The analysis might show that there is substantial uncertainty in the treatment strategy that requires additional dose-finding trials to be conducted. The key factors driving the uncertainty in treatment outcomes will be identified to guide what information needs to be obtained. The value here is generation of a more focused development strategy.

The evaluation of likely treatment outcomes is an iterative process that is repeated when novel information is

obtained from future trials on the NME or other compounds in the therapeutic area of interest. Later in development, when substantial clinical information on the drug candidate has been acquired, the models could be used to individualize treatment for specific subsets of the patient population if necessary (e.g. paediatric dosing).

For the optimization of dose-finding trials, the drug and disease models are used to predict the probability distribution of trial outcomes as a function of trial design and trial analysis strategies. Multiple trial-design strategies can be evaluated for their ability to reduce the uncertainty in treatment strategy to allow dose selection for full development. Alternative trial strategies can be evaluated in terms of structure (parallel, crossover, fixed escalation or adaptive), number of treatment arms, spacing of active doses, patient sample size, number of measurements, trial duration, analysis strategy and dose selection strategy. Depending on the outcome of this analysis several key decisions can be made:

- The analysis might show that a biomarker trial or focused dose-finding trial in the patient population can reduce the uncertainty in the key region of the dose-response relationship to allow dose selection for further development. The analysis will provide the best trial strategy, that is, the most efficient trial (in terms of cost, length and complexity) with the optimal information yield to make the decision of how to continue. The trial should also be sufficiently robust to provide an answer, while taking into account the uncertainty and assumptions (e.g. drug potency, placebo response) of the current model. The value to the company is a robust and cost-effective development strategy with a minimized risk of failure in later phases of development.
- The analysis might show that there is substantial uncertainty in the treatment strategy that cannot easily be addressed by a focused and robust dose-finding trial. For example, the sample size and range of doses of the trial might be too large to warrant the investment. In this case, the analysis will provide the best sequential trial strategy and interim analysis. The value to a company of such an outcome is to allow it to carefully manage the downside risk without wasting the upside potential.

The CATD process enables the development team to quantify the current certainty or uncertainty in the probable safety and efficacy profile of the compound in development. It also enables the evaluation of information provided by different trial strategies versus the investment of time and money. This enables the team to discuss trade-offs between alternative treatment strategies and alternative trial strategies. The process provides a platform for informing and setting appropriate expectations for a candidate molecule with senior management.

Although CATD offers a unique opportunity to enhance the drug development process, barriers exist which have the potential to limit its successful implementation. Such barriers include:

- The CATD process might be seen as an addition to the current established drug development process, rather than an alternative route to gaining regulatory approval.
- A general lack of in-house PK or PD modelling expertise in many pharmaceutical companies.
- Reluctance within companies to modify processes that are needed for the successful implementation of CATD.
- An overall reluctance to implement novel strategies when there is an avowed confidence that the currently employed processes yield optimal results.

In reality, it is clear that these barriers are of minor significance compared with the major issues that currently face the pharmaceutical industry. Novel methodologies and strategies take time to become embedded within the drug development process. Any cursory glance at issues impacting R&D productivity demonstrate that novel methodologies such as CATD are an essential component in bringing about improvements in productivity.

Conclusion

The appropriate and informed application of CATD will empower pharmaceutical companies to run clinical trials with greater certainty, increase trial information yield, quantify likelihood of success, omit uninformative trials from development programmes, select optimal dosing strategies, terminate 'failing' programmes earlier, maximize the likelihood of regulatory approval, and consequently get to market more rapidly. This methodology ensures that pharmaceutical companies can progress into and through clinical development programmes with a greater understanding of both the drug and disease state, and ensures that R&D spend is not wasted on clinical trials that have little chance of demonstrating the efficacy of the candidate molecule.

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