

## Commentary

# Role of modelling and simulation in Phase I drug development<sup>☆</sup>

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## Abstract

Although the use of pharmacokinetic/pharmacodynamic modelling and simulation (M&S) in drug development has increased during the last decade, this has most notably occurred in patient studies using the population approach. The role of M&S in Phase I, although of longer history, does not presently have the same impact on drug development. However, trends such as the increased use of biomarkers and clinical trial simulation as well as adoption of the learn/confirm concept can be expected to increase the importance of modelling in Phase I. To help identify the role of M&S, its main advantages and the obstacles to its rational use, an expert meeting was organised by COST B15 in Brussels, January 10–11, 2000. This article presents the views expressed at that meeting. Although it is clear that M&S occurs in only a minority of Phase I clinical trials, it is used for a large number of different purposes. In particular, M&S is considered valuable in the following situations: censoring because of assay limitation, characterisation of non-linearity, estimating exposure–response relationship, combined analyses, sparse sampling studies, special population studies, integrating PK/PD knowledge for decision making, simulation of Phase II trials, predicting multiple dose profile from single dose, bridging studies and formulation development. One or more of the following characteristics of M&S activities are often present and severely impede its successful integration into clinical drug development: lack of trained personnel, lack of protocol and/or analysis plan, absence of pre-specified objectives, no timelines or budget, low priority, inadequate reporting, no quality assurance of the modelling process and no evaluation of cost–benefit. The early clinical drug development phase is changing and if these implementation aspects can be appropriately addressed, M&S can fulfill an important role in reshaping the early trials by more effective extraction of information from studies, better integration of knowledge across studies and more precise predictions of trial outcome, thereby allowing more informed decision making. © 2001 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

COST B15 is an action sponsored by the European Community entitled ‘Modelling in drug development’. Its

main objective is to improve the predictive potential of scientific information gathered within the framework of development of new, efficacious and safe drugs, as well as sustainable industrial chemicals. To do this the action has been divided into three working groups:

- In vitro approaches to predicting kinetics and dynamics *in vivo*.
- Markers of pharmacological and toxicological action.
- Modelling and simulation in clinical drug development.

This commentary summarises the opinions and experiences expressed at an expert meeting in Brussels organised by the third workgroup, 10–11 January 2000.

<sup>☆</sup>Based on a COST B15 meeting held in Brussels, 10–11 January 2000. The expert panel members, all of whom approved this publication as an appropriate representation of the meeting, were: K. Bol (Belgium), M. Danhof (The Netherlands), T. Goggin (Switzerland), A. Grahnén (Sweden), A. Khan (UK), S. Marshall (UK), P. Milligan (UK), V. Piotrovskij (Belgium), H. Schaefer (UK), T. Shepard (UK), E. Snoeck (Belgium), J. Taubel (UK).

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The topic of the expert meeting was the status of modelling in phase I drug development and the role it should play in the future. The experts represented the pharmaceutical industry, contract research organizations and academia. Although coming from a variety of backgrounds, the experts all had extensive modelling experience.

The use of modelling in clinical drug development has increased during the last 10 years as evidenced by an increased presence in regulatory documents (ICH, 1997), reports from the pharmaceutical industry (Kroboth et al., 1991; Charnick et al., 1995; Samara and Granneman, 1997; Sun et al., 1999) and conference reports or position papers (Breimer and Danhof, 1997; Sheiner, 1997; Danhof and Steimer, 1998). Some studies have indicated that the approach has had economical benefit (Reigner et al., 1997). The focus of these efforts has been mostly on the analysis of data from patient studies. Although pharmacokinetic and pharmacodynamic modelling has been used in phase I for a longer time than in later phases, it does not today appear to have had a large impact on clinical drug development (Van Peer et al., 1993). However, current trends in drug development make this likely to change. For example: (i) the modelling and simulation of patient data, mentioned earlier, can often be more efficiently and reliably undertaken if models have previously been developed from rich, high-quality phase I data; (ii) the development of biomarker/surrogate models should ideally progress throughout drug development, including phase I and pre-clinical; (iii) clinical trial simulations, which have received increasing attention, are being used to guide the design of patient studies, based on models derived from early data in man.

As the role of modelling in phase I may change in the near future, for example with the pressure to go into patients earlier, the authors felt it opportune to convene a meeting focusing on this issue, specifically identifying the main advantages of modelling in Phase I and the main obstacles to its implementation. This report represents the consensus view of the experts that participated in the meeting and addresses the current and past practices, current issues and challenges, and expectation for the future.

## 2. Definitions

### 2.1. Phase I clinical studies

Phase I encompasses early human pharmacology studies usually, but not exclusively, carried out in healthy volunteers. By Phase I, we refer to the learning studies, which usually have non-therapeutic objectives, that precede the first studies in patients (i.e. traditional Phase II). Other definitions, however, often include studies carried out after initiation of Phase II. Studies conducted in Phase I

typically investigate the initial safety and tolerability, the pharmacokinetic drug profile and may also assess pharmacodynamics or other endpoints that may provide an early estimate of activity or potential efficacy. In addition to these core studies, ICH guidelines (ICH, 1997) list a number of other studies which can be considered to be part of Phase I. For many orally administered drugs, especially modified release products, the study of food effect on bioavailability is important. Obtaining pharmacokinetic information in sub-populations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, women and ethnic subgroups should be considered. Drug–drug interaction studies are important for many drugs, but these are generally performed at a late point in time in drug development. Due to the high level of uncertainty (this is largely ‘first-in-human’ activity), the studies early in the development process are often of exploratory nature, intended for quick company-internal decision-making for moving forward, stopping, or re-prioritizing a given project. In contrast, the Phase I studies in later stages of the development process are intended to obtain appropriate drug label advice for special subject populations. We focus herein on the ‘early’ studies.

### 2.2. Pharmacokinetic/pharmacodynamic modelling

For the purpose of this discussion, what we intend by the term ‘modelling’ is data-driven (exploratory) analysis based on a mathematical/statistical model. By ‘data-driven’ we mean that the model cannot be fully pre-specified (in the protocol) prior to the experiment, and may be developed or refined depending on the results, i.e. ‘driven’ by the collected ‘data’. A ‘mechanistic’ model was recently defined (Sheiner and Steimer, 2000) as a model whose parameters correspond to physical or conceptual entities in the subject-matter domain of the model. An ‘empirical’ model is a model without such mechanistic elements. In addition, Sheiner and Steimer distinguish between:

- “a ‘descriptive’ model which is a priori applicable only to a restricted set of circumstances (designs, patient groups)
- and a ‘predictive’ model which explicitly incorporates variables quantifying important design and baseline features so that the model can predict outcomes conditional upon arbitrary values of those variables.”

Sheiner and Steimer (2000) also describe the difference between model independent and model dependent approaches. “What is sometimes termed ‘model-independent’ actually means independence from assumptions and is achieved by focusing inference on the value of a simple statistic whose distribution depends on controllable study design, and not on the origin of the data (i.e. not on a ‘model’ for the data). Such approaches are generally

preferred in the confirmatory stage of drug development but they are less useful during the learning stage. While one might try to view learning as an exercise in confirming (for example, one might test the null hypothesis of no difference between outcomes of small vs. large doses), it is far more natural to view learning as the task of constructing a model of the input–outcome relationship itself. Thus a model suited to learning must interpolate between, and extrapolate beyond, the value of the conditions of the actual study (or preferably ‘studies’) available. The need for a predictive model directly drives the types of models that can be considered as useful learning model candidates: most importantly, they must be mechanistic as opposed to empirical. That is, to extrapolate beyond the bounds of the design on which they are defined, models must explicitly express the values of those bounds, and to provide credible extrapolations, models must incorporate the current scientific understanding of their subject matter field.”

Thus, for example, AUC calculations by trapezoidal rule and log-linear extrapolation is not considered as data-driven modelling, whereas the analysis of the same data by compartmental models is. Also, a single logistic regression of dose versus a binary outcome (e.g., presence–absence of an adverse event) is not considered as data-driven modelling. In contrast, for the same data, the selection of the exposure measure (dose, AUC,  $C_{\max}$  (of parent drug, of metabolite(s)), etc.) that is most likely to be associated with this event together with explanatory covariates is considered modelling, even if each ‘exposure measure–safety event’ relationship is analysed by logistic regression. Since modelling is ‘data-driven’, in the vast majority of cases it relies on multiple analyses of the same set of data, in an iterative mode, with successive and/or competing ‘models’.

Pharmacodynamic modelling is used to relate exposure to effect, where effects are measurements of safety, biomarkers or clinical response. Biomarkers, according to the NIH working group on definitions, are characteristics that are measured and evaluated as indicators of normal biological processes, pathogenic processes or pharmacological responses.

### 2.3. Simulation

Simulation is a term that encompasses both situations where random variables are absent (deterministic simulations) and present (stochastic simulations). An example of the former is when the multiple dose profile is predicted from the typical (mean) parameters as estimated from data from a single dose study. An example of the latter is when a possible outcome for all individuals of a future trial is simulated based on individual parameter values sampled from a probability distribution. In addition, simulation can be based on re-sampling procedures, where new data sets are produced by random sampling from empirical data bases. The ‘Bootstrap’, for instance (Efron and Tibshirani,

1993), is such a re-sampling technique increasingly popular for determination of uncertainty on estimated or predicted quantities (e.g., confidence intervals). The simulation model, built using early clinical data and, perhaps, preclinical data, must be viewed as a ‘working model’ which will become refined as more data and information become available. Consequently, the predictions of simulation models are only a guide to clinical trial design.

### 2.4. Combined analyses

Sometimes modelling of pooled data across studies is carried out to obtain information that could not, or not as easily, be obtained from separate analyses of the individual studies. We have on purpose chosen the term ‘combined analysis’, rather than ‘meta-analysis’. The latter is strongly associated with (joint) analysis of high level summary statistics (e.g., *P*-values in comparative studies), rather than (joint) analysis of (raw) data.

### 2.5. The population approach

The analysis of sparse pharmacokinetic and pharmacodynamic data in the target population by nonlinear mixed effects modelling has been termed population modelling or ‘the population approach’ (Rowland and Aarons, 1992). Nonlinear mixed effects model analysis can also be applied to rich data, for instance from a group of healthy volunteers, and the use of the term ‘population modelling’ in this instance is questionable, but is still used here for convenience.

### 2.6. Added value

It was found relevant to ascertain whether modelling has a low or high cost-to-benefit ratio. Modelling efforts should be more specifically assessed by their impact on productivity, where the future value of the ‘product’ of drug development (e.g., an improved label for the drug) and the probability of technical success (less risk of a failed study) would have a positive contribution to productivity, whereas the cost of modelling and any increase in cycle time (i.e. increased duration of clinical drug development) due to modelling would have a negative contribution. Modelling, on the other hand, may also lower cost (e.g., to reduce the *in vivo* experimental workload for formulation testing) or shorten cycle time (e.g., abbreviation of Phase II supported by a PK/PD model). In the following, when it is stated that modelling is ‘of value’, it should be interpreted as increasing the productivity or the benefit-to-cost ratio, by adding more information to the development process.

### 2.7. Pharmacometrics

Pharmacometrics is defined herein as the science of

developing and applying mathematical models and statistical methods for characterizing, understanding, and predicting a drug's pharmacokinetic and pharmacodynamic behavior over time, and for quantifying the uncertainty of information about that behavior.

### **3. Current practises (the views in this section were compiled from a questionnaire circulated to the experts prior to the meeting)**

Based on the experience of the experts, modelling is carried out in a minority of the Phase I studies, although modelling software packages such as WinNonLin and NONMEM are widely available in the pharmaceutical industry. There are several reasons for this. Modelling requires specialised software and experienced analysts. The shortage of analysts with training and experience in this area is one major impediment for the application of the methodology. In addition, the difficulty in automation, standardization and validation of the modelling process are causes of concern. The vast majority of Phase I studies are designed to be analysed primarily by non-modelling methods as these are easy to implement and validate. In such situations, modelling is not routinely required and should only be considered if it can provide a positive benefit-to-cost ratio with a valid rationale. Unfortunately, it appears that formal assessments of this benefit-to-cost ratio are lacking.

### **4. Value of modelling**

A number of examples of the benefits of modelling were presented at the meeting. These were classified into three categories, by the frequency with which they can be expected to be of value in Phase I programs.

#### *4.1. Situations where modelling is usually invaluable*

There are certain situations which can only be resolved by modelling. Characterisation of nonlinear pharmacokinetics to allow for estimation of parameters and prediction of concentration–time profiles is such a situation. Hierarchical mixed effects modelling is particularly suited to handle censoring of data due to, for example, assay limitation, which affects individuals differently, as they have different PK profiles (Schoemaker and Cohen, 1996). Exposure–response relationships may be difficult to quantify due to response data being sparse and/or low in information content, as is the case for many of the subjective safety assessments recorded as categorical data (e.g., mild, moderate, severe). Frequently the relationship between exposure and biomarker is complex in nature and the description of the time course of the biomarker itself requires a model (Francheteau et al., 1993; Fattinger et al.,

1996; Gisleskog et al., 1998). Another situation involving multivariate response data is when metabolites are of sufficient interest that their time-course and relationship to the parent drug needs to be quantified. In such cases, hypotheses about drug disposition and the contribution of various drug related components to the response can be assessed by modelling from appropriately designed studies (Karlsson et al., 1996).

There can be considerable value in complementing or contrasting preclinical results with in vivo results in humans. Several of the participating experts reported that a combination of PK models based on Phase I data and a PD model based on preclinical or biomarker data had been valuable for designing Phase II studies (Derendorf and Meibohm, 1999), in particular when information exists about the relative potency compared to a drug for which the response in patients is known. An example of the latter is the development of remifentanyl (Minto et al., 1997).

Phase I studies are often performed to study the influence of a specific, controlled factor. The limited range of dosing and covariate information can lead to imbalance and confounding. The interrelationships between multiple factors (such as gender, age, genotype, food/fasting, dose size, single/multiple dose) can be studied by pooling the data of many separate Phase I studies and then performing a model-based analysis of the joint data. The information in each of the separate studies is best transferred to the joint analysis if the raw data are used. However, sometimes a combined analysis of a derived parameter such as AUC can also provide considerable information not obtainable by other means (Steimer et al., 1998; Blychert et al., 1992). When combining data, attention has to be paid to differences between the populations that are to be combined. If patient data are to be combined with that from normal volunteers, it has to be made certain that both populations have similar properties. For example, patients can have much higher tolerability to drugs than normal, healthy volunteers. The population approach in clinical drug development was first applied because only sparse pharmacokinetic data could easily be obtained in the target patient population, and modelling was the only option to an adequate and efficient interpretation of such data. As experience with modelling of sparse data increases, there is a clear potential to reduce cost and inconvenience by reducing sampling also in Phase I. In some special populations studied in Phase I, such as children and volunteers with reduced organ function, it may be ethically difficult to motivate anything other than sparse sampling for PK purposes, with, as a corollary, the absolute need for a model-based analysis.

#### *4.2. Situations where modelling is often very useful*

The prediction of PK/PD exposure following multiple dosage regimes based on single dose data is usually the earliest and one of the most common extrapolations made.

In this extrapolation, models are convenient, but when the time profile is of interest a model is necessary. Also, once data from single and multiple doses are available, modelling is useful to determine the nature of, and quantify, deviations from PK dose proportionality. When time-dependent changes in the PK or PD processes do occur, modelling can again be of use to discriminate between rival hypotheses, as well as to quantify phenomena such as auto-induction or tolerance (Boddy et al., 1995; Hassan et al., 1999). For drug–drug interactions of major clinical importance, where the degree of interaction is dependent on drug(s) concentration, mechanistic models can be of value in anticipating results from patient studies, particularly for situations where a metabolic pathway displays polymorphism. Also for bridging results obtained from different ethnic groups, models which can take into account varying allele frequencies can be used to allow the response data base to be properly integrated across ethnic groups.

In formulation development, well-documented *in vitro* dissolution/*in vivo* absorption relationships may reduce the *in vivo* experimental workload for formulation testing. Deconvolution methods based on PK/PD models may allow the optimal input profile to be obtained based on the desired response-time profile (Park et al., 1998).

Especially in the case of complex molecules of biological origin, often consisting of different isoforms, it is useful to build models predicting the PK/PD relationship for each isoform or for clusters of isoforms based on clinical and pre-clinical data. The different isoforms are normally not measured separately in pharmacokinetic trials in humans. However, small differences in exposure to different isoforms, depending on their individual pharmacokinetic and receptor binding properties, can lead to a large difference in pharmacodynamic response. Without these models, built in early development, the results from Phase II/III trials can be difficult to interpret, even when comparing two bioequivalent products (de Leeuwe et al., 1996; Rombout, 1996).

To model sparse pharmacokinetic data obtained in the target population in a realistic fashion, additional information may be required. A model developed for healthy volunteer data, even though it is usually rudimentary in covariate relationships, allows subsequent modelling of patient data to be more predictable and efficient.

#### 4.3. Situations where value added by modelling is case dependent

Whereas characterisation of deviations from dose proportionality usually requires modelling, detection of dose proportionality can often be achieved using non-modelling methods. However, by considering the shape of the concentration–time profile, as well as summary measures, such as AUC, population modelling methods can be more

powerful for the detection of nonlinearity (Gisleskog et al., 1999).

Although it may be tempting to assume that modelling can be used to salvage a poorly designed study, it was generally recognized that such attempts often had low benefit-to-cost ratio and careful consideration is in order before a model-based re-analysis is initiated. In order to avoid poor design of a Phase I study, the design may be improved using predictions from a model based on a previous study. If adaptive designs are to be used in early development, a model-based interpretation of the observations and a model prediction as the basis for the next action may be the best choice.

## 5. Practical implementation

Several issues were discussed that could influence the quality and thus acceptance of a modelling exercise. The quality of the modelling exercise can be improved by increasing the quality and information content of the data going into the exercise and by increasing the quality of the evaluation itself.

### 5.1. M&S as a ‘study’ carried out ‘*in numero*’

In general, it was felt that, within drug development teams and line management, a skeptical attitude to modelling and simulation (M&S) approaches prevailed. This is largely due, as already mentioned, to the (present) absence of a clear indication of the cost–benefit for the activity. It is also due to the absence, until recently, of ‘Good Modelling Practices and Good Pharmacokinetic Practice’, which impede the visibility and acceptability of the technique, but progress has been made recently (Rombout, 1997; Holford et al., 2000a,b). Data driven PK/PD modelling is sometimes mentioned in the protocol of a clinical study as one of the explanatory data analysis techniques, but a detailed analysis plan is rarely included.

Table 1 gives the dimensions of a ‘modelling exercise’ as contrasted with an *in vivo* experimental study (Table 1, 2nd column). In contrast to past practices (Table 1, 3rd column) which limited the usefulness of modelling, modelling is considered to be an ‘*in numero*’ study, i.e. a particular investigation carried out with mathematical, statistical and numerical techniques (Table 1, 4th column), within a computing environment. The objective of the ‘*in numero*’ study is to answer a specific question pertinent to a drug in development, in order, for instance, to support the selection of the therapeutic dosing regimen, to provide a rationale for development decisions or to support a labeling claim in addition to experimental evidence. This can be in the general patient or special populations, or in healthy volunteers. It can either be prospectively planned as part of the strategic clinical development plan or started in reaction to an unexpected outcome from one or several

Table 1  
The dimensions of an 'in numero study' as contrasted with an in vivo experimental study

Item	In vivo experimental study	Modelling exercise	
		Practises that have limited usefulness of M&S	Practises that could increase the usefulness of M&S (in numero study)
Design	Specified in clinical protocol	Undefined, exploratory	Specified in M&S protocol
Data collection	Fully detailed	Use the data that is available and accessible	Selection of data and studies fully specified
Quality status	GCP, GLP, SOP	No rules	GPP, M&S good practices
Objectives	Prespecified	Not defined	Prespecified
Analysis	Prespecified, exploratory or confirmatory	Unspecified, improvised	Prespecified, exploratory or confirmatory
Reporting	Study report, according to guidelines	Memorandum	M&S report, according to guidelines
Priority/timelines	High/stringent	Normally low normally none	High/stringent
Sponsor	Project team	None	Project team
Investigator	Clinical team and external parties defined	Student to expert, often isolated	Evaluation team defined
Cost/budget	Approved/fixed	Undefined/none	Approved/fixed

clinical trials. The in numero study does not a priori require a new clinical trial but is based on (even more precisely, 'consists of') the mathematical modelling and statistical analysis of existing data, selected according to the objectives of the study. The M&S analysis will generally be a combined analysis and will involve the assembly of data from several clinical trials. An in numero study synopsis is written and agreed upon prior to the analysis in order to outline the objectives, the major *modelling* steps including the data selection criteria and the expected outcomes, the model validation step and the simulation step if any. Such more rigorous practise is likely to increase the usefulness of the modelling activity (see details in Table 1) and to make its deliverables more acceptable to internal as well as regulatory reviewers. M&S per se can lead to more efficient strategies for internal decision-making, and can in patient studies provide supportive evidence to primary clinical data (e.g., dose-exposure–response information). Of course, in cases where *confirmatory* clinical data are needed, e.g. for regulatory purposes, M&S cannot replace an experimental study (although it helps to plan it properly).

### 5.2. Data information content

The limitations found when evaluating data are often caused by a lack of information due to study design issues.

Several examples were presented where a modelling approach would be limited by a priori built in limitations:

- Fixed protocols which would not enable changes based on unexpected findings during the study.

Other types of study designs might supply more in-

formative data, for example adaptive dose design, in which future experimentation is based on information gathered to date, rather than on fixed rules in a protocol. Flexibility should exist for dose selection as well as for PK/PD sampling. Modelling is an essential tool to guide adaptive study design. Although flexible protocols are common in oncology, they put a high demand on data management and blinding/unblinding procedures to preserve both the reliability and credibility of the results and enable timely decision making.

- Designs in first-in-human studies.

Parallel designs do not give information on intrasubject variability in PK/PD parameters. The pharmacological effect is evaluated against the placebo effect in a separate, normally very small group of placebo-treated subjects. A cross-over design would be an alternative, but this would mean starting with high dosages in some volunteers which is not possible on safety grounds. A compromise was presented whereby at each dose escalation step the subject receives placebo or active in a cross-over design. The extra time needed for these cross-over study types is marginal and, related to the overall Phase I or total clinical development time, negligible.

### 5.3. Methodology

Both individual and population (nonlinear mixed effects) modelling can be used to assess many Phase I data sets. Population modelling was acknowledged to have several general advantages and specific examples were cited (Schoemaker and Cohen, 1996; Gisleskog et al., 1999; Nichols et al., 1997).

The advantages of population modelling include:

- a direct estimate of the population characteristics of PK/PD parameters is obtained;
- studies or dose steps can be modelled and optimized based on current knowledge;
- it is more likely to detect departure from dose proportionality in pharmacokinetics and determine the parameters involved;
- a smaller number of samples per individual, which is ethically desirable, can be used;
- imbalance in data, which can occur in dose-escalation studies or when some samples are below the limit of quantification, is handled in a proper fashion;
- combined analyses can be performed at the level of the raw data;
- complex models can be evaluated when data from many subjects are analysed together.

In contrast, since nonlinear mixed effect modelling methods have often been created to handle sparse data, they may not always be optimal for the analysis of data from rich Phase I studies. Thus the choice of estimation method is of importance and further methodological work is needed for these type of studies. Nonlinear mixed effect modelling may also be impeded by long run times with complex models and numerical difficulties with the estimation routine. The estimation of variability in PK/PD studies can be affected by the assumptions made about the parameter distributions and can also be influenced by 'outliers'.

## 6. The role of modelling in a changing Phase I environment

Clinical drug development is often described as consisting of four temporal phases (ICH, 1997). The ICH document 'General Considerations for Clinical Trials' already recognises that Phase I may not typically refer any longer to the first-in-human studies in healthy subjects.

The assignment of studies to a particular phase of the drug development sequence is, in fact, not necessary. A revised concept of drug development, based on frequent interaction between learning and confirming periods, might be more effective in providing adequate feedback to drug discovery teams and to improve the quick and reliable identification of beneficial products. The classification into four phases may disappear and evolve into a process with an initial learning stage in healthy subjects, a 'Proof-of-Principle' (or 'Proof-of-Concept') stage in healthy subjects and patients (still mostly a 'learning' phase), and a confirmatory stage for evaluation of therapeutic benefit (a true 'confirming' phase).

Preclinical, mechanistically relevant PK/PD data are modelled to scale from animals to man and to improve the likelihood of selecting the appropriate range of human

doses. There are emerging trends that PK/PD modelling may enable the pharmaceutical industry to move into patient studies faster and safely. The emphasis in early studies may well shift to innovative designs, ad hoc measurements and combined routes of administration. Currently, most of the modelling activity in the pharmaceutical industry is based on scientists' personal interests or is issue triggered. This role will be different in the new paradigm, and expanding. The mathematical model would form one basic repository of summary information that can be carried forward from the preclinical phase through the clinical phases. The opportunity to perform data-driven modelling as a key element for decision-making will, in turn, influence the design of Phase I studies and the nature and frequency of the measurements to be performed. 'Exposure' as derived from pharmacokinetic measurements will play a central 'bridging' role. The pharmaceutical industry is starting to invest resources so as to improve the predictability of outcomes of clinical (especially therapeutic) studies. Already standard in other knowledge-based industries, computer simulation is increasingly being used to aid clinical trial development. If this trend persists, trained scientists will increasingly be needed, and modelling and simulation projects will become integrated into development plans.

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