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Review article

Modelling during drug development

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Abstract

With the advancement of both biological and computer sciences, new drug development faces the challenge to integrate a huge amount of knowledge accumulated from the very early quantitative structure–activity relationship investigations of the candidate molecule to the large scale clinical trials in patients. Whereas pharmacokinetics and pharmacodynamics are fields in which modelling has long demonstrated its value, its potential in many other areas of drug development has recently been the object of intensive scientific activity. The present review places emphasis on these newer applications; it includes the opinion of many experts in often highly specialised areas such as in vitro to in vivo extrapolation, toxicokinetics, non-continuous response models, population approaches and computer assisted simulation of clinical trials. It is most probable that in the near future many of these areas of research will be the objects of intensive and interesting developments. This will undoubtedly lead to improve developmental strategies for new drugs as well as more individualised pharmacological strategies for patients.

Keywords: Modelling; Drug development

1. Introduction

Research and development of new drug entities is becoming more complex with the advancement of basic sciences [1]. At one end of the drug development process, computer-calculated structures of receptors are progressively used to design new chemical entities with specific pharmacological/therapeutic activities. Due to remarkable progress in molecular biology and gene technology, it has become possible to develop simple assays by which a large number of compounds may be tested in regard to their biological efficacy. Automation of these tests with computer-controlled robot systems has made it possible to evaluate up to 1 million substances per robot per year. Therefore, large numbers of compounds with potential therapeutic activity will become available. A critical issue is, however, how information obtained from these test systems can be extrapolated to the in vivo situation. At the other end of the drug development programme, new software is presently under development to simulate large scale clinical trials including hundreds of patients in order to optimise clinical trial designs before they are performed in the real clinical world.

It must be stressed that modelling during drug development is not a new discipline. It has been performed for years, especially for pharmacokinetic data obtained in healthy volunteers during Phase 1 studies [2]. More recently, as the power of computers has increased, more complex modelling is being performed and efforts are being made to integrate knowledge obtained during all phases of drug development. The present review does not cover the different aspects of modelling during drug development with equal emphasis: the classical ones are briefly summarised whereas more space is devoted to specific areas where intensive scientific activity is ongoing. Because these are often highly specialised areas, the present article was conceived as a forum for experts to summarise the most recent advances in their field of activity and their perspectives for the future. It reproduces large extracts of recent articles and conference proceedings (in a different lettering) with the aim of providing the reader with a brief survey of a field teeming with new developments. In particular, reference is often made to lectures presented at the 1998 meeting on 'Measurement and Kinetics of In Vivo Drug Effects: Advances in Simultaneous Pharmacokinetic/Pharmacodynamic modelling' held in Noordwijkerhout [3], which are not readily available and clearly deserve a larger audience. The bibliography is far from being exhaustive. It should nevertheless provide directions for a possible more focused literature search in computerised databases.

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2. Models: mechanistic versus empirical

There have been many proposals for the terminology used to characterise models. These concepts may not get approval by all scientists in the field, but may help open the discussion on modelling during drug development. An elegant presentation of the distinction between mechanism-based models and empirical models has been given by Thakur [4].

> We will design two types of models: systems analytic or mechanistic and empirical, often designated as statistical (although the present author has some problem in using 'statistical' as a synonym for 'empirical'). A mechanistic model, as the name implies, should have as many features of the primary system built into it as observations or data will allow. Such a model should be consistent with the observed behaviour of the system – retrodiction; it should further be predictive of the system's future behaviour or behaviour under perturbation – prediction. One must have some knowledge of the primary system in terms of structural connectivity and functional mechanisms. Some prefer to call this type of models realistic, intrinsic, and various other names. Many great discoveries in biology, medicine and other branches of science have been made using such models. In this context one must remember that such models do not necessarily have to have an explicit mathematical expression; they could be just conceptualisations.
>
> On the other hand, when the system under study is complex and hardly anything is known about its structural connectivity and functional mechanisms, yet one has to produce hypotheses about it based on some external characteristics such as a dose response (secondary system), one often relies on mathematical functional forms for such a system. These mathematical functions are empirical models. They may incorporate some mechanistic assumptions so that they may look realistic. Numerically, these models are generally easier to handle as opposed to many mechanistic models. Most normal theory based statistical hypothesis testing and confidence interval procedures are based on such models. One should not get the wrong impression that mechanistic models are not useful for such statistical techniques; they may be more difficult to handle numerically from estimation standpoints. Some people would call empirical models extrinsic because they are based purely on the external behaviour of the system. Some call them statistical models. As mentioned earlier, it is unfair to assume that statisticians always like to use empirical models for their purposes. The reasons why there is abundance of this type of models in literature are obvious. Our knowledge about the primary system may be inadequate to negligible to allow us the formulation of a mechanistic model or one may not be interested in understanding the inherent structure of the system. In the present author's mind, the phrase statistical model includes both types of models. One must remember that an empirical model may be 'retroactive' (explaining what happened from a secondary system) and even locally 'predictive' (i.e. interpolation may be performed within the range of observations) but it is, in general, not globally 'predictive' (indicating outcome of future experiments). In fact, empirical models should never be used with any authority for extrapolative purposes.

If this distinction between mechanistic and empirical models is accepted, one may conclude that, until today, in the majority of cases, pharmacokinetics (PK) has used empirical models. Pharmacodynamics (PD) has searched to use mechanistic models more diligently than pharmacokinetics, but it is only in recent years that the concept of mechanism-based modelling has really been promoted as a tool useful not only for academic work, but also for a more rational drug discovery and development process.

3. Theoretically derived physicochemical properties

Physicochemical properties include calculated molecular weight, solubility, lipophilicity, hydrogen bonding, potential or dynamic molecular surface properties which are fundamental attributes of xenobiotics. They are extensively used in quantitative structure–activity relationship (QSAR) investigations and efforts have been made to use them, as early as possible, in the development of new drugs not only for prediction of pharmacological activity, but also for toxicology, membrane passage forecast and clearance [5,6]. This is important in the context of the immense number of molecules synthesised by combinatorial chemistry methods.

At the same level, one may consider genetic information obtained from molecular biology, which is a fundamental property of individuals. This information may be associated with 'kinetics oriented properties' of individuals, such as the genotype for metabolising enzymes, or with 'dynamics oriented properties' such as receptor polymorphisms. Presently there have been few attempts to use this information for modelling purposes, with notorious exceptions such as molecular modelling of cytochromes P450.

4. In vitro methods

4.1. In vitro/in vivo extrapolation for PK and PD

It is very important to determine (or at least predict) at

an early stage of drug development the kinetic properties of a drug candidate. This means absorption, distribution, metabolism and excretion (ADME) [7]. As important is the prediction of the release characteristics of the active principle from a pharmaceutical formulation and its dynamic properties. These include characterisation of the molecular targets for biological effect, the concentration–effect relationship, the reversibility and time course of effects, as well as potential adaptive changes. Finally, the possibility of either kinetic or dynamic interactions must be assessed.

One major aim of in vitro/in vivo modelling is to provide screening tools for drugs at a very early stage of development. Such screening tools should allow 'high-throughput' capacities: they should be rapid, easy to use, require small amounts of compound, be relatively inexpensive and, last but not least, result in reliable predictions. These predictions may serve as a basis for the choice of the second animal species for early toxicology studies (e.g. monkey or dog) next to the usually studied rat.

From a kinetic point of view a series of methods have been developed. They include various subcellular and cellular systems for measuring permeation, membrane transport, absorption, distribution, metabolism and excretion. These systems also include in vitro testing in cells modified by genetic engineering. Among such systems, one may list:

- partition coefficients (usually water-octanol) [8,9];
- Caco-2 cell monolayers (for gastrointestinal absorption) [10];
- plasma protein binding (animal and human);
- microsomes (animal and human, for hepatic metabolism) [11,12];
- hepatocytes (animal and human) [11,12];
- recombinant expressed enzyme systems (animal and human).

From a pharmacodynamic point of view, one may mention systems available to determine in vitro both affinity and intrinsic efficacy of new drug candidates.

Most models display a relatively good predictive value from a qualitative point of view, but usually lack accuracy to predict quantitatively the in vivo behaviour. Another problem is that in vitro models are strongly dependent upon experimental conditions so that important differences are often observed between results obtained in different laboratories. There is, however, considerable work presently done to improve the predictability of such models. As stated by Tucker in a recent symposium on the prediction of in vivo metabolism in man from in vitro data: 'In Vitro Veritas? Not yet, but we are getting closer!' [13].

4.2. Biopharmaceutical in vitro/in vivo correlations

In vitro methods and modelling are also very important for the development of pharmaceutical formulations [14–16]. According to Dunne and colleagues [17],

> A major goal of the pharmaceutical scientist is finding a relationship between an in vitro characteristic of an oral dosage form and its in vivo performance. One such relationship between drug dissolution (or absorption) in vivo and that in vitro is known as an 'in vitro–in vivo correlation' (IVIVC) whose importance stems from the fact that it may be used to minimise the number of human studies required during drug product development, assist in setting meaningful in vitro dissolution specifications and justify biowaivers for scale-up and post-approval changes. A number of ways of describing an IVIVC have been reported. In the majority of cases reported to date, both the model and the statistical methods employed for level A IVIVC are very simplistic. The model assumes that the rate and extent of dissolution in vivo are the same as those in vitro. The statistical methods ignore the repeated measures nature of the data and use a response variable as an independent variable without accounting for measurement error.

As a consequence, more elaborate models are under development to predict in vitro–in vivo relationships. Another point of importance addresses the experimental protocol for the in vivo study. As a matter of fact a multitude of variables can influence rate and extent of absorption after intake of an oral formulation. For the measurement of consistent in vivo parameters within and between pharmacokinetic studies, it is of primary importance that such variables be recognised and controlled [18].

5. Animal experimentation

The pharmacokinetic development programme is well defined for xenobiotics of smaller molecular weight. Products from the biotechnology area may present particular problems. At an early stage of drug development (e.g. prior to the 'first into man' administration), a 'classical' kinetic programme may include:

- single- and multiple-dose studies in up to three or four species;
- toxicokinetics;
- preliminary metabolic elucidation.

Similarly, a 'classical' pharmacodynamic programme may include:

- pharmacological testing;
- safety pharmacological testing;
- preliminary toxicology.

5.1. Animal pharmacokinetics and toxicokinetics

A few years ago, the development programme of a new drug depended heavily on animal pharmacokinetic studies as a tool to predict behaviour in man. Every drug company

had a 'standard programme' for drug candidates which, for example, included both intravenous and oral administration of 'standardised' doses to rats. Today, more emphasis has been given to human derived sub-cellular or cellular systems as described above. Animal pharmacokinetic studies are nevertheless still of crucial importance because they constitute the bridging studies to validate animal exposure in toxicological investigations and 'extrapolability' of these results to humans.

In toxicokinetics, various modelling methods are used, including population methods when sparse sampling is performed. More recently, it has been advocated to apply pharmacokinetic/pharmacodynamic modelling in toxicology [19].

> Pharmacokinetics aids interpretation of the dose–response relationship in individual toxicology studies. When used to compare across studies, even in a single species, other factors, including variation in pharmacodynamic response, must be taken into account. Variation in pharmacodynamic response becomes more profound when one compares across species. Examples do occur where plasma concentration-response relationships are constant across species, particularly when corrected for unbound drug. These examples should not be taken as support, however, of a general universal principle. Owing to multiple factors such as species differences in receptors, enzymes and ion channels, dose or plasma concentration–response relationships can vary enormously across species. In the light of this, the results of toxicology studies should be viewed as qualitative rather than quantitative.

As described by Balant et al. [2], precautions are needed when analysing samples from animals sacrificed at different times.

> When analysing a series of data obtained by 'destructive' sampling, it is important to realise that it can be misleading to regard such a series as coming from a 'typical' animal. There is a great need to account for the fact that the destructively obtained samples came from a population with more variability than the traditional experimental error. Once this provision is made, the data can be analysed using the population kinetic or other ad hoc approaches. The precision of the parameter estimates is then a function of the underlying structural model and the sampling strategy. Therefore, tissue concentrations should be carefully analysed in terms of their relevance for toxicological, clinical and pharmacokinetic aspects. In particular, drug persistence in a given tissue does not imply that, from a pharmacokinetic point of view, a 'deep compartment' is being observed.

5.2. Animal pharmacodynamics

This area of research has seen important developments in recent years. For example, animal models have been used successfully to develop new concepts of drug treatment or they have been refined in a way to demonstrate that the concentrations at which measurable pharmacological and toxicological effects occur are similar in experimental animals and humans. Genetically modified animals play a role that becomes more important as the causes of diseases are now better understood at the molecular level.

5.3. In vivo PK/PD modelling in animals

Until recently, animal pharmacokinetic and pharmacodynamic investigations were usually performed in different departments of the pharmaceutical company. To some extent, pharmacokinetics was performed with doses that were dictated more by analytical sensitivity than by effects in animal models. On the other side, pharmacologists were usually not interested by blood concentrations at which effects were obtained. This separation of activities is now progressively changing and more integrated approaches are tested [20–23]. The principle of PK/PD modelling is briefly summarised by Derendorf and Meibohm [24].

> Pharmacokinetic/pharmacodynamic modelling links dose–concentration relationships and concentration–effect relationships, thereby facilitating the description and prediction of the time course of drug effects resulting from a certain dosing regimen. PK/PD-modelling approaches can basically be distinguished by four major attributes. The first characterises the link between measured drug concentration and the response system, direct link versus indirect link. The second considers how the response system relates effect site concentration to the observed outcome, direct versus indirect response. The third regards what clinically or experimentally assessed information is used to establish the link between concentration and effect, hard link versus soft link. And the fourth considers the time dependency of pharmacodynamic model parameters, distinguishing between time-variant versus time-invariant. Application of PK/PD-modelling concepts has been identified as potentially beneficial in all phases of preclinical and clinical drug development.

5.4. Mechanism-based PK/PD modelling

As emphasised by Van der Graaf et al. [20], the need for a more mechanism-based approach in PK/PD modelling is increasingly being recognised.

> Receptors are the most important targets for therapeu-

tic drugs. In the past decade, the tremendous progress in the area of molecular biology has yielded many new insights in the structure and function of receptors. In particular, important new ideas have been developed recently into the regulation of agonist efficacy by variable receptor expression and novel concepts such as inverse agonism and constitutive receptor activity have been introduced. Furthermore, by means of antisense technology it has become possible to inhibit the expression of receptors which could lead to the development of a new generation of pharmacological tools for the treatment of disease. The science of pharmacology has been built upon the concept that physicochemical properties of receptors are often highly conserved among individuals and species. This concept has been the cornerstone of modern, 'rational' drug discovery that is based on the search for novel ligands that display selectivity for a particular receptor system of interest. This search for selectivity of a drug always involves the concepts of *affinity*, describing how well the drug *binds* to the receptor, and *intrinsic efficacy*, describing to what extent the drug can *activate* the receptor. Importantly, however, even though these two properties are assumed to be fixed for a particular drug-receptor combination, the pharmacological effect generated is highly dependent on the biological system it is measured in. In particular, receptor density and the efficiency of receptor–effector coupling are believed to be major determinants of pharmacodynamic variability and it is well established that one drug can act as a full, partial, inverse or silent agonist (i.e. antagonist) at the same receptor expressed in different systems.

To date, however, almost all research in these new areas have been confined to in vitro studies in isolated tissues and cells or subcellular fractions. In such studies, pharmacological responses can usually be isolated to the extent that they can be attributed directly to the interaction of a ligand with one receptor system. In in vivo systems, however, there are a great number of factors present that can modulate a particular drug–receptor interaction and the primary response generated by it. Therefore, results from in vitro studies cannot be extrapolated in a simple and direct manner to explain and predict drug action in vivo. In fact, isolated tissue assays can be unreliable predictors for the in vivo activity of a drug simply because receptor expression and coupling are different. Furthermore, variable receptor expression is a major cause for the problems associated with quantitative between-species extrapolation. Even less is known about the relationship between expression and regulation of receptors and inter-individual variability in drug effects, but receptor adaptation appears to be a major cause for pharmacodynamic changes that are often seen following chronic treatment and in certain diseases. Overall, therefore, it is important to start to explore the mechanisms of receptor modulation and drug action in intact in vivo systems.

5.5. 'Scaling up' and 'first into man'

For drug candidates, an important aim of modelling at this stage is to predict the first dose to be administered to the first volunteers of Phase 1 investigations. Attempts have been made for this type of prediction [25] using the simple allometric approach (i.e. clearance and volume of distribution extrapolation based on body weight only). This simple method has been largely unsuccessful in prospective prediction, essentially because interspecies differences in drug metabolism, as well as dynamic effects, are neglected by the model [26]. More elaborate physiological models, integrating kinetics and dynamics, probably represent a better approach and should be more intensively investigated [27–31]. Recently, modelling based on the population approach led to promising results. Information on this subject is, however, still scarce.

6. Phase 1 studies

6.1. Pharmacokinetic modelling

Phase 1 studies are usually conducted in order to characterise the basic properties of a new drug in humans in the expected therapeutic dose range (i.e. to determine its 'fingerprint'). This usually includes:

- single and multiple dose kinetics at three dose levels;
- metabolic profile;
- bioavailability investigations;
- formal PK drug-drug interaction studies.

Phase 1 PK is the area where modelling has been most extensively applied not only for drug development, but also for investigations of drug behaviour not necessarily aimed at fulfilling regulatory purposes. As a consequence, this is the area where most experience is available and it represents a pivotal body of knowledge from which it is possible to judge modelling efforts in other areas of drug investigations.

Pharmacokinetic data analysis always postulates models. It is thus necessary to challenge the term 'model-free pharmacokinetics', which is a 'non-sense' concept because data analysis is always based on some form of hypotheses. According to Balant et al. [2], different types of pharmacokinetic models can be distinguished, according to whether they are pure mathematical formulations or may integrate, to various degrees, physiological concepts such as blood flow to different organs.

6.1.1. Empirical models

The calculation of the area under the concentration-

versus-time curve (AUC) by the trapezoidal rule and of C_{max} and T_{max} by visual inspection of the curve, as often performed in bioavailability studies, is a good example of an empirical model. This model is essentially based on the hypothesis that the disposition kinetics of the parent drug are linear and that the area under the curve is related to dose and clearance.

Often, sums of exponentials may be used to describe the behaviour of a drug after a single dose and to predict concentrations after multiple dosing. Here again, the only hypothesis underlying the model is linearity of disposition.

It thus appears that empirical models may be very useful in many situations. Their use as sole means for data interpretation is, however, usually not sufficient for drug registration.

6.1.2. Compartmental models

Compartmental models are still the most commonly used models for pharmacokinetic data analysis and there is presently little reason to believe that the situation will change in the near future. From the calculated micro-constants and volume terms, it is possible to obtain clearance values, volumes of distribution and systemic availability. Most computer programs available on PCs are based on compartmental models and parameter estimation by non-linear regression.

Compartmental models may also be formulated directly as a function of clearance terms, with the advantage to provide variance estimates for clearance and volume rather than for microscopic rate constants. In any case, parameters derived from compartmental models should be interpreted with caution as to their physiological meaning.

6.1.3. Clearance-based models

Clearance-based models used for classical pharmacokinetic data analysis do not fundamentally differ from compartmental models. They may, however, be more useful, for example if data obtained in healthy volunteers are to be compared with data obtained in patients with renal insufficiency and modified plasma protein binding. Thus, clearance-based models are most useful for comparison of the behaviour of drugs in health and disease, where the objective is the quantification of changes in systemic availability, clearance and volume of distribution. The use of the clearance concept may also be relevant if plasma protein binding is concentration-dependent.

6.1.4. Full physiological models

Full physiological models including blood flow to all major organs of distribution and elimination are not considered as classical tools in Phase 1 studies. The main drawback of these models is the high number of variables, which necessitates even more data points if reasonable estimates of the parameters are to be calculated.

6.1.5. Perspectives

Recently, population modelling has also been applied in the data rich situations encountered in Phase 1 studies [32].

It is probable that when medical imaging becomes more easily available for the study of drugs under development, new modelling methods will be necessary to handle real time data, multi-tissue concentrations and short-lived isotopes among other factors.

6.2. Pharmacodynamic modelling

Pharmacodynamic modelling cannot usually be performed in healthy volunteers for therapeutic effects or surrogate endpoints of clinical manifestations of a disease. However, one area of PD that has been neglected is modelling unwanted effects that may often be observed in healthy subjects as well as in patients.

Despite limitations for the measurement of therapeutically relevant effects in healthy volunteers, the present tendency is (whenever possible) to integrate PK and PD modelling already in Phase 1 studies. According to Van Peer et al. [33],

> Early investigation of pharmacokinetic–pharmacodynamic relationships in Phase 1 may facilitate the further clinical development of a new drug. Although some pharmacology assessments in Phase 1 are often only surrogates for the therapeutic effect, PK/PD modelling of those effects provides in general crucial information on the drug's potency in vivo. A mathematical PK/PD expression allows explorative simulations on the rate of onset of drug action, on the intensity and duration of the effects for doses in future clinical trials, or in situations of altered drug kinetics. Furthermore, understanding of the PK–PD relationship early on in drug development may anticipate unnecessary exposure of human subjects to inappropriate drug doses or trials.

7. Phase 2 studies

7.1. Primary aims of Phase 2 modelling

The early studies in patients (Phase 2a) are performed in order to confirm that the expected therapeutic effect can be observed at doses well, or at least acceptably, tolerated. The Phase 2b studies are performed in order to 'prepare the ground' for the large-scale (and expensive) Phase 3 clinical trials. Presently, attempts are made to see whether it is feasible to replace part of the Phase 2b programme by simulations

using specific software. An example is provided by Yu et al. [34].

Pharmacokinetic variability is an important component of the total variability in drug response, but Phase 2 dose–response trials frequently are designed without considering this important factor. Simulation can be performed to examine overlap of patient AUC values between doses for drugs with differing inter- and intra-patient pharmacokinetic variability. Based on the results of such simulations, a dose increment can be estimated to ensure that drug exposure does not overlap in at least 50% of the patient population for a drug that exhibits a given amount of variability. Results may lead to a more aggressive choice of administration increments and a better separation in systemic drug exposure between doses. Such predictions need, however, to be balanced against the therapeutic window of an individual drug product.

This new approach still needs to be thoroughly investigated before it can be validated. In particular, it is not yet clear how much a priori knowledge on the new drug and the target population is needed in order to obtain reliable predictions for the outcome of Phase 3 clinical trials. Activity in this field is presently going on in a few centres.

7.2. Integrated PK/PD models

PK/PD modelling has been promoted for many years, essentially in academia [35,36]. For many years these proposals have encountered little interest in the pharmaceutical industry because pharmacokinetic and pharmacodynamic departments essentially used to work without strong concertation. As discussed by Sheiner and Beal [37], recent work has focused on the development of new models that allow to account for different kinds of pharmacodynamic data.

As interest in using PK/PD models to represent and forecast clinical outcomes increases, the task of defining appropriate structural and statistical models for such PD responses becomes pressing. These responses are often non-continuous; that is, dichotomous, categorical, time-to-event, or counts.

Generalisations of the so-called indirect PD models recently discussed by Jusko and co-workers [38], provide a flexible framework for structural modelling of the complex dynamical relationships between PK and PD. These models, in their most general form, postulate:

1. a pharmacokinetic model linking dose (D) to observed concentration (C);
2. a biophase model linking C to biophase concentration (C_e);
3. a biosensor model linking C_e to the rate of synthesis or degradation of a biosignal molecule (R);
4. a transducer model linking R to an observable PD response.

Indeed, the history of PK/PD modelling can be seen as a progression from relating pharmacodynamic effects first to dose (D), then, successively, to concentration (C), then to biophase concentration (C_e), and more recently biosignal molecules (R). In the rest of this section, the pharmacodynamic 'stimulus' will be termed generically as S and S thus may represent D, C, C_e or R.

Despite the fact that current models allow the PK/PD chain to consist of all of the above four stages, the last step, linking S to the observed PD response, must still often summarise a complex and intricate chain of events. Thus far, for this last step in whole animal PK/PD models, empirical models have been used almost exclusively. Indeed, this sub-model is most commonly taken to be quite simple, often the identity transformation, thus viewing S itself as the expected value of a continuous PD response.

For continuous responses, the structural modelling task at the last stage is that of specifying the relationship between S and the expected observation. The probability model, per se, is one for the noise, that is, for the deviation of actual observations about their expectations.

When the observed response is dichotomous (e.g. response to a noxious stimulus versus no response), one imagines that the probability of 'response' is related to the level of S. As the former is constrained to lie between 0 and 1, and the latter is continuous, it is necessary to use specific links to relate response to S. This is, for example, a commonly used clinical endpoint in anaesthesia.

Categorical responses can be regarded as generalised dichotomous responses: several distinct responses are possible, not just one. A common variant of a categorical response is an ordered categorical response: the various possible responses lie on an ordinal scale: e.g. 'poor', 'average', 'good'. Here again, specific models must be used. A recent example of the use of such a model is an analysis of analgesic trial data, where the ordered categorical response is subjectively rated pain relief, on a 0–4 scale, and S is taken to be C_e. The analysis is additionally interesting in that it deals explicitly with non-random censoring of data: individuals experiencing excessive pain could demand and receive a rescue analgesic, thereby terminating the pain relief time-series attributable to the test drug, and likely selectively censoring subsequent poor relief scores.

Time-to-event data record the time elapsing from some natural origin of the time scale to an event. Such data is quite common in clinical trials where, for example, the time scale runs from the time of randomisation to the time of occurrence of a clinical endpoint (the 'event'), such as response, recovery, relapse or death. It is somewhat less usual to see repeated measures time-to-event data, but such data can arise whenever the 'endpoint' is repeatable. For example, one might record the time between seizures or migraine attacks, and treat such data as repeated measures time-to-event data. One complication of time-to-event data is that such data typically exhibit censoring (although such censoring is usually not regarded as informative). Thus, for example, when death is the endpoint, for a study terminating at a fixed time, all one knows is that for all those not dead at the time of study termination, the time to death is no less than the observed time on study.

A problem with directly modelling the mean or median time to event is that such a model cannot deal with time varying risk when the kinetics of such variation are on the same scale as the time to the event. When the event is onset or offset of analgesia, for example, analgesic drug concentrations might well vary over a considerable range before the 'event' is observed.

Time-to-event models can be extended to deal with data which report only the number of events in a time interval, rather than the time of each event. This is an instance of so-called 'count' data, which reports the number of events in a volume of space or time. Models for count data can be regarded as extensions of dichotomous repeated-measures data, or of time-to-event data.

These models are under intensive development both in academia and in the pharmaceutical industry and many methodological issues remain to be addressed [39].

7.3. Biomarkers

One area of great interest and activity is the development, validation and application of biomarkers. Biomarkers are characteristics that are used as indicators of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. They are essential in the global assessment of the efficacy and safety of drugs on the basis of PK/PD. To date there are unique opportunities for the development of new biomarkers (i.e. on the basis of genomics, proteomics and new imaging techniques). However, a critical issue is their validation. Ideally, biomarkers are functional and mechanistic. They can be developed in animal studies, on the basis of a combination of in vitro and in vivo technologies. Subsequently, biomarkers can be validated as surrogate endpoints of the clinical effect on the basis of clinical trials. The development and validation of biomarkers requires a multidisciplinary approach involving specialists in disciplines such as pharmacology, toxicology, advanced PK/PD data-analysis and the clinical sciences.

7.4. Modelling pharmacodynamic variability

According to Levy [40], prediction of effective drug concentrations for individual patients, taking into account pharmacodynamic variability factors, is a field where modelling may play an important role.

Variability in the relationship between pharmacological effect intensity and drug concentration (pharmacodynamics) is pronounced, usually exceeding pharmacokinetic variability. Whereas inter-individual differences are large, intra-individual differences are much smaller, unless the individual experiences certain pathophysiological changes such as deterioration of renal function or progression of a chronic disease (for example, Parkinson's disease). Failure to appreciate the magnitude of inter-individual variability in the pharmacodynamics of a drug can compromise fixed dose clinical trial outcomes, making the drug appear less effective or more toxic. In the face of pharmacodynamic variability it becomes important to identify useful predictors (covariates) of pharmacodynamic individuality to facilitate individually optimised pharmacotherapy. This requires clinical trial designs that incorporate extensive patient profiling, well beyond the usual short list of demographics (such as age, gender, race, bodyweight and smoking habits). In searching for predictors, it is helpful to appreciate the factors that may account for inter-individual differences in the relationship between pharmacological effect intensity and drug concentration in plasma or other appropriate fluid. They include receptor density and affinity, the formation and elimination kinetics of endogenous ligands (such as the enkephalins), post-receptor transduction processes, homeostatic responses and the kinetic characteristics of transporters involved in drug transfer between fluids of distribution and the biophase. Correction of drug concentrations in plasma for protein binding, consideration of active and interactive metabolites, stereospecific assays and attention to drug distribution disequilibria are essential for successful identification of factors affecting pharmacodynamic variability.

Levy further emphasises the need to search for predictors of pharmacodynamic variability, taking into account the most recent advances in the biological sciences [41].

Molecular genetic studies of receptors and other phar-

macological targets, an increased understanding of the interacting components of transduction processes, and further mechanistic exploration of relevant homeostatic and functional tolerance processes will eventually facilitate the search for clinically useful covariates of pharmacodynamic individuality. That will take many years and until then the search must be largely empirical. It is necessary therefore to establish very comprehensive patient profiles as part of Phase 2, Phase 3 and/or other large population studies. Moreover, the study populations must be representative of the target patient population with respect to age, gender, race, environmental and pathophysiological characteristics. Absent these requirements, the search for relevant and useful covariates of pharmacodynamic individuality may not be successful.

It is most probable that presently, these recommendations will be more easily implemented into Phase 2-type clinical trials than into large scale Phase 3 clinical trials.

8. Phase 3 studies

The kinetics of a drug are most relevant in the population in which the drug is going to be used. The kinetics in normal young men are only relevant in obtaining the 'fingerprint' of the drug, but kinetic parameters of prime importance such as clearance, volume of distribution, half-life and systemic availability should be known in the relevant population. Therefore, drugs likely to be affected by patho-physiological factors prevalent in the target population should be the subject of some kind of 'population kinetics' studies. This is particularly pertinent for drugs with a narrow therapeutic range. Before population kinetics studies are carried out, the basic pharmacokinetic information should be available. Therefore, the objective of population studies is not to replace but rather to supplement the information provided by previous thorough evaluation of drug kinetics, metabolism and dynamics. Different types of population approaches may be considered, depending on study design and objectives.

8.1. The pharmacokinetic screen

The concept of pharmacokinetic screen has been advocated by the US Food and Drug Administration [42,43]. For a long time, it has been the object of controversy but today, more positive views are usually expressed.

The pharmacokinetic screen involves the determination of one concentration in virtually all patients in Phase 3 trials. The pathophysiological condition, as well as the dosage regimen, are recorded and statistical methods such as multiple linear regression are used to explore the relationship between dose-corrected plasma levels and certain pathophysiological features. According to Balant et al. [2], the strengths offered by this methodology are the following:

- The collection of blood samples does not, generally, interfere markedly with the Phase III programme.
- Simple data analysis techniques are used, based on standard statistical methods.
- The identification of outliers is fairly objective, since they are defined as having a trough concentration differing from the mean by a preset factor.
- The data are representative, since one blood sample is taken for all patients.

Main weaknesses can be described as follows:

- The method is qualitative because uncertainties about compliance do exist and, usually, no firm quantitative conclusions can be drawn.
- No information on pharmacokinetic parameters such as clearance, volume of distribution or systemic availability can be obtained from one single point per patient.
- No information can be obtained on intraindividual variability.
- A large number of patients is necessary for each condition to obtain a strong enough signal.
- The conclusions are tentative, since independent variables are not controlled.

8.2. Formal pharmacokinetic studies

Such studies are usually performed to identify populations at risk (e.g. the elderly, patients with renal insufficiency or hepatic failure) or to investigate about possible drug-drug interactions. The study design is formal in the sense that parallel groups or cross-over studies are usually performed. The strengths of this approach are the following [2]:

- The studies are well suited to estimate the magnitude of effects.
- The study methodology is familiar and of proven validity.
- Individual kinetic parameters are estimated separately for each subject, using well-defined pharmacokinetic methods.
- Conclusions can be firm because the variables are well controlled.

The most obvious weaknesses are as follows:

- Relatively large numbers of subjects are needed because a priori the interindividual variability is unknown.
- Studies conducted with too few subjects lead to inconclusive results.
- The total cost is high because each study is costly and many studies are usually required to explore the entire range of the target population.
- The ethics of giving a drug to patients who may run additional risks with no personal benefit is questionable.

8.3. Population pharmacokinetics: basic concepts

Even though Sheiner and Beal introduced population

pharmacokinetics in the 1970s [44,45], it took almost 20 years for the methodology to be generally accepted as a useful tool during drug development. This approach is particularly beneficial if intensive blood sampling is not attainable, such as in children and patients with cancer and AIDS, but it may also be applied in other situations encountered in Phases 1 to 3 of drug development. This type of integrated modelling has been one of the main areas of activity of the European Concerted Action COST B1 [46–48].

The approach relies on several samples per patient, drawn at different times with respect to the previous dose. For a successful study, it is important to be confident about the compliance with the dosage regimen and with the timing of the samples relative to the most recent dose. By means of specific software, average pharmacokinetic parameters, their inter-individual variability, their possible dependence on covariables, and the unexplained residual variability can be estimated [46,49–51]. According to Balant et al. [2], the strengths of this approach are as follows:

- Valid information on clearance, volume of distribution and systemic availability may be obtained.
- Separate components of inter-individual and intra-individual variability can be determined.
- Little interference with the Phase 3 clinical trial programme occurs.

Weaknesses are the following:

- The conclusions are still partly tentative because some variables are uncontrolled.
- The clinical staff must be trained and motivated to collect and handle the blood samples in an appropriate way.
- Data analysis is complex using population software and the computer time needed to run the program successfully for a medium-size data set is very important.

Despite the fact that powerful software is now available [52], more work is needed before this methodology (which is still largely the activity of specialists) can be used by a broader set of scientists with a degree of confidence that is compatible with the requirements of drug development. In particular, study design, quality of data, covariate assessment communication, protocol design or strategies for data analysis need to be refined [53]. This is one of the aims of Action COST B15 entitled 'Modelling During Drug Development' and carried out within the frame of the European Cooperation in the Field of Scientific and Technical Research.

Today many pharmaceutical companies have introduced this approach or use it routinely during drug development. Advocacy by the US Food and Drug Administration for pharmacokinetic screening during Phase 2 and 3 studies was an important factor in the widespread adoption of this approach even though, to some extent, it also led to opposition and resistance within some companies. An even more important factor was the gradual realisation by the pharmaceutical industry that the approach was cost effective in revealing clinically important information about the determinants of inter-patient pharmacokinetic and pharmacodynamic variability [49]. In addition, population modelling is expected to act as the vehicle to propagate information within and between the successive phases of clinical evaluation. In particular, decisions at Phase 1/Phase 2 and Phase 2/Phase 3 transitions may be better informed due to modelling and simulation.

8.4. Regulatory authorities and population methods

Regulatory authorities tend to have diversified opinions about population modelling in Phase 3 studies. Some authorities like the U.S. Food and Drug Administration encourage the use of population methods, whereas in Europe various attitudes may be encountered and no formal Notes of Guidance exist on the subject. The opinion of U.S. regulatory authorities may be summarised as follows [54]:

- The application of population approaches to drug development is recommended in several U.S. Food and Drug Administration (FDA) guidance documents.
- Population pharmacokinetic and pharmacodynamic techniques enable identification of the sources of inter- and intra-individual variability that impinge upon drug safety and efficacy.
- Certain preliminary information, such as the compartment model used in describing the pharmacokinetics of the drug, is required for a population pharmacokinetic study.
- The practical design considerations of the location of sampling times, number of samples/participants and the need to sample an individual more than once should be borne in mind.
- Simulation may be useful for choosing the study design that will best meet study objectives.
- The objectives of the population pharmacokinetic study can be secondary to the objectives of the primary clinical study (in which case an add-on population pharmacokinetic protocol may be needed) or primary (when a stand-alone protocol is required).
- Having protocols for population pharmacokinetic studies is an integral part of 'good pharmacometric practice'.
- Real-time data assembly and analysis permit an ongoing evaluation of site compliance with the study protocol and provide the opportunity to correct violations of study procedures.
- Adequate policies and procedures should be in place for study blind maintenance.
- Real-time data assembly creates the opportunity for detecting and correcting errors in concentration-time data, drug administration history and covariate data.
- Population pharmacokinetic analyses may be undertaken in three interwoven steps: exploratory data analysis, model development and model validation (i.e. predictive performance).

- Documentation for regulatory purposes should include a complete inventory of key runs in the analyses undertaken (with flow diagrams if possible), accompanied by articulation of objectives, assumptions and hypotheses.
- Use of diagnostic analyses of goodness of fit as evidence of reliability of results is advised.
- The use of stability testing or model validation may be warranted to support label claims.

A specific FDA guidance has been issued on this topic [55].

8.5. Computer-assisted simulation of clinical trials

A further step in modelling is provided by attempts to simulate the outcome of clinical trials performed under a variety of conditions [56–58]. As emphasised by Gieschke et al. [59],

> Computer simulations have been successfully applied in various industries (e.g. automobile, aerospace) to make product development more efficient. It is now suggested to use simulations in support of clinical drug development for predicting clinical outcomes of planned trials. The methodological basis for this approach is provided by pharmacokinetic and pharmacodynamic mathematical models together with Monte Carlo techniques. It is hoped that computer simulation helps to evaluate consequences of design features on safety and efficacy assessment of the drug which are not easily obtained otherwise.

8.6. Simulation of specific clinical trial designs

Computer-assisted simulation of clinical trials has been advocated to test specific designs that are not commonly used. An example is provided by Hale [60].

> The randomised concentration-controlled trial (RCCT) design has been proposed as an efficient means of reducing within group inter-patient pharmacokinetic variability, and thereby decreasing variability of clinical response [61]. These benefits add to the RCCT inference advantage of reducing confounding of pharmacokinetic and pharmacodynamic effects making the RCCT design a worthy candidate for studies whose purpose is to explore and better define PK/PD relationships. However, evaluation of study characteristics, such as sample size, statistical power, pharmacokinetic control schemes, expected reduction in pharmacokinetic variability, etc., is complicated for this non-traditional design, with the usual study planning tools providing little help.
>
> Computer simulation of clinical trials is an emerging technology which allows the trial planner to evaluate the joint effect of trial design and assumptions. Virtual clinical trials are created in computer software, embodying study design parameters along with mean, variance, and covariance models. Those virtual trials may be repeated many times to provide probability distributions for trial performance measures. By varying the trial design parameters and assumed models, stochastic simulations may reveal the impact of those parameters and models on trial outcome and performance. The trial planner may use this information to choose a design best suited to meet study objectives, with attention paid to designs resistant to failure of assumptions. Computer simulation is thus an attractive method to evaluate a complex trial design, such as an RCCT.
>
> The background information needed for planning an RCCT is more extensive and technical than for the traditional trial, such as the randomised dose-controlled trial. Construction of the computer model representing the trial involves the explicit specification of factors, distributions, and models. The factors are those elements, controlled or uncontrolled, thought to possibly influence study performance, such as number of patients, dose, or plasma area under the concentration–time curve. Distributions provide a probabilistic description of factor behaviour, such as proportion of factor values within a given range. The models may describe relationships among the factors, among factors and outcomes, or even between factors and distributions, e.g. distribution of AUC values will depend on the value of dose. The virtual trial allows for evaluation of study impact resulting from interplay between factors, distributions, and models.

Similar considerations have been made for the simulation of 'pharmacologic-effect-controlled' randomised clinical trials without or with pharmacodynamic hysteresis [62,63].

8.7. Modelling specific aspects of clinical trials: compliance

Non-compliance or partial compliance represents an important challenge in the analysis of Phase 3 clinical trials and various approaches have been tried to overcome this problem. According to Urquhart [64].

> Electronic monitoring has revealed the 'drug holiday' as a prominent feature of ambulatory patients' dosing: three or more consecutive days of lapsed dosing. In patients unselected for prior compliance, ca. one in six have a monthly holiday, and a further one in six have a holiday about every 3 months. Thus, the holiday-based, 'on–off–on' pattern of drug exposure is common, more so among patients reaching the upper steps of stepped-care dosing schemes, as poor

compliers are usually mistaken for drug non-responders.

'Drug holidays' are also a pharmacometric challenge. Striking dynamic asymmetries between 'on' and 'off' responses, which can be of either direction, indicate the need for routine inclusion of 'off' responses in basic PD studies. These asymmetries may sometimes change during extended periods of treatment, but it is not a commonly studied PD attribute, not the least because such information undermines dosing recommendations and dose-dependent product revenues. Without 'off' response data to constrain them, PD models based solely on 'on' response dynamics are likely to be seriously or fatally under-constrained and thus poor simulators of the time course of drug concentrations in plasma. Thus, model-based statistical interpretation of common patterns of non compliant dosing awaits adequate PD models.

Some longer-acting pharmaceuticals are now being promoted on the basis of their superior ability to 'forgive' 1–3-day lapses in compliance, which are the most commonly occurring dosing errors made by ambulatory patients. These claims are based on results of controlled substitutions of placebos for active drug, which is one of the first innovations in trial design prompted by the reliable dosing histories gathered with electronic monitoring.

9. Post-marketing studies

Once a drug is on the market, its 'scientific life' is by no means ended. As a single example, one may imagine that an unexpected drug–drug interaction is observed. In order to understand the mechanisms and potential kinetic and/or dynamic consequences of this interaction, it is necessary to take into consideration and analyse all information gathered during the pre-registration phases. Here again, integrated modelling strategies are probably the tool of choice.

Therapeutic drug monitoring is particularly well suited for providing a large amount of data in patients. The use of the population approach has been advocated to individualise dosing regimen in individual patients [65,66]. Population models permit the application of Bayes' formula to obtain improved estimates of an individual's pharmacokinetic and pharmacodynamic parameters in the light of observed responses. As underscored by Minto and Schnider [65],

> An important challenge to clinical pharmacology is to identify the drugs that might benefit from such adaptive-control-with-feedback dosing strategies. Drugs used for life threatening diseases with a proven pharmacokinetic-pharmacodynamic relationship, a small therapeutic range, large inter-individual variability, small inter-occasion variability and severe adverse effects are likely to be good candidates. Rapidly evolving changes in health care economics and consumer expectations make it unlikely that traditional drug development approaches will succeed in the future. A shift away from the narrow focus on rejecting the null hypothesis towards a broader focus on seeking to understand the factors that influence the dose–response relationship – together with the development of the next generation of software based on populations models – should permit a more efficient and rational drug development programme.

The construction of databases summarising the PK/PD behaviour of the drugs to be monitored during clinical use will certainly also contribute to the validity of monitoring procedures for patient care individualisation [67].

10. Concluding remarks

This review has attempted to highlight some of the areas where work is presently in progress in the field of 'Modelling During Drug Development'. It does not pretend to have covered the whole field of PK/PD modelling. Artificial neural networks [68,69], the fractal approach [70] or fuzzy logic [71] are among the techniques currently being tested in the field of new drug development.

A survey of the integration of pharmacokinetic and pharmacodynamic principles in clinical drug development in a major pharmaceutical company has been performed recently [72]. It has shown that the use of the pharmacokinetic–pharmacodynamic guided approach had contributed to making clinical drug development more rational and more efficient. The recommendation was that opportunities to apply the PK/PD approach should be identified in each project and a project-specific strategy for the PK/PD guided approach should be defined during the very early phases of drug development. This is a welcome change as compared to earlier developmental strategies based essentially on 'trial and error' methodologies. It is probable that the ability to model drug behaviour and effects more efficiently has greatly promoted the more scientifically based strategies of drug discovery and development, without forgetting their more rational use in individual patients.

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