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PK/PD modelling and simulations: utility in drug development

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Pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation can be used as an 'applied science' tool to provide answers on efficacy and safety of new drugs faster and at a lower cost. PK/PD modelling can be used from the preclinical phase through all clinical phases of drug development. Optimal use of PK/PD modelling and simulation will lead to fewer failed compounds, fewer study failures and smaller numbers of studies needed for registration. For PK/PD modelling to fulfil its potential in drug development, it needs to be embraced across the industry and regulatory agencies, and more education on this topic is required.

Increasing costs of drug development and reduced pipeline productivity have been growing concerns for new drug development in recent years [1,2]. A number of potential reasons for this outcome have been considered. One of them is a general perception that applied sciences have not kept pace with the advances of basic sciences. Therefore, there is a call for the use of alternative tools to get answers on efficacy and safety faster, with more certainty and at lower cost [3]. Some of the alternative approaches to drug development include the use of adaptive trial designs [4], more extensive use of biomarkers [5], developing personalised medicines and the use of pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation. PK/PD modelling and simulation can add value in all stages of drug development, from the preclinical discovery stage to late stage clinical development. Its use in drug development, to make crucial decisions early, may lead to significant cost reductions in both early and late drug development [6–8].

Understanding of the value and use of PK/PD modelling is often limited to the specialists in the field (i.e. pharmacokineticists). However, in order to reach fully its potential as an alternative method to aid drug development, modelling needs to be understood and embraced by drug development teams and regulators alike. Merits of PK/PD modelling and simulations in different stages of drug development are summarised and discussed below, in an effort to raise awareness for its potential in drug development.

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PK/PD modelling and simulations: definitions

Modelling can be considered '*in numero*' studies: a particular investigation carried out with mathematical, statistical and numerical techniques. The term PK/PD modelling refers to a data (pharmacokinetic and pharmacodynamic)-driven exploratory analysis, based on a mathematical/statistical model. A PD response does not generally parallel drug concentrations (PK); therefore, models can help us understand this relationship and its change as a function of drug intake and other variables. A model cannot be fully pre-specified before experiment and may be developed, or further refined, depending on the results. A mechanistic model is one in which parameters correspond to physical entities in the subject matter of the model, while an empirical model is without such mechanistic elements. Additional definitions include a descriptive model, which is *a priori* applicable only to a restricted set of circumstances (patients, designs and so on) and a predictive model that explicitly incorporates variables quantifying important design and baseline features so that the model can predict outcomes conditional upon arbitrary values of those variables. Modelling and simulation analysis is generally a combined analysis of data from several studies [9–11].

The discipline of modelling is data-driven, and it relies on multiple analyses of the same dataset in an iterative mode with successive and/or competing models. It is possible to extrapolate beyond the boundaries of the design on which models are defined. To do this, models must explicitly express the values of those boundaries and, to provide credible extrapolations models, must

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incorporate the current scientific understanding of their field [8,11]. However, the art of modelling is, to a large extent, in finding what aspects are important and which approximations may safely be made.

The simulation model built using preclinical and early clinical data should be considered a working model that will become refined as more data become available. Thus, PK/PD models are continuously updated throughout different stages of drug development to incorporate relevant new data. These updated models and simulations assist in formulating how the next step in development should be performed. A full simulation model will typically consist of a number of submodels, which will include aspects such as dose (concentration)–clinical response, baseline response, covariates response, time response, disease progression, compliance, variability, sample size and commercial aspects. Finally, well-defined models and simulations can be used to predict trial outcomes through the use of hundreds of individual patients' data and a number of different trial designs and covariates [2,12].

Value of modelling in drug development

Modelling can add value in all stages of drug development. However, its use and value will greatly depend on the amount of data already existing for the particular compound or data for related compounds. To utilise PK/PD modelling and simulation in its optimal potential for drug development, models should be developed early in programme development, preferably during the preclinical phase. Such models are continuously updated and refined as more data become available. Their validation is necessary during development, and they will then provide valuable support to make important decisions, with an increased confidence level around the analysed data [13,14]. Potential benefits of modelling and simulation in different phases of drug development are discussed below.

Benefits of modelling in preclinical phase

The preclinical phase of drug development includes a number of *in vitro* and animal studies to screen compounds for efficacy and safety. The most promising compounds are further scrutinised, using more specific models, to select optimal compounds to test in humans. PK/PD modelling offers the greatest value if preclinical data can be modelled in combination with existing clinical data on related compounds (internal or competitors data) [15]. Some of the potential benefits of modelling in preclinical phase are listed below:

- Selecting the optimal compound, if more than one is available.
- Predicting clinical potency estimates (EC50).
- Providing the guidance for the dose range to be tested in early clinical trials.
- Providing guidance for optimal sampling.
- Assessing the margin of safety on the basis of target efficacy concentrations.
- Predicting oral bioavailability.
- Predicting hepatic clearance.
- Assessing the potential for drug–drug interactions.

Modelling here is often based on assumptions such as the relative efficacy and potency in animal efficacy models between the new compound, and comparators are predictive of relative efficacy and potency in humans and that allometric scaling gives a reasonable estimate of the clearance in humans [16,17]. PK/PD models should include the rate-limiting component from the mechanism of action (e.g. receptor binding, protein synthesis). Other covariates, such as protein binding, receptor occupancy (species difference), active metabolites and competitive endogenous ligands can all affect a model's predictivity and need to be considered, if possible.

For confidentiality reasons, published examples of modelling data for compounds in preclinical and early clinical development are rare. A recent example is the publication on the *in vivo* characterisation of a new TGF-β kinase antagonist, based on a PK/PD modelling approach to assess tumour growth inhibition [18]. Signal transduction mechanisms are described in many areas of pharmacology and are reflected as a delay in the observed response. Quantitative description of the time course of the signal, once the drug has reached its target, is lacking, and this may be addressed through the use of mathematical models. The above model is based on a chain of transit compartments to predict tumour stabilisation. It assumes that inhibition of tumour growth is mediated by the decrease in phosphorylated Smad, a biomarker of tumour growth inhibition. The model describes the data for the tumour size/time profile very well. The model was used to simulate the course of both tumour growth and tumour size as a function of dosing schedule, which will be useful for designing clinical studies. The additional benefits of these results include findings that the signal transduction efficacy is tumour-specific and that there is the possibility of a benefit if signal transduction modulators, acting on different pathways with different dynamics, are combined. Finally, since the signal transduction is a drug-independent process, this model can be used, together with PK and biomarker information, to simulate tumour response of other new compounds with the same mechanism of action [18].

Another example of the value of modelling in the preclinical phase relates to the modelling of the PK and PD data for a new blood-pressure-lowering drug. On the basis of the potency data (EC50), the new compound was expected to be less potent than the comparator. However, the maximal effect model (E_{max}), built using the PK and efficacy data from animal models and human data for the comparator, predicted that the new compound would have a higher E_{max}, suggesting a superior efficacy at higher concentrations [14]. Thus, a compound initially seen as non-competitive was, as the modelling predicted, of superior efficacy in the clinic. The greatest cost saving potential of modelling in preclinical phase is allowing the selection of the optimal drug candidate and abandoning early those which are not predicted to exhibit required efficacy or safety [8].

Benefits of modelling in early clinical development

Phase I

Phase I studies provide initial human data for the tested compound and include a small number of short studies in healthy subjects or patients. They provide early data on human tolerability, PK and sometimes PD. Owing to their short duration and small size, clinical efficacy endpoints can rarely be tested in these studies.

A model developed during the preclinical phase can be further refined to incorporate early clinical data for the compound [19]. Modelling of early clinical data can sometimes provide invaluable information as in some of the cases below:

- If PK is non-linear, only modelling can help in estimation of relevant parameters and concentration/time profiles.
- In complex relationships between PK and PD, only modelling can describe the course of the PD in question.
- If sparse sampling is the only option (e.g. in a paediatric population), modelling is the only option for an adequate and efficient interpretation of the data.
- A PD model based on preclinical or biomarker data, or a PK model based on Phase I data, can be valuable for designing Phase II trials. This is especially useful for compounds with a known potency that can be compared with a drug with a known response in patients.
- Modelling of the multiple dose data can be used to identify enzyme auto-induction or the development of tolerance.
- Modelling based on *in vitro* dissolution/*in vivo* absorption relationship may reduce the *in vivo* experimental workload for formulation testing.
- Modelling to compare merits of sparse and intensive blood sampling may help to select the optimal number and time points [2,19]

Population PK modelling, based on Phase I data, should be pooled across multiple studies. However, the expected PK variability in patient population and specific covariates cannot be reliably identified in Phase I studies. Yet, the information obtained using such preliminary model of Phase I data together with protein binding and *in vitro* efficacy data is needed to enable selection of the most efficacious dosing regimen and sampling for Phase II. Early modelling can also enhance confidence in predetermined crucial success factors, aiding the decision making process.

Phase II a/II b

Phase II includes studies in carefully selected patients from the patient population of interest. They provide data across a dose range and help to assess a dose–response relationship. Customarily, Phase II consists of a fairly large number of studies, which run in parallel or sequentially, in order to provide sufficient information to guide Phase III planning. PK/PD modelling and simulations can significantly reduce the number of Phase II studies needed to provide the data required for further development. Modelling and simulation in Phase II can be used to

- Develop a drug–disease model to understand the time course of disease progression and dose–response to interventions.
- Test different study designs (including ones that are not customarily used) and assist in selection of the optimal design for the given conditions.
- Assess the probability of success, given a study design.
- Design optimal dosing and sampling schemes.
- Simulate outcome, given assumptions and study design considerations.
- Assess the impact of covariates, using a population PK/PD model.
- Assess the efficacy/toxicity profile, relative to comparators [2,15,20,21].

PK/PD modelling in early clinical development may enable crucial decisions (e.g. go/no go) to be reached earlier, based on PK and PD characteristics of the compound, especially if models include comparators' data. Abandoning compounds with suboptimal PK/PD characteristics early in their development leads to significant cost reduction [20]. Conversely, by applying a baseline–response model (e.g. adjusted for disease severity), it is sometimes possible to discern desired efficacy in compounds initially considered as non-competitive [2]. With a good time–response model, it is possible to estimate steady-state effects and predict results for varying study durations and optimal timing of the study visits.

Modelling and simulation of the data from only a few well-designed studies can provide sufficient information that would otherwise come from a larger number of separate studies [2,19]. This can potentially provide a significant saving by reducing the total number of Phase II studies needed. Additionally, a well-defined model will help to reduce the number of failed studies owing to design failure. Finally, if an unfavourable outcome is predicted from modelling of a 'registration trial', the programme may be terminated before investment into the next, more costly, phase of development.

Dose selection for Phase III pivotal trials may be based on the PK/PD modelling and simulation analysis of the data from only a few studies [22–24]. Apart from the obvious use of efficacy data (PD effect/biomarkers), safety data can also be incorporated into the model. Even if a model is developed using data from fewer studies, it can still enable selection of optimal dose and sampling schedule. However, if modelling is used as a basis for dose selection for registration trials, regulators should be comfortable with the selected dose and the rationale behind the plans for their use in confirmatory trials. It is prudent to reach an agreement with the regulators on dose selection for pivotal studies before their start. This, in turn, highlights the need for a closer interaction between industry and regulators through all stages of drug development (dose selection based on modelling and simulation is now frequently discussed at the end of Phase II a meetings with the FDA).

Benefits of modelling in late clinical development

Phase III

Phase III studies provide the final confirmation of the efficacy and safety of the tested drug in a wide patient population of interest. They provide the ultimate safety and efficacy data for approval of drug's use in clinical practice.

Once the target effect is identified, the focus of modelling and simulation can fully move on to the optimisation of the study design to demonstrate robustly the effect and reduce the risk of failed study design [25]. Modelling and simulation can utilise both efficacy and safety data to build adequate models. Modelling in Phase III can be used to

- Assess the impact of applicable covariates (patient subpopulations–demographics, co-morbidities, concomitant medication and so on).
- Validate the population PK/PD model.
- Establish or confirm dose exposure–response relationship in target population/subpopulation.
- Assess need for dose adjustment in special populations.

In the case where there are favourable efficacy data provided from one large Phase III (pivotal) trial, the ultimate benefit of modelling and simulation would be in obviating the need for a

second large trial. Current expectations from most regulators are for substantial evidence of effectiveness to come from at least two adequate and well-controlled (AWC) trials (Phase III). In Europe, the existing guidance (CPMP/EWP/2330/99) does not formally require two or more pivotal studies but suggests that, in most cases, a Phase III 'programme with several studies is the most feasible way to provide the variety of data needed to confirm the usefulness of a product in the intended population' [26]. The FDA Modernisation Act of 1997, and its subsequent relevant guidance, allowed for the use of exposure–response information in combination with a single pivotal clinical trial as sufficient evidence of effectiveness [27,28]. This approach has, for example, been successfully used in registration of gabapentin for post-herpetic neuralgia that was based on efficacy data and exposure–response analysis and extrapolations from the two trials using different doses (i.e. efficacy data for relevant doses were not replicated in the second trial). For the first time, exposure–response (PK/PD) analysis was used to establish a linkage across two clinical studies to provide confirmatory evidence of dose response [29]. FDA requested that in order to replicate the clinical trial, this PK/PD analysis had to withstand the same qualitative and quantitative review as the data from an AWC. The PK/PD results indeed confirmed the evidence of efficacy across the studied doses so that additional clinical trials were not needed for approval. The Package Insert for gabapentin refers to 'PK/PD modelling that provided confirmatory evidence of efficacy across all doses'.

Adopting a new standard of a single clinical trial plus confirmatory evidence would lead to more efficient drug development. There still needs to be more guidance on the standards required for 'confirmatory evidence'. Recently, a case has been made that convincing evidence of the pharmacologic mechanism of the clinical effect of a drug serves the same purpose as the second large clinical trial [30]; this evidence could come from a single well-designed Phase II trial. The real cost saving benefits would be achieved if this confirmatory evidence was acceptable when generated from pooled data from earlier and smaller studies. In assessing the potential for pooling of the data factors, such as design of available studies, treatment duration and other relevant covariates, will need to be considered.

Finally, modelling and simulation could become the ultimate 'outcome' of Phase III development. Modelling and simulation provide the opportunity to simulate different trials using hundreds of patients' data *in silico* to predict trial outcomes. Some of the simulated trial models have already been tested against outcomes of 'real' clinical trials, showing good accuracy with a very high correlation between the simulated and actual results [31,32]. Once a PK/PD model is developed, it could be tested prospectively in an AWC trial for its predictive value. If a model is sufficiently predictive and accurate in this test, it could then be used to simulate the second large trial and its outcomes. Thus, the second large trial would be 'performed' only *in silico*. On the basis of adequate models, simulations could provide predictions for both efficacy and safety data. The desired (and required) variety of data that customarily comes from several separate studies can be provided through a well-defined and validated model. This approach would be easier to advocate for new compounds where a sufficient amount of safety data have already been generated throughout their clinical development and for new compounds where a large amount of safety and efficacy data have been acquired on the basis of similar compounds (class) and used to validate the model. Thus, reduction in number and/or size of Phase III studies could be seen as the ultimate potential benefit of modelling and simulations in drug development.

There are currently some efforts to build comprehensive models for different disease states (e.g. diabetes, cardiovascular disease, asthma) that use public domain medical knowledge in relevant disease to enable translation of short biomarker response into clinical outcomes [33,34]. Building of such disease models requires a large patients' database with a large variability in relevant covariates. Some of these data are already published in different epidemiological and outcome studies [31,32]. However, pooling patients' data from different databases that exist across industry would provide invaluable source of information for disease modelling. Industry may choose to form syndicates, similar to those advocated for validation and qualification of biomarkers. The predictive value of such disease models will be tested prospectively against large clinical outcome trials. If validated, they can greatly help Phase III design and target population selection across the industry.

Modelling and simulation *versus* other novel/alternative drug development approaches

Modelling can be a complimentary tool in deployment of other new approaches in drug development, such as adoptive trial design, personalised medicine and extensive use of biomarkers. Indeed, modelling is an important tool to guide adaptive study design [4]. If adaptive designs are to be used in early clinical development, a model-based interpretation of the observations and model prediction as the basis for the next action may be the best choice for the programme.

The concept of personalised medicine is becoming increasingly popular [35,36]. One of the cornerstones of personalised medicine will be to provide flexibility to adjust the dose for a particular patient, according to patient's specific rate of drug elimination, gene polymorphisma (for efficacy or metabolism), disease resistance and responder rate. Drugs, such as herceptin and gleevec, are now prescribed on the basis of the outcome of specific tests [36,37,38]. A challenge for this concept will be the greater range of doses, which may lead to an increased risk of mis-dosing. Modelling will be the perfect tool to provide the required efficacy and safety information across a range of different doses that may not all be tested in empirical trials.

Pharmacodynamic response used in PK/PD analyses is often derived from the effects on various biomarkers. Modelling is, therefore, highly dependant on the quality of PD data and the level of confidence in biomarkers used in PK/PD analysis. There is an obvious incentive for having a greater number of 'validated' and 'qualified' biomarkers to aid refinement of PK/PD models [5].

Requirements for use of PK/PD modelling in drug development

The use of modelling and simulation must be accompanied by the crucial infrastructure elements to be successfully deployed in drug development. Modelling requires specialised software and experienced analysts. It is generally felt that there are not enough experienced analysts in the field at the moment and that more

training is needed [2,9]. Crucial infrastructure needs to be developed to enable efficient pooling of data across trials and across programmes. There are different, commercially available software packages that can enable integration of *in silico* predictions and modelling, as well as different simulation software packages, that are applicable to different disease models. Acquiring and upgrading relevant software requires additional investment and close collaboration with different service providers.

Relevant guidelines for modelling and simulations are being developed and they need to be followed as appropriate. Adherence to recently developed Good Modelling and Simulation, practice needs to be encouraged [39]. This will include

- A synopsis of the analysis plan to be written and agreed upon before the analysis, in order to outline objectives.
- Development of detailed analysis plans for PK/PD modelling prospectively and throughout the drug development (e.g. specified in study protocols or related documents).
- The analysis plan stating details such as major modelling steps to be deployed, data selection criteria, expected outcomes, validation step and simulation step (if any).

Only this, a more rigorous practice, can make PK/PD modelling and simulation results more acceptable to regulatory reviewers [9,40].

Development teams also need to understand the value and meaning of modelling. This will require clarity on the use of modelling and simulation within organisations that will lead to truly integrated teams, trained in the use and value of modelling [41]. Complex mathematical equations used to develop and describe models are often not easily appreciated by non-experts in the field. As modelling experts strive to make their models more accurate, the ability of others to understand them can decrease. In spite of that, achieving universal transparency is not the goal here and accuracy of models must not be compromised or replaced by greater transparency [42]. However, the goal is to bring everyone to the level of confidence they need to trust the model. This is best achieved by demonstrating that the model calculates accurately or predicts real events. Therefore, modelling results need to be communicated in a way that would ensure general understanding within development teams and regulators, without compromising the model's accuracy [42]. More educational work is needed here to ensure sufficient level of understanding across the industry and regulatory agencies [2,40]. There are several options for this education to be organised in a more structured way including the regular (e.g. annual) symposia between the industry and regulatory agencies and specialised training courses on the basis of PK/PD modelling to be held at agreed intervals.

Conclusion

PK/PD modelling and simulation can be an invaluable tool for making crucial decisions for drug development. These may include decisions on compound selection, dose selection, study design or patient population, all of which can lead to a considerable reduction in cost of development. Thus, the optimal use of modelling and simulations will lead to fewer failed compounds in late stage development, fewer study failures and smaller number of studies needed to support the registration. Mathematical modelling will, in the future, form one basic repository of summary information that can be carried forward from the preclinical phase thorough clinical phases. Because knowledge is accumulated during the development, the value estimates will be continuously updated and formally incorporated into the decision making process.

The use of PK/PD modelling and simulations for regulatory submission should be considered and discussed with the regulators as early as is feasible. In cases where confirmatory clinical data are needed, at present, modelling and simulations cannot replace an experimental study but will help in the more efficient planning of such a study. In the future, models could become both the instruments and the aims of drug development programmes. Computer simulation is already standard in some knowledge-based industries. Ultimately, models may become the primary outcome of drug development programmes.

Lack of crucial infrastructure elements is a major impediment in the successful deployment of modelling and simulations in drug development. In addition, better understanding of PK modelling and simulation concepts needs to be achieved across the industry and regulatory agencies. Open workshops or similar educational opportunities that would provide real examples of modelling and simulations applications could be valuable.

Conflict of interest

The author is employed by Novartis Pharma AG and does not report any actual or potential conflicts of interest, including any financial, personal or other relationships with other people or organisations within three years of beginning the work submitted that could inappropriately influence (bias) this work.

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