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MODELLING AND SIMULATION OF PHARMACOKINETIC AND PHARMACODYNAMIC SYSTEMS - APPROACHES IN DRUG DISCOVERY

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ABSTRACT

Pharmacokinetics and pharmacodynamics in drug discovery are often viewed as simple data generation processes. Candidate compounds are screened for various ADME and physico-chemical properties together with their potency *in vitro* and their effectiveness in *in vivo* models. In many cases simple summary parameters are used for comparison between drug candidates and for project decision-making. However, weighing the relevance and importance of such data in isolation or in a qualitative manner is not a simple task. Modelling and simulation provides a framework for integrating these data, providing outputs that contain more information than can be elucidated from the data in isolation. The use of biologically realistic models allows for the separation of the biological and compound-specific components of the pharmacokinetic and pharmacodynamic systems. One can then begin to develop a generic approach that is applicable to the drug discovery process. Physiologically based pharmacokinetic (PBPK) modelling is integral to Roche's approach. PBPK models, by design, are capable of integrating information about various pharmacokinetic processes, including absorption, metabolism and distribution. They can be used not only to estimate summary *in vivo* pharmacokinetic parameters, but also to predict the complete drug concentration time-course in both plasma and tissues. However, a commonly held view is that PBPK models are complex and data-intensive, and therefore, not applicable to the early phases of drug development. Many of the biochemical and physico-chemical parameters are generated routinely *in vitro* in the lead generation and optimization phases.

Quantitative structure-activity relationships and mechanism-based *in silico* models exist for estimating other drug properties, most critically, the partitioning of drugs into different body tissues. *In vitro* - *in vivo* scaling methods are becoming routine for the estimation of hepatic metabolism. The necessary physiological and anatomical data (e.g. tissue volumes and blood flows) are available in the scientific literature for many commonly used laboratory animals and humans. In short, most of required data are already available.

By combining PBPK models with simple pharmacodynamic models, for example based on *in vitro* or *in vivo* efficacy data, the link between basic compound properties and effect *in vivo* is made. This allows the project teams to compare compounds with the target profile and with each other over a range of simulated doses and regimens. Crucially, an attempt at predicting drug effect *in vivo* in the target species, human, can be made long before the drug reaches the clinic.

INTRODUCTION

Advances in technology in drug discovery have improved the process of identifying biologically active compounds. However, choosing potential medicines from these compounds is difficult, and the pharmaceutical industry is still plagued with high failure rates at all stages of the drug development process [1]. Historically a high proportion of these failures have been due to poor pharmacokinetic properties. Candidate compounds are now routinely screened for their ADME (absorption, distribution, metabolism and excretion) and physico-chemical properties, in the attempt to discriminate between medicine-like and non-medicine like compounds. These data, together with *in vitro* and animal pharmacology data, are used to make both comparative and absolute assessments about whether compounds are likely to be effective and safe in the target population. Such assessments are essential from both an ethical and business perspective, allowing resources to be allocated to drug candidates which are likely to be both effective and safe. However, the ultimate integration and use of these data is a complex and uncertain task. Fortunately, modelling and simulation, utilizing the principles of pharmacokinetics and pharmacodynamics, provides a natural and rational framework for integrating these data. Such tools provide outputs that contain more information than can be elucidated from the data in isolation and allow for clear and consistent management of unknowns and uncertainties. By using biologically realistic models and methodologies, one can separate the pharmacokinetic and pharmacodynamic characteristics of a drug candidate into compound and biology-specific components.

The main advantage of such an approach is that one makes use of prior knowledge, for example animal and human physiological and anatomical data, to reduce the unknowns in an effort to minimize uncertainty and increase predictivity. In the following sections pharmacokinetic and pharmacodynamic systems will be discussed in terms of biologically-based mathematical modelling and their application in drug discovery.

PHARMACOKINETICS AND PHARMACODYNAMIC SYSTEMS

Pharmacokinetics (PK) is the study of the time-course of a drug in the body. Correspondingly, pharmacodynamics (PD) is the study of the time-course of drug action and is intrinsically linked to pharmacokinetics [2]. Figure 1 illustrates the concepts and the interdependence.

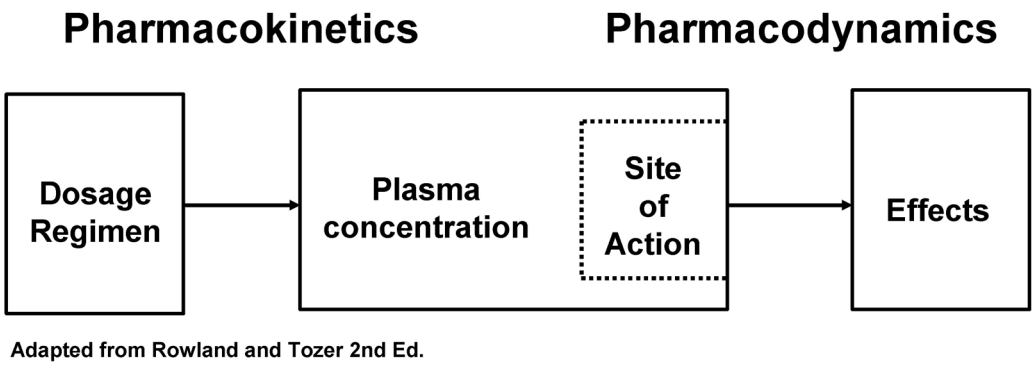

Figure 1. Illustration of the dose-response relationship of a drug in terms of pharmacokinetics and pharmacodynamics.

As can be seen from Fig. 1, by applying the principles of pharmacokinetics and pharmacodynamics the dose-effect relationship for a drug is defined. Implicit within this approach is the use of mathematical models to approximate the pharmacokinetic and pharmacodynamic systems for a drug or drug-candidate. For the drug discovery scientist the interest in PK/PD modelling and simulation lies in its ability to estimate the likely dose-response of drug-candidates in human patients from limited animal and *in vitro* data. If these methods can be shown to be consistently predictive the impact on the drug development process in terms of both attrition rate and resources will be high. Approaches which are being developed and applied by Roche, in the attempt to predict human dose-response in the discovery stage of drug development, will be discussed in the following sections.

Pharmacokinetic Modelling

In order to estimate the dose-response relationship in the target population one first requires an estimate of the pharmacokinetics in the target population. The approaches used to predict human pharmacokinetics tend to fall into two categories: empirical interspecies scaling, based primarily on animal pharmacokinetic data and physiologically-based pharmacokinetic (PBPK) modelling [3-7]. With the recent developments of in silico and in vitro tools together with a marked increase in computing power, PBPK modelling is rapidly becoming a powerful tool for predicting human pharmacokinetics. Therefore, the focus of this paper is on physiological models and the reader is referred to the literature for further discussion on animal scaling methods [8-11].

Although as the title of this paper implies, pharmacokinetics should be viewed as a system of interlinked processes, it is often convenient to sub-divide the system into simpler components for the purposes of discussion. Therefore, PBPK modelling will be discussed initially in the context of absorption, distribution, metabolism and excretion processes.

Absorption

Oral absorption is determined by complex mechanisms which are governed by physiological and biochemical processes (e.g. pH in the various sections of the gut, gastric emptying, intestinal transit, active transport and intestinal metabolism), drug-specific properties (e.g. lipophilicity, pK_a, solubility, particle size, permeability, and metabolism) and formulation factors (e.g. release kinetics, dissolution kinetics). These are some of the main determinants which should be an integral part of a biologically-based absorption model. The interplay of parameters describing these processes determines the rate and extent of absorption. The available simulation tools to predict oral absorption in animals and humans have been reviewed recently [12-14]. Different absorption models have been developed and in part described in the literature. These physiological gut absorption models are developed to a degree that they are commercially available as software tools e.g. GASTROPLUS® from Simulations Plus Inc. (see Fig. 2). In brief, these models are physiologically based transit models segmenting the gut into different compartments, where the kinetics of transit, dissolution and uptake are described by sets of differential equations. The simulation models for oral absorption use a variety of measured or calculated *in vitro* input data such as permeability, solubility, pK_a and dose.

With the provided *in vitro* data, the rate of absorption into the portal vein is often only estimated as an intermediate step, from which the cumulative extent of absorption is derived as a point estimated for a given drug candidate and/or formulation.

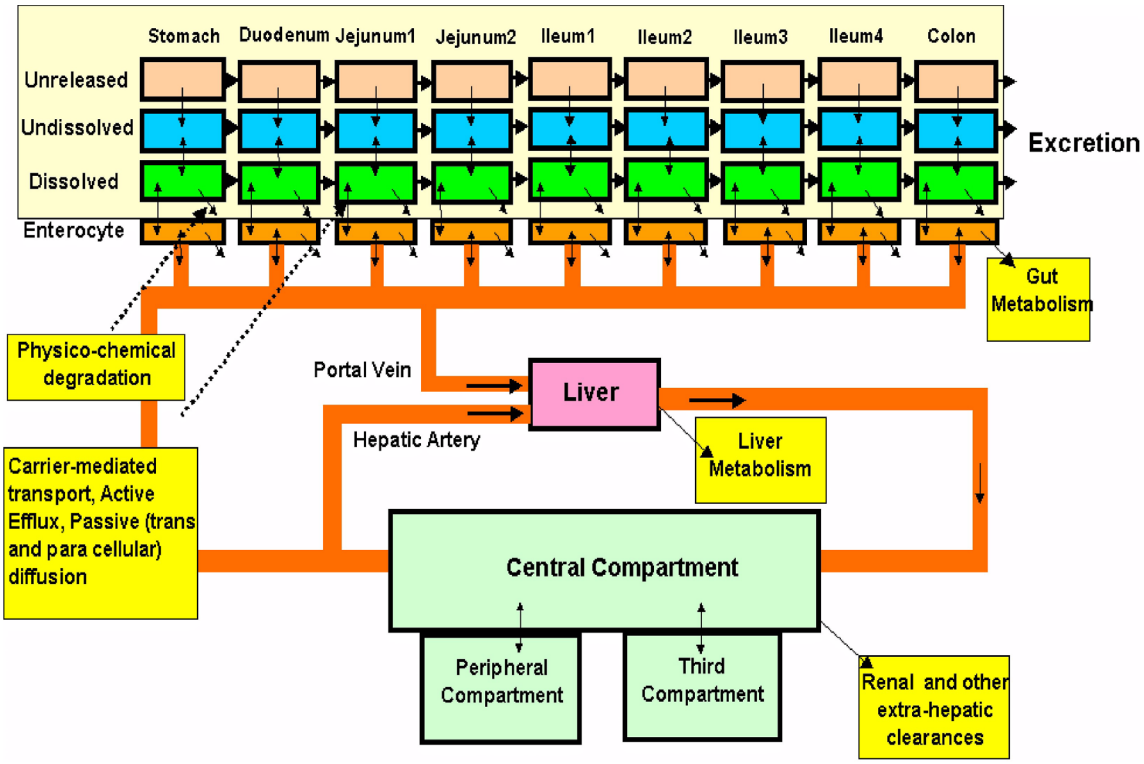

Figure 2. Physiological Gut Absorption Model GASTROPLUSTM (with permission Simulations Plus Inc.).

Distribution

The distribution and disposition of a drug can be determined by using the principles of mass conservation [5]. If an organ or tissue is considered as a set of compartments representing the volumes of the different fluid spaces within the tissue, the rate of change of drug mass in the tissue can be described by mass-balance ordinary differential equations. A general kinetic model of a tissue or organ is shown in Fig. 3A. The tissue is split into three compartments representing blood in the tissue, the interstitial space (IS) and intracellular space (IC), respectively. The interface between the blood and interstitial space compartments represents the blood vessel walls and the interface between interstitial and intracellular spaces represents cell membranes. The rate of change of amount of drug in tissue blood is:

$$\frac{dA_{VT}}{dt} = Q_T.C_A - Q_T.C_{VT} - FLUX_{P,IS}$$

where A_{VT} is the mass of drug in plasma, Q_T is the tissue blood flow, C_A is the concentration of drug entering the tissue in arterial blood, C_{VT} is the concentration of drug in effluent venous blood and $FLUX_{P,IS}$ is the net rate of movement of drug across the capillary walls. The rate of change of amount of drug in the interstitial space is:

$$\frac{dA_{IS}}{dt} = FLUX_{P,IS} - FLUX_{IS,IC}$$

where A_{IS} is the mass of drug in the interstitial space and $FLUX_{IS,IC}$ is the net rate of movement of drug across the tissue cell membrane. Correspondingly, the rate of change of amount of drug in the intracellular space is:

$$\frac{dA_{IC}}{dt} = FLUX_{IS,IC}$$

where A_{IC} is the mass of drug in the intracellular space. These models assume that there are no metabolism or excretion processes in any compartments. The flux or rate of transfer of drug across the interfaces (capillary walls and cell membranes) can be by numerous transport mechanisms. The simplest is by Fickian (passive) diffusion, which is of the form:

$$FLUX_{a,b} = P.SA.(Cu_a - Cu_b)$$

where P is the permeability coefficient of the drug across the membrane, SA is the membrane surface area and Cu_a and Cu_b are the unbound concentration of drug on each side of the membrane.

When drugs can move freely from capillaries into interstitial fluid and tissue cells, i.e. capillary walls and cell membranes offer virtually no resistance to the movement of drug, the rate-limiting step controlling movement of drug into and out of an organ is the perfusion or blood flow to the organ.

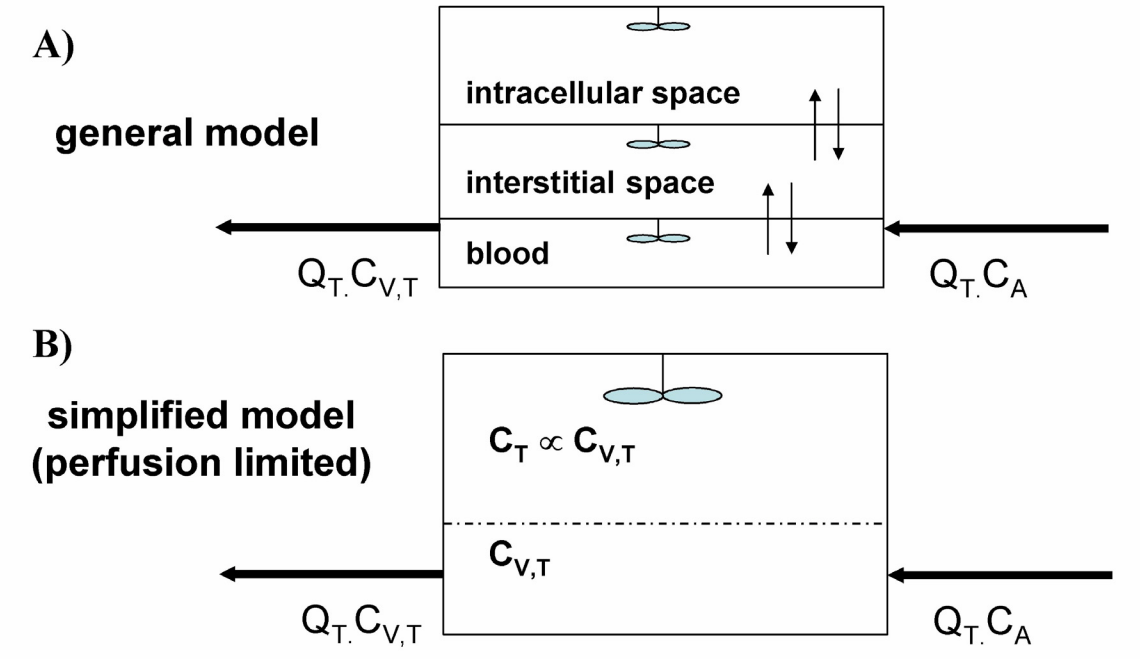

Figure 3. A general and simplified organ kinetic model.

Using this assumption the general model described above reduces to a single compartment. Known as the perfusion-limited or venous equilibration model (see Fig. 3B) the rate of change of amount of drug in the tissue is defined as:

$$\frac{dA_T}{dt} = Q_T.C_A - Q_T.\frac{A_T}{V_T.K_p}$$

A_T is the mass of drug in the tissue, V_T is the anatomical volume of the tissue and K_p is the equilibrium tissue: plasma partition coefficient. As can be seen from the above equations the parameters can be separated into physiological/anatomical values and compound-dependent parameters. Values of tissue blood flows and anatomical volumes for many common laboratory animals and humans are available [15]. Thus, the key determinant, which requires estimation, is the K_p for each tissue in each species of interest. These values can be estimated using *in vivo*, *in vitro* and more recently *in silico* techniques [16, 17]. *In silico* methods are the most applicable to drug discovery and complement the high-throughput methodologies used by most pharmaceutical companies [17].

Metabolism

Drug metabolism is often the key route of elimination of the drug from the body. In general, the liver is the organ responsible for the metabolism of most drugs. Therefore, most pharmaceutical companies now routinely screen compounds for the metabolism properties using *in vitro* systems incorporating various animal and human liver preparations. To quantitatively estimate the rate of metabolism or clearance (CL) in humans *in vivo* the *in vitro* data must be extrapolated to the *in vivo* condition. A number of methodologies have been proposed in the literature and all require the use of mathematical models of the liver in order to make the extrapolation [18-22]. Such a methodology is shown in Fig. 4. A number of different liver models have been proposed including the venous equilibrium (well-stirred) model, the undistributed sinusoidal (parallel-tube) model and the dispersion model [23,24].

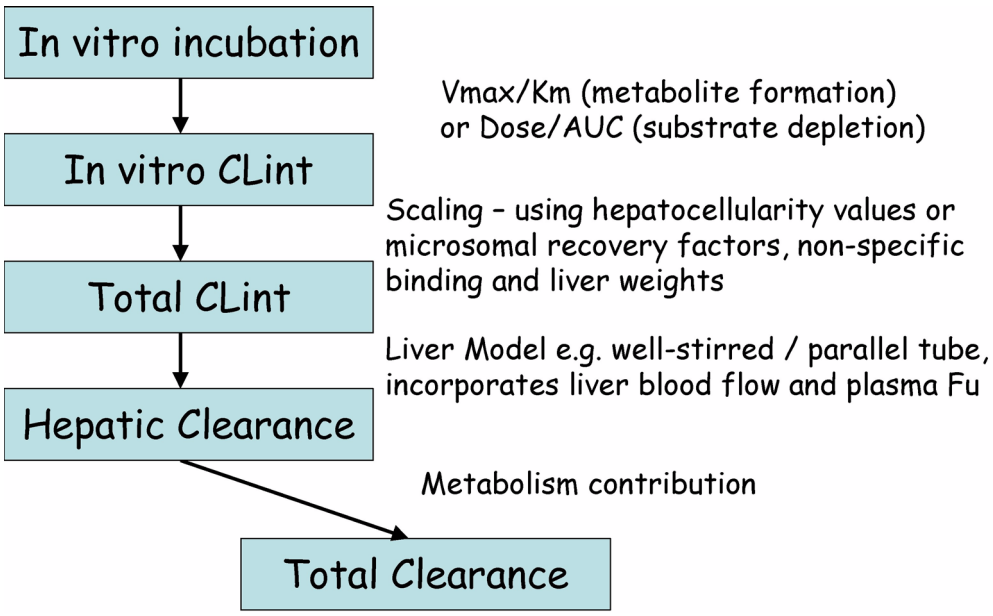

Figure 4. Liver metabolism *in vitro-in vivo* scale up methodology (adapted from Houston, 1994 [18]).

In theory, this approach can be applied to any tissue or organ which metabolizes the drug. However, limiting factors for expanding this approach to other tissues in a drug discovery setting are the availability of tissue or high-throughput assays and lack of quantitative information required to scale from the *in vitro* system.

Excretion

Other routes of elimination of a drug from the body include excretory processes in the kidney and into the bile from the liver. Filtration by the kidney has been well characterized and glomerular filtration rate can be used to estimate this part of renal clearance (C_{LR}) [25]. Although there has been considerable research in recent years on the active mechanisms in renal and biliary excretory processes, high-throughput assays and quantitative *in vitro-in vivo* correlations are currently lacking.

Integration - whole body models

Physiologically based pharmacokinetic models combine the models of absorption, distribution, metabolism and excretion in the attempt to predict the time-course of drug concentration in bodily fluids, normally blood or plasma, and the time-course of concentration in tissues [3-7]. An illustration of a PBPK model is shown in Fig. 5.

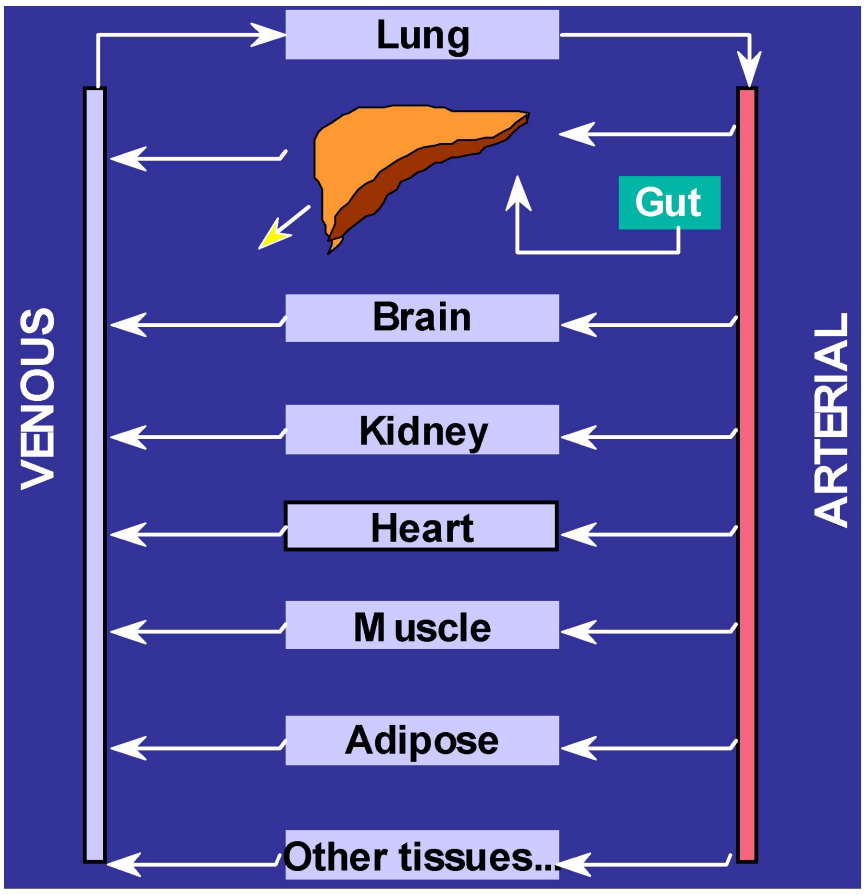

Figure 5. Schematic of a whole-body PBPK model.

Obviously every model is an abstraction or simplification and PBPK models are no exception. Normally, models of organs responsible for elimination of the drug are represented discretely in the whole body model. Large diffuse tissues such as fat, muscle and skin generally provide the largest storage capacity for drugs and so are also represented. Kinetic models of target organs are normally incorporated, while tissues that have negligible impact on the distribution of the drug are often ignored. All tissue models are connected together according to the design of the circulatory system.

Pharmacodynamics

Development of a model that will accurately simulate the pharmacokinetic system of a drug candidate is an achievement in its own right. With the addition of simple assumptions about therapeutic concentrations at the site of action such models can be used to give a first approximation of the dose-therapeutic response relationship. However, as the drug concentration (C)-effect (E) relationship is most frequently highly non-linear (see Fig. 6) [26], inclusion of pharmacodynamic models is often necessary to truly characterize the dose-response relationship. This is of particular importance when trying to make comparisons between drug-candidates in order to select the most suitable candidate for further development.

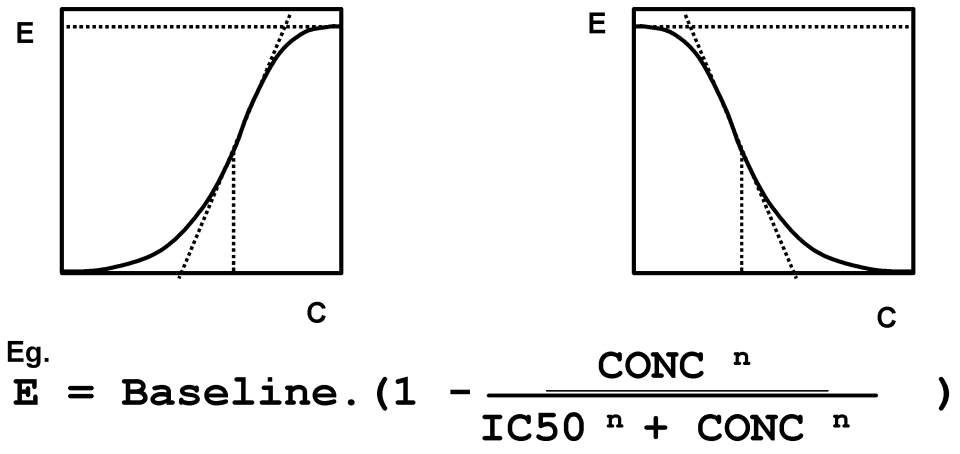

Figure 6. Example of direct pharmacodynamic effects.

In the early stages of lead optimization when compounds are being tested for potency, ADME and physico-chemical properties and *in vitro* potency data (e.g. IC_{50} from a binding assay study) can be used as first approximation to define a pharmacodynamic relationship as per Fig. 6 [27, 28].

If such a model is combined with a PBPK model, quantified using the ADME and physico-chemical screening data, the likely dose-response, in terms of target (e.g. receptor or enzyme) inhibition or agonism at least, can be estimated. Thus, modelling and simulation can serve as an *in silico* screen utilizing the available data. Normally, as the number of suitable drug-candidates is reduced the remaining candidates are screened using *in vivo* animal pharmacology models. Often it is possible to establish pharmacodynamic relationships and models from the data obtained in these *in vivo* studies. Data can range from a simple *in vivo* confirmation of *in vitro* potency data, e.g. plasma enzyme inhibition, and more complex biomarkers of disease such as changes in hormone levels to complex behavioural changes in nervous system function. Models based on these data can be used in combination with PBPK models to first approximate the animal data (see Fig. 7) before attempting to extrapolate to humans.

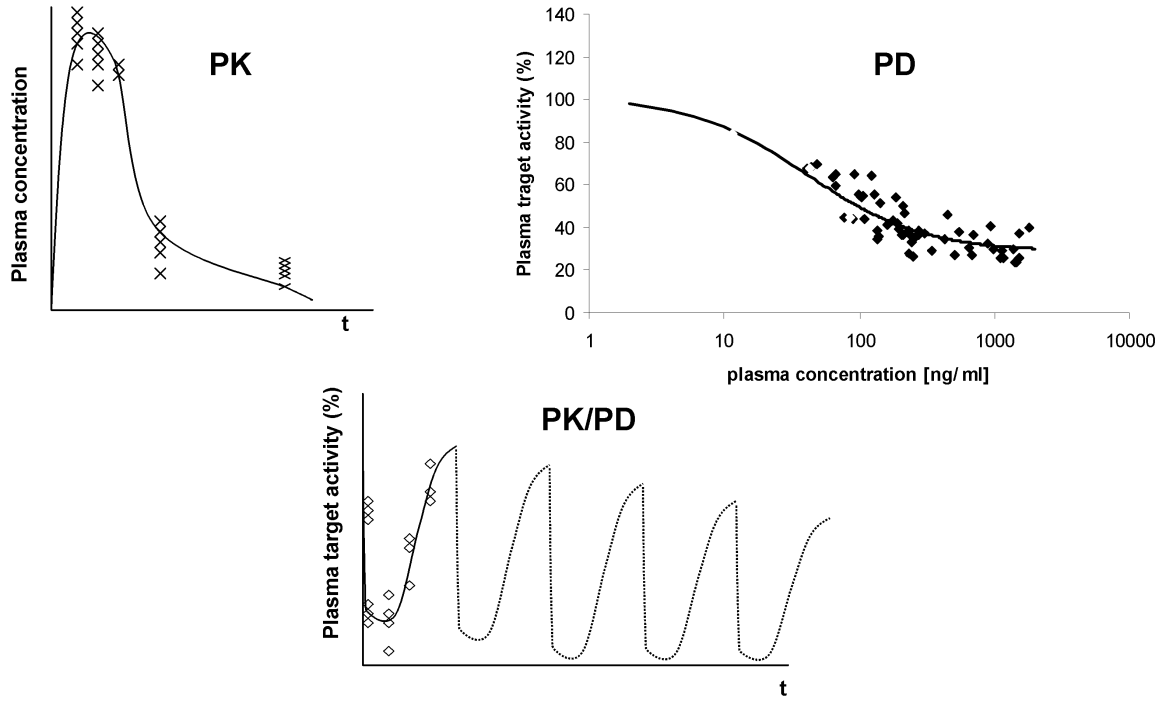

Figure 7. PK/PD Approach using *in vivo* animal data.

The advantages of using a modelling approach as opposed to using just the data, are that one can quantitatively incorporate independent data, any assumptions are explicated and models allow both interpolation and extrapolation beyond the conditions in which the experimental data were originally obtained. In particular, PBPK models can be used to estimate human kinetics from limited *in vitro* and *in silico* data.

The main uncertainty in such a combined PK/PD approach is scaling the pharmacodynamic model from the animal pharmacology model to the human situation. For drug targets that are situated in the blood this can be relatively straightforward. Although one cannot usually make predictions about final clinical endpoints, one can often extrapolate simple drug effects or biomarkers of clinical response. This becomes increasingly difficult when the target is not easily measurable even in animal models. It is also difficult when a link between responses in animal models and changes in disease state are not well understood. These uncertainties will decrease as more experience is obtained in the use of animal disease models, as our knowledge of human disease increases and as our current knowledge is applied quantitatively in an effort to predict human disease states and the therapeutic effects of drugs. A good example is the company Entelos Inc. [29, 30], which has developed sophisticated, mechanistic computer models of human physiology and disease. Models of this type can be used at many stages of the drug development process including drug discovery. When used in combination with predictive pharmacokinetic models, such as PBPK models, the dose-clinical therapeutic response of drug-candidates can be estimated long before the drug reaches the clinic.

CONCLUSION

Modelling and simulation based on the principles of pharmacokinetics and pharmacodynamics are useful tools in drug development. Biological system-based models allow one to separate the pharmacokinetic and pharmacodynamic characteristics of drug candidate into compound and biology-specific components. Advances in high-throughput experimental methods means that compound-specific data are generated for many drug-candidates at early stages of drug discovery. *In silico* tools have been developed to predict parameters that cannot be routinely measured. Biology-specific data are readily available in the scientific literature. With the advancement of sophisticated human physiology, disease and toxicity models the relationships between drug targets and clinical outcome are increasingly quantifiable. A combination of drug discovery data and computer methods allows scientists to explore the possibilities of novel drug targets or novel uses of existing targets at the beginning of a discovery project. In lead optimization one can discriminate between drug-candidates based on desirable pharmacokinetic properties and/or likely dose-effect characteristics in the target population.

Systematic use of these tools should lead to better clinical drug-candidates and a corresponding reduction in attrition during the far costlier clinical phases of drug development.

REFERENCES

[1] DiMasi, J.A. (2001) Risks in new drug development: approval success rate for investigational drugs. *Clin. Pharmacol. Therapeut.* **69**:297-307.

[2] Rowland, M., Thomas, T.N. (1988) *Clinical Pharmacokinetics. Concepts and Applications*. 2nd Edn, p.3. Lea and Febiger, Philadelphia.

[3] Gerlowski, L.E., Jain, R.K. (1983) Physiologically based pharmacokinetic modeling: principles and applications. *J. Pharmaceut. Sci.* **72**:1103-1127.

[4] Andersen, M.E. (1995) Development of physiologically based pharmacokinetic and physiologically-based pharmacodynamic models for applications in toxicology and risk assessment. *Toxicol. Letters* **79**:35-44.

[5] Lutz, R.J., Dedrick, R.L., Zaharko, D.S. (1980) Physiological pharmacokinetics: an *in vivo* approach to membrane transport. *Pharmacol. Therapeut.* **11**:559-592.

[6] MacDonald, A.J., Rostami-Hodjegan, A., Tucker, G.T., Linkens, D.A. (2002) Analysis of solvent central nervous system toxicity and ethanol interactions using a human population physiologically based kinetic and dynamic model. *Regulat. Toxicol. Pharmacol.* **35**:165-176.

[7] Poulin, P., Theil, F.P. (2002) Prediction of pharmacokinetics prior to *In Vivo* studies. II. Generic physiologically based pharmacokinetic models of drug disposition. *J. Pharmaceut. Sci.* **91**:1358-1370.

[8] Boxenbaum, B., D'Souza, R.W. (1990) Interspecies pharmacokinetic scaling, biological design and neoteny. In: *Advances in Drug Research*. (Testa, B., Ed.), pp. 139 -196. Academic Press, London.

[9] Lin, J.H. (1995) Species similarities and differences in pharmacokinetics. *Drug Metab. Disposit.* **23**:1008-1021.

[10] Lavé, T., Coassolo, P., Reigner, B. (1999) Prediction of hepatic metabolic clearance based on interspecies allometric scaling techniques and *in vitro-in vivo* correlations. *Clin. Pharmacokinet.* **36**:211-231.

[11] Zuegge, J., Schneider, G., Coassolo, P., Lavé, T. (2001) Prediction of hepatic metabolic clearance in man - comparison and assessment of prediction models. *Clin. Pharmacokinet.* **40**:553-563.

[12] Agoram, B., Woltosz, W.S., Bolger, M.B. (2001) Predicting the impact of physiological and biochemical processes on oral drug bioavailability. *Adv. Drug Deliv. Rev.* **50**:S41-67.

[13] Grass, M., George, J., Sinko, P. (2002) Physiologically-based pharmacokinetic simulation modelling. *Adv. Drug Deliv. Rev.* **54**:433-451.

[14] Parrott, N., Lavé T. (2002) Prediction of intestinal absorption: comparative assessment of Gastroplus ^{TM} and Idea ^{TM}. *Eur. J. Pharmaceut. Sci.* **17**:51-61.

[15] Brown, R.P., Delp, M.D., Lindstedt, S.L., Rhomberg, L.R., Beliles, R.P. (1997) Physiological parameter values for physiologically based pharmacokinetic models. *Toxicol. Indust. Hlth* **13**:407-484.

[16] Poulin, P., Theil, F.P. (2000) *A priori* prediction of tissue:plasma partition coefficients of drugs to facilitate the use of physiologically-based pharmacokinetic models in drug discovery. *J. Pharmaceut. Sci.* **89**:16-35.

[17] Poulin, P., Theil, F.P. (2002) Prediction of pharmacokinetics prior to *in vivo* studies. 1. Mechanism-based prediction of volume of distribution. *J. Pharmaceut. Sci.* **91**:129-156.

[18] Houston, J.B. (1994) Utility of in vitro drug metabolizing data in predicting *in vivo* metabolic clearance. *Biochem. Pharmacol.* **47**:1469-1479.

[19] Iwatsubo, T. *et al.* (1997) Prediction of *in vivo* drug metabolism in the human liver from *in vitro* metabolism data. *Pharmacol. Therapeut.* **73**:147-171.

[20] Lavé, T. *et al.* (1997) The use of human hepatocytes to select compounds based on their expected hepatic extraction ratios in humans. *Pharmaceut. Res.* **14**:152-155.

[21] Obach, R.S. *et al.* (1997) The prediction of human pharmacokinetic parameters from preclinical and *in vitro* metabolism data. *J. Pharmacol. Expl Therapeut.* **283**:46-58.

[22] Jones, H.M., Houston, J.B. (2004) Use of the substrate depletion approach for determining *in vitro* metabolic clearance: time dependencies in hepatocyte and microsomal incubations. *Drug Metab. Disposit.* **32**(9):973-982.

[23] Pang, K.S., Rowland, M. (1977) Hepatic clearance of drugs. I. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. Influence of hepatic blood flow, plasma and blood cell binding, and the hepatocellular enzymatic activity on hepatic drug clearance. *J. Pharmacokinet. Biopharmaceut.* **5**:625-653 .

[24] Wilkinson, G.R. (1987) Clearance approaches in pharmacology. *Pharmacol. Rev.* **39**:1-47.

[25] Rowland, M., Thomas, T.N. (1988) *Clinical Pharmacokinetics. Concepts and Applications*. 2nd Edn, pp. 160-163. Lea and Febiger, Philadelphia.

[26] Gabrielsson, J., Weiner, D. (2000) *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*. 3rd Edn, pp.175-257. Swedish Pharmaceutical Press, Stockholm.

[27] Visser, S.A.G. *et al.* (2003) Mechanism-based pharmacokinetic/pharmacodynamic modeling of the electroencephalogram effects of GABAA receptor modulators: *in vitro-in vivo* correlations. *J. Pharmacol. Expl Therapeut.* **304**:88-101.

[28] Gomeni, R., Bani, M., D'Angeli, C., Corsi, M., Bye, A. (2001) Computer-assisted drug development (CADD): an emerging technology for designing first-time-in-man and proof-of-concept studies from preclinical experiments. *Eur. J. Pharmaceut. Sci.* **13**:261-270.

[29] Musante, C.J., Lewis, A.K., Hall, K. (2002) Small- and large-scale biosimulation applied to drug discovery and development. *Drug Discov. Today* **7**:s192-s196.

[30] Kansal, A.R. (2004) Modeling approaches to type 2 diabetes. *Diabetes Technol. Therapeut.* **6**:39-47.