Exposure response modelling – a safe and profitable way to speed drugs to market

The applicability of physiologically-based pharmacokinetic modelling (PBPK) far exceeds that of classical PK in predictive pharmacokinetics, tissue dosimetry, drug efficacy, and drug safety. This *in silico* technique, in conjunction with *in vitro* and *in vivo* studies, can greatly reduce drug failure rates, improve time to market and decrease overall R&D costs. In addition, PBPK extends our ability to understand drug-human interaction in more quantifiable terms which will, in the end, result in more safe and effective drugs on the market and for a more diverse cross-section of the human population.

By Dr Gregory Fisher and Dr Arthur L. Craigmill

It has been estimated that R&D costs for a new drug averages $850 million, average time to market is 14 years and 70% of drugs that enter the market will not generate sufficient revenue to recover these costs. One of the most apparent cost drivers in the R&D process is the failure to identify poor candidate compounds early in the development process. Almost half of the drugs that fail Investigational New Drug (IND) filings do so as a result of ADME/Tox deficiencies. It has been stated that improving failure detection by even 10% before clinical trials could reduce R&D costs by $100 million per drug[1].

While pharmacokinetic modelling techniques are being employed by many pharmaceutical companies, it is seen more as an ancillary activity than part of the mainstream R&D process. To the extent that it is employed, classical PK techniques are used primarily in discovery, while PBPK is employed later in the development process. There appears to be little model reuse between discovery and development groups, as scientists involved in discovery and development tend to be disparate groups with independent processes.

Classical pharmacokinetic studies use abstract mathematical compartments to model the movement of a chemical in the body (**Figure 1**). These compartments generally are not specifically identified with actual organs. PBPK modelling offers the ability to extrapolate across species (pre-clinical), gender, or in specific populations not actually included in the study, which is difficult and sometimes impossible to do with classical pharmacokinetic modelling. PBPK is based on modelling tissue-types (or organs) as individual batch reactors linked together (**Figure 2**). In fact, it is based on chemical engineering principles that were first proposed for physiological processes in 1937.

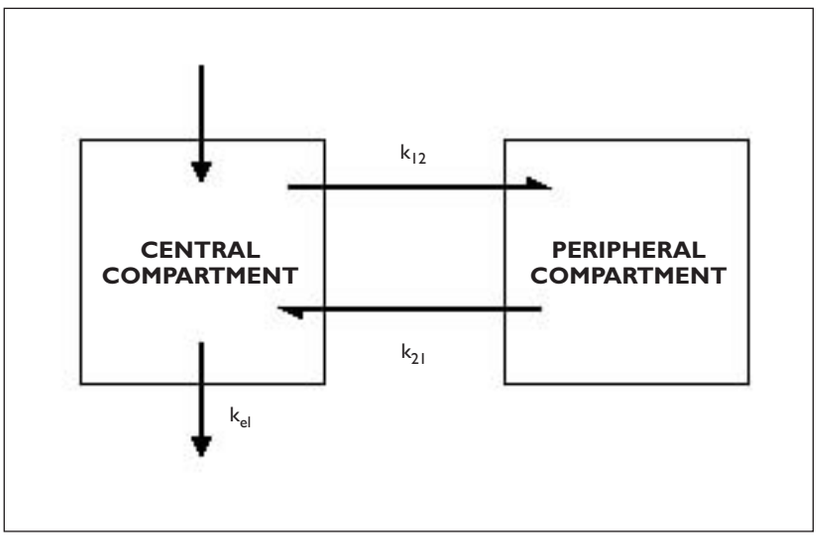


Figure 1: An example of a classical PK model displaying two-compartments. The model shows the rate of elimination (k_{el}), and movement between the central and peripheral compartments (k_{12} and k_{21}, respectively), but is apparent that the compartments are abstract representations of anatomical structures

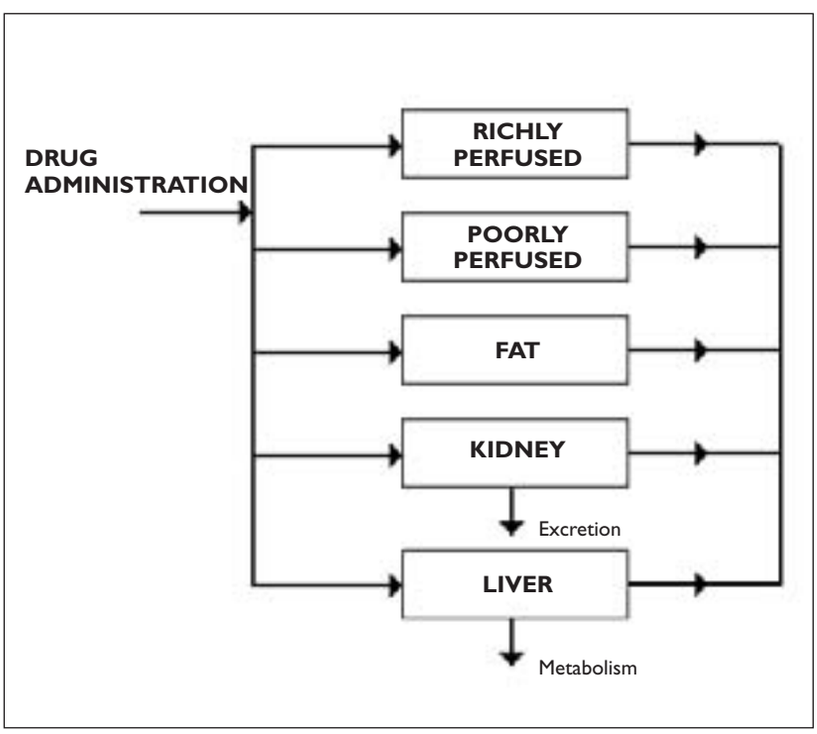


Figure 2: An example of a typical PBPK model for oral or dermal exposure. Similar tissue types are grouped together – eg, the richly-perfused compartment represents tissues with considerable blood flow, such as muscle. Organs with specific involvement – such as metabolism by the liver and excretion by the kidney – can be separated out and specifically studied

However, PBPK was impractical until recent improvements in computing power and available software enabled its use on the desktop computer. Although PBPK modelling requires more effort than the classical PK models, its potential predictive power is vastly greater.

PBPK techniques provide researchers with a flexible *in silico* framework to model the pharmacokinetics and pharmacodynamics of chemical compounds. During the early phases of drug development, PBPK can be used to estimate the time-course and distribution of the chemical within a specific population and at various dose levels. In later phases, the results of PBPK models are validated with *in vivo* tests, and may require fewer individuals than are now required.

Other uses of PBPK modelling that are gaining substantial interest include species extrapolation during the pre-clinical stage and, later, toxicity risk assessment, and assessing safety and efficacy in specific human populations such as paediatrics and adolescents.

The FDA Critical Path Initiative calls for innovation over stagnation and, to some extent, criticises current evaluation techniques as being out of date. Meanwhile, pharmaceutical companies are under major time-to-market pressure and are rightfully cautious about regulatory submissions that cause delays in the approval process. The regulatory environment could do much to encourage innovation through more formal adoption of *in silico* results in the evaluation process.

Finally, expanding the role of Exposure Response Modelling serves to minimise the use of animal subjects in the R&D process. PBPK modelling provides an ideal environment in which to optimise the use of existing animal data and to minimise the need for future animal experimentation.

Overall description

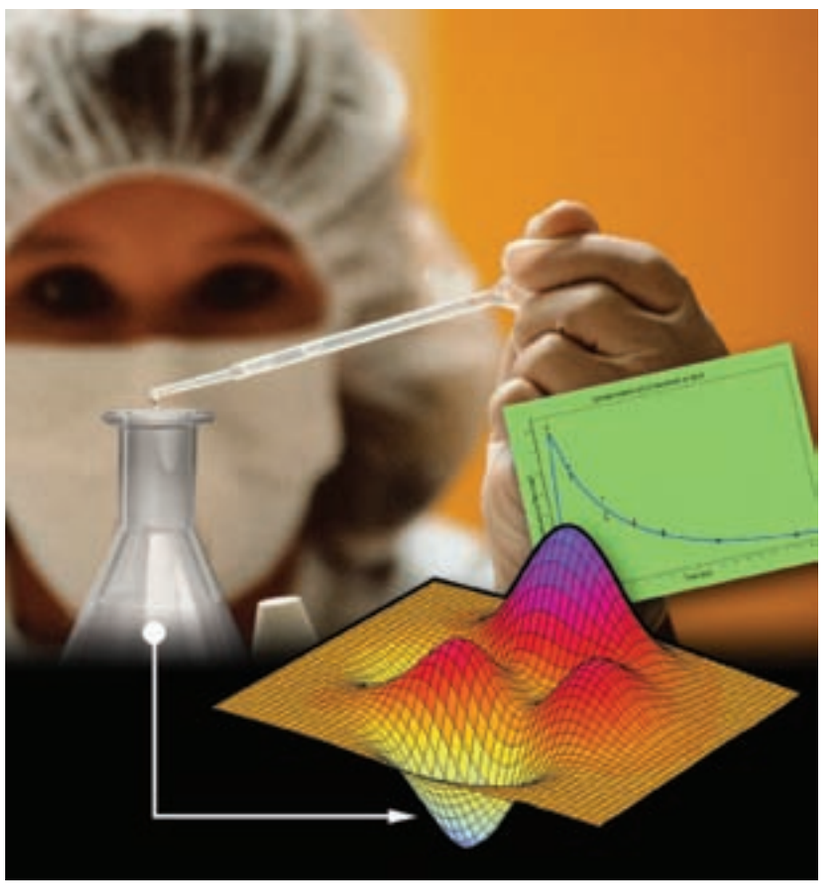
There is no single PBPK model but rather variations on a general theme. All PBPK models use a series of simultaneous differential equations to follow the movement of a chemical compound through the body as various tissues and organs act upon it. A specific example is shown for oxytetracycline (OTC) in sheep exposed by intramuscular/subcutaneous injection (**Figure 3**). In this model, the chemical is transported to each tissue/organ by arterial blood where it distributes within the tissue/organ (partitioning) and may or may not be metabolised and/or excreted. The compound leaves each tissue/organ by the venous blood where it is mixed with the blood leaving the other tissues/organs and is then redistributed again.

The various anatomical and physiological parameters – eg, blood flow and organ size – is usually already present in the published literature for many species, strains and ages. Individuals with compromised kidney function, therefore, can be modelled by employing the appropriate blood flow, metabolism or excretion rate.

PBPK modelling is now a valuable tool in the drug development process: during preclinical development, clinical development, mechanistic understanding and risk assessment. An informal poll on an industry website (www.PBPK.org) showed that the predominant uses of PBPK models are in drug development (38.5%) and as a research tool (30.8%). Other uses are to estimate the first dose in human clinical trials (11.5%), chemical risk assessment (11.5%) and for toxicological evaluation (7.7%).

PBPK models have great potential during preclinical development, human drug development, the drug approval process and in environmental risk assessment. In the early phases of selecting promising drug candidates, PBPK modelling allows researchers to assess tissue concentrations and pharmacokinetics with more insight than is otherwise possible. Because the basic anatomical values (eg, liver size, blood flow, etc) are independent of the model and readily accessible in the literature, a preliminary PBPK model can be built. The parameters specific to a chemical (eg, partition between a given tissue type and the blood) can be estimated from *in vitro* tests or approached from a structure activity relationship (SAR) with a similar compound. These values can be put into a rough model and simulated at a variety of dosing levels relatively quickly.

Once the number of potentially viable drug candidates is reduced to a workable value, PBPK models can be developed using more accurate data than is typically available in samples obtained from *in vivo* steady-state exposures in one or more animals. These values would be used in the model along with the specific metabolic profiles for the chemical that are most likely obtained from *in vitro* studies. This also alerts investigators to issues that may arise with subpopulations having different metabolising patterns – eg, different proportions of cytochrome P450 isoenzymes. The modelling process looks at various dosing levels, even to the point of overwhelming detoxification pathways, to find where efficacy fails and toxicity sets in. All of these characteristics of PBPK modelling can help to appreciably eliminate chemicals in the drug selection process that would later prove toxic or ineffective (tissue dosimetry), set dose levels, identify subpopulations that may have idiosyncratic response, describe the pharmacokinetics in the entire body and specific tissues/organs, and improve assessment of drug efficacy and safety.



acslXtreme enhancement that features parameter optimisation, sensitivity analysis and Monte Carlo simulation

Applications of PBPK models

There are examples of regulatory evaluation involving PBPK model results. One example was in the approval process for SDZ IMM 125 (IMM) by Sandoz of a cyclosporin A derivative. R Kawai et al (1994) demonstrated not only the utility, but also the flexibility, of PBPK modelling. An advantage of the PBPK model – especially during the validation stage of the model building process – is that it brings to light unknown processes or factors. When these factors are identified, the model can be modified and adjusted to incorporate actual physiological parameters. When their initial PK characterisation did not match experimental results, Kawai was able to identify influencing factors – eg, slower than expected membrane transport became a limiting factor. The model also included three pathways for compound elimination: metabolism, biliary secretion and glomerular filtration. The model ultimately showed IMM concentrations in

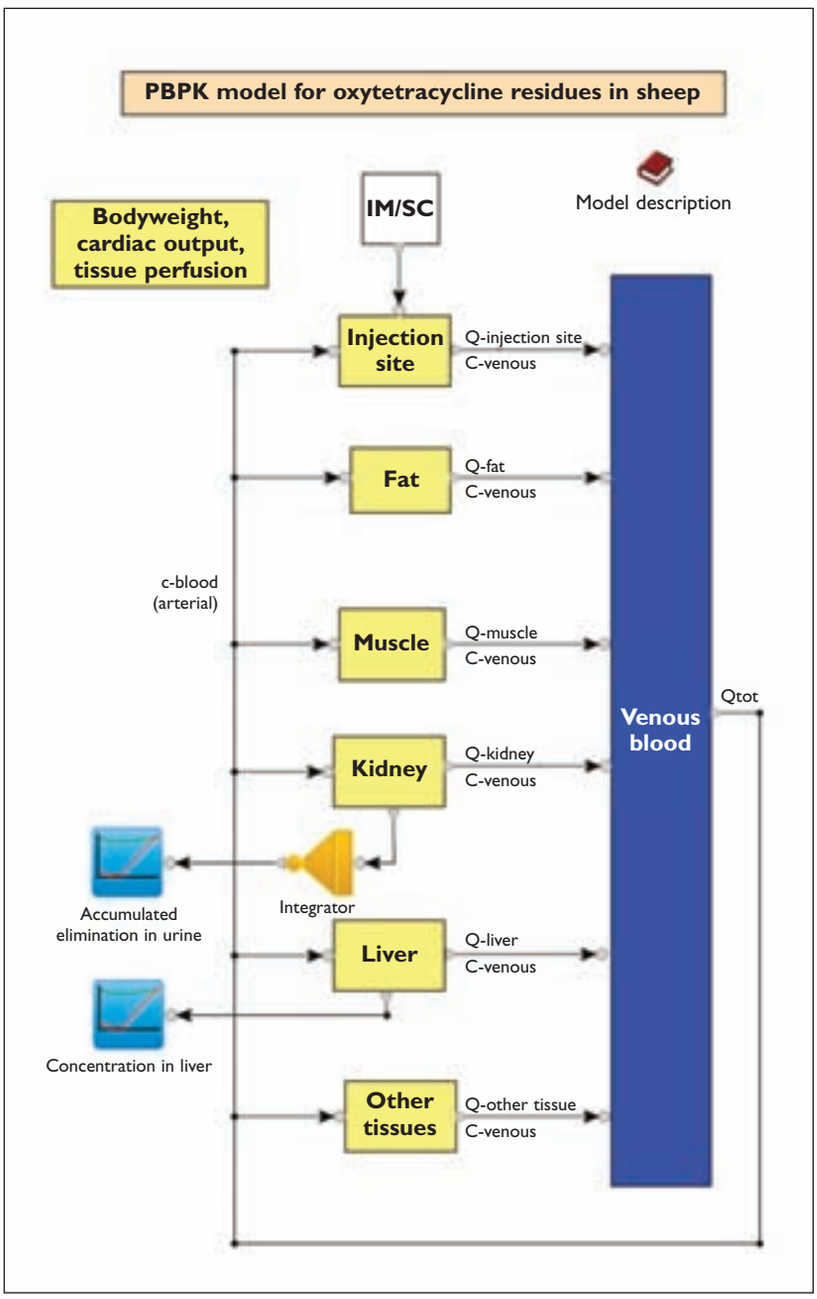


Figure 3
A specific example of a PBPK model (using acslXtreme® modelling and simulation software from Xcellon™) for oxytetracycline (OTC) in sheep exposed by IM/SC injection. The OTC is followed in each tissue-type/organ whereby the concentration at any given time can be determined. The model allows for various dose levels, and can include different physiological parameters – such as studying individuals with compromised kidney function or subpopulations with specific genetic makeup (pharmacogenetics)

14 tissues/organs and arterial blood. The model was scaled up from the original rat model and agreed well with dog and human results.

Another practical application of PBPK modelling for FDA approval is providing information about the safe and effective use of drugs in paediatric populations. Pre-clinical studies using animal models do not generally characterise the pharmacokinetics in human children. When the disease, therapy and outcome are the same for children and adults, the dose level given to the children is set at a level comparable to that given to adults to produce the same exposure level. However, when the disease is confined primarily to children, more information is necessary for safety and efficacy assessment. PBPK offers investigators a potentially powerful tool for assessing this population. It can also offer researchers a better indication of dosing levels before clinical trials are run on this susceptible population.

Determining the pharmacokinetics and tissue dosimetry of drugs during pregnancy and lactation is of considerable concern in not only efficacy, but in safety and risk assessment. PBPK models allow a window for viewing a number of possible variables and parameters that is not otherwise available without significant *in vivo* measurements. Acquiring data from such areas as placental transfer and fetal blood circulation is difficult, at best.

Beyond the efficacy interest, safety and risk assessment concerns being studied using PBPK include complex problems such as identifying and assessing estrogenic endocrine disruptors and chemical mixtures. These models have been helpful in the understanding and risk assessment of lead, arsenic, mercury and TCDD (dioxin), just to mention a few. Additionally, PBPK models were included in setting permissible exposure levels to the solvent trichloroethylene, and helpful in understanding the large difference in toxic outcomes for mice and rats from exposure to formaldehyde.

PBPK modelling also has great potential in other areas. Arthur Craigmill's (University of California, Davis) model, mentioned above for OTC in sheep (Figure 3), illustrates how PBPK modelling has the potential to open doors for drug approval in minor markets – areas currently unprofitable due to pre-market studies[2]. Generally, the only feed animals tested are cow, swine and poultry. However, PBPK modelling creates a bridge whereby information from these animals can be extrapolated and validated for smaller markets.

In research, preclinical and the earlier clinical trials (Phase I) only healthy humans are studied. However, most drugs are used as therapeutic

agents for people with compromised or impaired health. PBPK modelling can be used to bridge this gap in information. For example, He Sun (OCPD/CDER/FDA) et al used PBPK modelling to help explain the adverse effect of acidosis on lidocaine given to patients with cardiac arrhythmias in emergency situations. The acidosis increases the plasma concentrations of lidocaine and is also associated with CNS toxicity.

Model development and validation

In PBPK modelling, the computer model is created first and then validated by adjusting it to fit the experimental data. These models allow physiological and metabolic parameters to be incorporated into the model, something that cannot be done using classical PK models.

Creating PBPK models requires three general steps: (1) obtaining and organising model parameters; (2) optimising the parameters using nonlinear-regression techniques or maximum-likelihood estimation techniques; and (3) validating the model using experimental values.

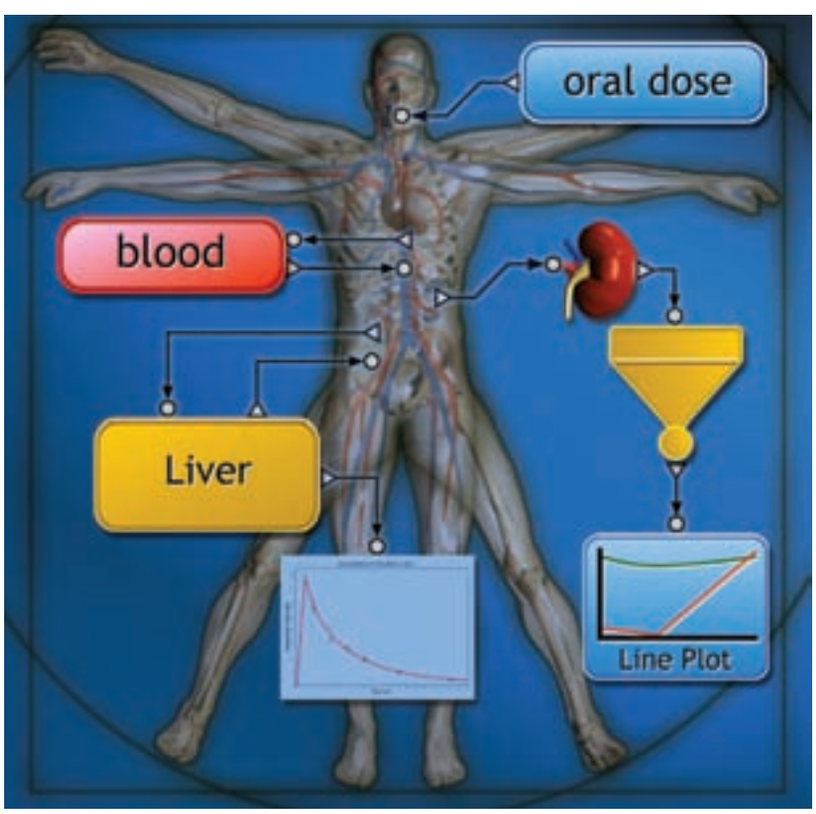
In the first step, the body is represented by a series of similar tissue types linked by the cardiovascular system. With simpler models, the tissues/organs are fat, muscle (or richly-perfused), kidney and liver, with lung being incorporated for inhalation exposure. The required anatomical and physiological values (individual organ volumes, cardiac output and specific organ blood flows) are available in the published literature. Of note, however, is the increased interest in children and adolescents where values are still being collected and standardised. Often these values are identified by sex, age, species and even strain.

Typically, the most challenging aspect of this first step comes next with determining the partition co-efficients. These are the ratios of the chemical concentration in each specific tissue with that chemical in the blood; volatile chemicals must be further measured for the blood-air partition co-efficients. Often, the drug is infused into several animals until steady-state conditions are achieved. Then the tissues (including blood) are collected and analysed, and the partition coefficients determined specifically for the chemical and animals used in the particular model. This is the typical, albeit most time-consuming, part of model building. Obtaining accurate values for the partition coefficients requires a level of expertise that is one of the major hurdles for investigators beginning in the field. Values are not only chemical-specific, but may be species, age, sex, etc dependent.

Another necessary parameter inherent with a chemical in living organisms is that of metabolism. This can greatly influence the activity of the compound. However, unlike the partition co-efficients, which are determined *in vivo*, metabolism can usually be studied by *in vitro* techniques.

Still in the first step, the specific equations are then incorporated into the model with the various parameters and values entered. The computer software program is run and the series of simultaneous differential equations are solved to quantify tissue concentration and establish the tissue and entire animal pharmacokinetics.

The second step is parameter optimisation. Leading up to this step, one often finds that the model structure accurately represents the necessary physiological elements, but that model results do not correlate well with experimental data. Model assumptions about partition co-efficients and other model parameters are typically the culprit and must be optimised against experimental data. Parameters are optimised to fit experimental data. This step also involves sensitivity analysis to determine which model parameters affect model results. For example, does the amount of body fat significantly affect the clearance rate, or does the activity level of a specific isoenzyme affect residue levels? This is a computationally intensive operation, but



acslXtreme pharmacokinetic software enables researchers to build PK/PPPK models to safely speed drugs to market

References

1 Boston Consulting Group. 'A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry'. PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2002/2003.

2 Craigmill, AL (2003). A Physiologically Based Pharmacokinetic Model for Oxytetracycline Residues in Sheep. http://www.aegisxcellon.com.

is relatively straightforward and efficient with today's sophisticated software programs.

The third and final step is model validation: does the model provide a good fit with experimental data in the general case? Typically, the model is tested against experimental values from studies that were not used for parameter optimisation. This may include more extensive serum and/or tissue levels of drugs from several individual animals, testing the model over several exposure levels, or a different route of administration. Model deviation from actual data may not mean that the model is wrong but may, instead, indicate that other processes may be involved. For example, deviations at high doses can result from saturation of detoxification pathways or indicate an unknown parameter – such as a change in the animal's breathing rate in response to noxious volatile chemicals.

Summary

PBPK modelling has grown considerably with the advent of the personal desktop computer and available software. Many companies and regulatory agencies have expressed considerable interest in utilising PBPK models for drug development and approval, risk assessment and research. But the adage that a private company wants to market safe drugs and the government wants no toxic drug holds the conservative climate of both science and the regulatory drug approval process to require a substantial number of validated PBPK models before the process is accepted. In the meantime, PBPK modelling offers considerable efficiency and effectiveness in the drug development process, reducing both time and money required to bring a successful drug to market.

Of particular note was a workshop held by the Center for Drug Development Science (CDDS) at Georgetown University in 2002 (http://cdds.georgetown.edu/conferences/PBPK2002.html) that addressed many of the applications and advantages of PBPK modelling. It requires more effort than classical PK studies, but offers much more information – both predictive and explanative. Not all, however, are convinced of its universal application. One criticism is that PBPK models assume that each tissue/organ is homogeneous. This is overcome by incorporating protein-binding, membrane transport, etc into the model, making the model more complex. One pitfall that follows is making the model hyper-parametised. It is important to realise that any model is a simplification of what is happening at the anatomical and physiological level. In that sense, and taken to extreme, all models are wrong. But PBPK modelling provides an invaluable tool for reducing the number of potential drugs entering serious consideration (from high throughput screening), selecting compounds with likely pharmacokinetic and pharmacodynamic success and increasing drug safety and effectiveness. DDW

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