Optimisation of first clinical studies in special populations : towards semi-physiological pharmacokinetic models

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Chapter 1

Optimisation of first clinical studies in special populations: towards semi-physiological pharmacokinetic models

Abstract

Special populations represent groups of patients that respond differently to drug treatment as a result of a variety of genetic, (patho-)physiological and/or environmental factors. The assessment of the influence of these intrinsic/extrinsic factors the pharmacokinetics (PK) and/or pharmacodynamics (PD) requires collection additional data to support label requirements as imposed by regulatory agencies. The execution of first clinical studies in special populations is difficult due to many ethical and practical barriers which preclude large sample size and repeated sampling of PK and/or PD in vulnerable and heterogeneous patient groups. This makes it a challenge to harness the limited data collected to inform safe and effective dosing. In this perspective, the use of model-based approaches is necessary to leverage knowledge for the optimal design of the study and the analysis of the study results. This article reviews (i) the physiological basis and the regulatory requirements for the performance of first clinical studies in special populations and; (ii) the traditionally used model-based approaches that are used for prediction of (variation in) the PK in these populations, i.e., compartmental PK models and physiologically-based pharmacokinetic (PBPK) models. Of the available models, compartmental PK models are generally of limited value for prediction as this can typically be achieved by allometric scaling. In contrast, PBPK models are maximally useful for extrapolation and prediction but their inherent complexity limits the application for optimal design and data analysis techniques. Here, we propose the use of semi-physiological PK models, which combine a compartmental structure to mechanistically describe plasma protein binding with well-established physiological equations to describe the absorption, the distribution and the elimination. It is concluded that semi-physiological PK models are most useful for optimal design and data analysis of first clinical studies in special populations.

Introduction

"Dosage and administration" is an important section of a drug label, which provides all the relevant information that is needed for the safe and effective dosing to patients. Therefore, early and late stage clinical studies are designed and geared towards the collection of key data (pharmacokinetic (PK), safety and efficacy) to be included in the label to inform patients representing a wide range of demographics (age, race, ethnicity and sex) on the optimal dosing. Yet, historically, clinical studies are focused on patients who are representative for the target population, while excluding special populations, such as children and patients with co-morbidities like hepatic and/or renal impairment.

Special populations is a general term referring to groups of patients that (may) respond differently to drug treatment as a result of a variety of genetic, (patho-)physiological and/or environmental causes. This impels the collection of additional data to support label requirements for special populations as imposed by drug regulators. As a result, clinical studies in special populations have become an important part of drug development so that safe and effective doses can be established. Complicating factors in these studies are the inherent heterogeneity of these patients groups and the practical and ethical barriers. As a result the sample sizes are often small, which may lead to underpowered studies for the detection of efficacy and safety signals. This is especially the case in paediatric clinical studies, where for ethical reasons only sparse data can be collected compared to traditional phase I studies.

Altogether, these factors can undermine the objective of the clinical studies when these are not well-designed. Therefore, throughout drug development, the application of model-based approaches becomes essential to obtain the pertinent information on (the variation in) the PK and/or the exposure-safety/efficacy relationship in special populations. Here, model based approaches enable optimisation of the design of the studies and evaluation of critical key data. The use of model-based approaches for the prediction of (variation in) PK in special populations is increasingly recognised as an essential tool for optimisation of the design of first clinical studies in special populations.

In this chapter, we review the physiological basis and the regulatory requirements for first clinical studies in special populations. The focus is on the traditionally used model-based approaches for prediction of (variation in) the PK in these populations. In addition to compartmental and physiologically-based pharmacokinetic (PBPK) models, the concept of a semi-physiological PK model for prediction of PK in special populations is proposed.

First clinical study in special populations

Special populations can respond differently to drug treatment depending on multiple factors causing changes in the PK and/or safety and efficacy profiles. These changes have been observed as a result of: changes in physiology (e.g. paediatrics and geriatrics), disease state (e.g. hepatic, renal impairment), lifestyle (e.g. obesity) and genetics (e.g. extensive/poor CYP2D6 metabolizers) [1]. In each of these special populations, changes in drug treatment response can be the result of the influence one or more intrinsic/extrinsic factors. A comprehensive overview of intrinsic/extrinsic factors that may affect the response to drug treatment is provided in Table 1.1 [2].

Table 1.1 Overview of intrinsic and extrinsic factor affecting drug treatment response

Intrinsic			**Extrinsic**
Genetic		*(Patho-) Physiological conditions*	*Cultural and Environmental*
Sex Race		Age (children-elderly) Pregnancy/lactation	Climate Pollution
	Height Body weight		
		Hepatic Renal and Cardiovascular functions	Socio-economic and educational status Smoking habits Alcohol consumption Diet (food)
Genetic polymorphism			Therapeutic approach Polypharmacy (drug interaction) Drug compliance
Genetic disease		Diseases Organ dysfunction	

Adapted from [2]

The assessment of the influence of multiple intrinsic/extrinsic factors on the PK and/or the pharmacodynamics (PD) of a drug requires collection of additional data to support label requirements as imposed by drug regulators via various guidelines [1-13]. Generally, these guidelines identify situations where investigation of the influence of intrinsic/extrinsic factors on the treatment response is required. The influence of several intrinsic factors, such as weight, food intake and sex, can mostly be assessed within the pivotal study population, but for other factors, such as ethnicity/race, decreased renal and hepatic function and age, the results from dedicated clinical studies may be required.

The rationale for the performance of a dedicated clinical study in special populations is related to the lack of (sufficient) representation of patients in the pivotal clinical studies. Frequently, these first clinical studies in special populations are studies into the PK, of which the results can then be used to extrapolate efficacy and safety data from pivotal study populations to special populations. Table 1.2 shows an overview of ICH and regulatory guidance on clinical pharmacology per special population.

Table 1.2 Overview of regulatory guidances on clinical pharmacology per special population

Population	**ICH**	**EMA**	**FDA**
Ethnicity and race	Ethnic Factors in the Acceptability of foreign clinical data E5 (1998)		Collection of Race and Ethnicity Data in Clinical Trials (2005)
Hepatic impaired		Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired	Pharmacokinetics in Patients with Impaired Hepatic Function: Study, Design, Data Analysis, and Impact on Dosing and

		Hepatic Function (2005)	Labeling (2003)
Renal impaired		Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Decreased Renal Function (2014-draft)	Pharmacokinetics in Patients with Impaired Renal Function- Study, Design, Data Analysis, and Impact on Dosing and Labeling (2010 - draft)
Geriatrics	Studies in support of special populations: geriatrics E7 (1993)		
Paediatrics	Clinical Investigation of Medicinal Products in Pediatric Population E11 (2000)	Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (2007) Guideline on the investigation of medicinal products in the term and preterm neonate (2010)	Exposure-Response Relationships — Study, Design, Data Analysis, and Regulatory Applications (2003) General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (2014-draft)

Ethnicity and race

The traditional definition of race refers to genetic factors while ethnicity refers to cultural and environmental factors [14].

With regard to the role of genetic factors, variation in PK may be observed due to diversity in the expression (i.e. amount and variety) of enzymes of the cytochrome P450 enzyme family (e.g. CYP2D6 and the CYP2C subfamily), transporters (e.g. P-glycoprotein) and/or plasma binding proteins (e.g. alpha 1 acid glycoprotein) [15-17]. Warfarin is the example of a drug that well illustrates the importance of understanding genetic factors influencing pharmacology, both with regard to the PK and the PD [18]. To date, genetic variation in CYP2DC9 has explained part of the differences in the maintenance dose observed for African-Americans (average 6 mg/day), Asians (average 3.5 mg/day) and Caucasians (average 5 mg/day) [19].

Although genetic variation may be substantial, the influence on drug therapy might be insignificant in up to 50% of the cases where physiological and environmental factors are predominant [20]. An example of a physiological factor is body weight which has been often shown to explain a significant part of the differences in PK between Caucasians and Asians [16, 17, 21]. The cultural and environmental factors include, for example, induction (partially) of alcohol dehydrogenase or cytochrome P-450 metabolised drugs as a consequence of higher alcohol consumption habits [22].

In cases where there are concerns that factors varying with ethnicity and/or race may influence the PK, safety and efficacy of the drug in a new region, regulatory authorities may request the conduct of additional clinical studies. The available guidances [2, 3] specify dedicated clinical studies and the characteristics of foreign clinical data, that will facilitate their extrapolation into the population of a new region. Further, these guidances describe the development of strategies to characterise the influence of ethnic factors and the regulatory strategies to reduce duplication of clinical data.

Hepatic impaired patients

The liver is a vital organ with respect to detoxification of endogenous toxins and drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion. Decrease in hepatic function directly results in drug accumulation or, less often, failure to form an active metabolite. In addition, decrease in hepatic functions leads to accumulation of endogenous toxins involved in the impairment of cardiovascular, hepatic and renal function [22].

Hepatic function normally decreases as a consequence of ageing or disease. The most common causes of chronic liver disease are hepatitis B and C infections and excessive alcohol consumption. Progression of chronic liver disease ultimately leads to liver cirrhosis which is characterized by replacement of liver tissue by fibrotic tissue and destruction of the normal architecture of the organ. As the disease becomes more severe, there is a progressive decrease in uniform perfusion (i.e. shunting), in hepatocellular distribution (plasma protein binding; permeability; expression and function of uptake transporters at the basolateral membrane) and in hepatocellular function (biliary secretion, biotransformation). Child-Pugh scores are used to classify the state of disease progression into mild (A), moderate (B) and severe (C) [23]. To date, well-established markers for the severity of hepatic function are not yet available.

The regulatory guidances [4, 5] recommend that a PK study in patients with decreased hepatic function is conducted for every drug that is likely to be administered to these patients and for drugs where hepatic metabolism and/or excretion accounts for a substantial portion (>20 percent of the absorbed drug) of the elimination of a parent drug or active metabolite. For drug with a narrow therapeutic range, PK studies are recommended also to drugs which are eliminated by metabolism to a lesser extent (< 20 percent).

Renal impaired patients

Although elimination can occur through a variety of routes, most drugs are cleared by elimination of unchanged drug by the kidney and/or by metabolism in the liver. Even when the route of elimination is mainly by metabolism of the drug in the liver, kidneys are still likely to be involved in the elimination of the metabolites. Therefore, decrease in renal function is expected to lead to higher drug/metabolite exposures. Decrease in renal function might be associated with changes in absorption, hepatic metabolism, plasma protein binding, active transport in the kidney and in drug distribution [22, 24].

Likewise hepatic function, decrease in renal function can also be a consequence of ageing or disease. Renal function is usually assessed through serum-creatinine based equations that provide an estimation of creatinine clearance (i.e., Cockcroft-Gault) or glomerular filtration rate (eGFR) [25, 26]. Generally, the various degrees of renal impairment are defined as mild (creatinine clearance: 60-89 mL/min), moderate (creatinine clearance 30-59 mL/min), severe (creatinine clearance:15-29 mL/min), and end-stage renal disease (creatinine clearance: <15 mL/min or requiring dialysis treatment). Effects of severe renal disease on non-renal elimination mechanisms have been suggested to be caused by the accumulation of uremic factors that inhibit or suppress metabolising enzymes and transporters [24].

According to the regulatory guidances [6, 7], a PK study in patients with decreased renal function should be conducted for drugs that are intended for chronic administration or continuous infusion, also when the drug/major active metabolite is not primarily eliminated by the kidneys. For a drug

intended for a single or occasional administration, a study in patients with decreased renal elimination capacity should be considered if a prolonged elimination of the drug/active metabolite is a safety concern. If no study is performed in patients with decreased renal elimination capacity, a justification should be given.

Geriatric patients

Ageing of the population is taking place in nearly all the countries of the world. The global share of elderly people (aged 60 years or over) increased from 9.2 per cent in 1990 to 11.7 per cent in 2013 and will continue to grow as a proportion of the world population, reaching 21.1 per cent by 2050. In absolute numbers, the elderly population (aged 60 years or over) is expected to increase from 841 million people in 2013 to more than 2 billion in 2050 [27]. Accordingly, the regulatory agencies are more and more recognizing that the evaluation of geriatric patients should also be integrated during drug development [28].

Intrinsic factors affecting drug treatment response in geriatric patients are related to physiological and (co-existent) disease related changes. These changes are due to changes in body composition (e.g., decreased total body water and lean body mass) and progressive decline in the functional reserve of multiple organs and systems (e.g. decrease in renal function due to co-existent diseases, decrease in liver size). In addition, drug treatment response in geriatric patients may also be affected by factors such as polypharmacy, frailty, and disability. As a result, large variation in drug disposition is particularly prominent. Hence, drug treatment in this special population of patients tends to follow the aphorism "start low, go slow" [22, 29, 30].

For harmonization of the development of drugs in geriatric patients, an ICH guidance has been implemented [8]. This guidance focuses on new molecular entities that are intended for the treatment of diseases that are typically observed in the aging population, and diseases that are known to affect substantial numbers of geriatric patients older than 65 years. In pivotal clinical studies, geriatric patients should be included in meaningful numbers and to the extent possible, patients aged 75 years and above should be included. Also, patients with co-existent disease should not be unnecessarily excluded. For investigation of the influences of aging, co-medication and hepatic and renal function, dedicated PK studies should be performed in healthy (geriatric) subjects.

Paediatric patients

Paediatric patients have for many years been deprived from scientifically sounded drug treatment, as most of the medicines on the market have only been investigated for adult use. Without information on the safe and effective dosing (regimen) in children, clinical practitioners depended on linear scaling of the adult dose with body weight and/or body surface area [31]. The use of this linear size-adjusted dosing is based on the implicit assumption that children are small adults (i.e. that differences between adults and children are dependent on differences in size rather than function). A major argument against this assumption is the observations that the physiological changes in the first years of life show a high non-linearity [22, 32]. For example, in neonates, the immaturity of metabolising enzymes in the liver and immaturity of the kidney function may require the administration of doses lower than the linear size-adjusted doses, whereas in infants, a relatively higher metabolic capacity may require the use of doses higher than the linear size-adjusted doses.

The lack of accuracy of linear size-adjusted dosing reinforces the need of collecting critical data in paediatric clinical studies to establish safe and efficacious dosing regimens. However, the

performance of paediatric clinical studies was largely considered unethical due to the vulnerable characteristics of this population. This situation only started to change in recent years, when regulatory agencies in the US and EU have released specific paediatric regulations for committing sponsors to go beyond voluntary execution of paediatric drug development [33-37]. In contrast to other special populations, dosing recommendation and labelling in children may require the performance a (full) drug development programme, including the execution of juvenile animal studies, PK(-PD) dedicated studies and safety and efficacy studies [12, 13].

As a consequence of the paediatric regulations, guidance on the design and analysis of paediatric clinical studies has been implemented in the US and in EU [9, 11-13]. In addition, an ICH guidance addresses important issues such as: when to initiate a paediatric programme, the timing of the initiation of paediatric clinical studies, the types of paediatric clinical studies to be executed, the ethics of paediatric clinical investigations and the age ranges to be studied. The paediatric age ranges are commonly categorized as in terms of neonates (birth to 1 month), infant (1 month to 2 years), children (2 to 12 years) and adolescents (12 years to <16 years in the US or <18 years in the EU) [10].

Model-informed drug development in special populations

The diversity of special populations requires the performance of dedicated clinical studies during drug development. The execution of these studies is not easy due to many ethical and practical constraints which may lead to underpowering of a study to detect potential safety and efficacy signals. The challenge becomes how to harness the limited data to drive an informed decision-making process. In this perspective, the switch to model-informed drug development becomes a necessity.

Model-informed drug development uses modelling and simulation to improve knowledge management and decision-making in drug development [38-40]. The hallmarks of model-informed drug development are the "learn and confirm" cycles where the learning phase involves utilisation of *prior* knowledge and assumptions to construct an appropriate model that aims to quantitatively address questions; while the confirming phase corroborates the predictions from the learning phase so that the model can be further refined and updated [38, 41, 42]. In this context, modelling and simulation involves the use of i) PK-PD, disease and placebo models, ii) meta-analysis of drug and competitor data, iii) design consideration and trial execution models, iv) data analytical models, v) quantitative decision criteria and vi) trial performance metrics [38].

Although model-informed drug development starts before the compound is selected for pre-clinical investigation, in this manuscript the focus is on the use of this paradigm to improve clinical drug development in special populations. An overview of the components of model-informed drug development applied to special populations is illustrated in Figure 1.1. Model-informed drug development in special population starts with the use of model-based (scaling) approaches in combination with *priors* aiming to optimise the design of the first clinical study in special populations and ends with the use of analytical models that will aid in as justification of the drug label. Other aspects of model-informed drug development components, such meta-analysis of drug and competitor data, are of less applicability for dose labelling in special populations as drug development in these populations is often driven by regulatory requirements and less by internal company decision.

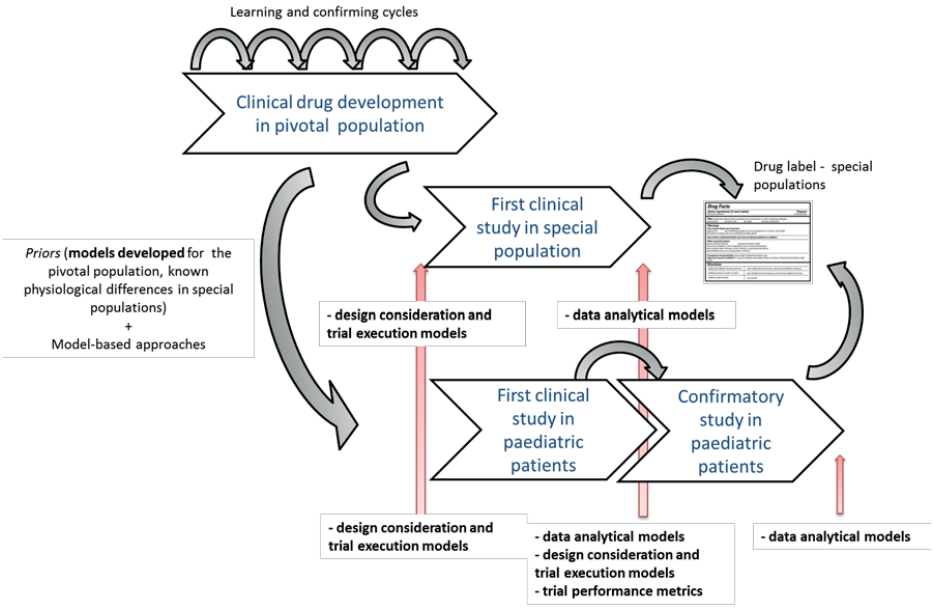

Figure 1.1 Application of model-informed drug development in special populations.
The grey arrows indicate the learning and confirming cycles; the bold texts are the components of that can be applied to special populations.

In special populations, other than children, establishing safe and effective dosing mostly requires the execution of one small dedicated study while in paediatric patients, establishing safe and effective dosing requires the execution of at least two clinical studies: one small dedicated study and a subsequent confirmatory study. In both cases, for ethical and practical reasons establishing safe and effective dosing relies on a very small amount of clinical data. In this respect, it becomes crucial that prior knowledge is used to optimise the design in order to increase the chances of gathering informative data and to empower the analysis of the study results by diminishing the uncertainty in the parameter estimates [43, 44].

The model-based (scaling) approaches utilise data and/models developed using data from the pivotal study population and *prior* knowledge on the expected physiological differences that may impact the PK and/or the PK-PD relationship in the target special population. In general, these model-based approaches are useful for optimising the design of the clinical studies (e.g., dose, number of patients and PK sampling scheme). The importance of leveraging *prior* knowledge for the optimisation of the design of the first clinical study in children has been nicely demonstrated by Jadhav [43, 44]. Currently, a challenge in the use of model-informed drug development in special populations relies on the simultaneous applicability of model-based (scaling) approaches for prediction and optimisation of the design of the first clinical study in special populations and; on the integration of the model-based approaches used for predictions with the data analytical models used for evaluation of the results of the clinical studies.

Traditional model-based approaches

Traditionally two types of model-based approaches are used for prediction of (variation in) the PK in special populations: compartmental PK models and PBPK models.

Compartmental pharmacokinetic models

Compartmental PK models are models that utilise mathematical functions to describe drug concentration in the body as a function of time. The compartments can be arranged in series or parallel to each other and do not have a physiological basis. Therefore, compartmental PK models are referred to as empirical models. In the compartmental PK models the number and the arrangement of the compartments is mainly driven by the availability and description of the data (i.e. data-driven approach) [45-47].

Although the various compartments typically do not have a physiological meaning, useful PK parameters can be derived, which can be used for prediction of the time course of drug concentration under different physiological conditions/populations [45, 46]. The compartmental PK models become even more valuable when these are incorporated into an appropriate statistical framework that allows estimation of fixed (i.e., PK parameter) and random effects (i.e., variability) parameters. Hence, compartmental PK models can be used in combination with a non-linear mixed effects model for description of the variation in the individual plasma concentration time profiles. This is important as the variability in drug disposition between subjects can be substantial [48-50]. Also, this statistical framework allows application of optimal design and data analysis techniques [51-53].

In these so called "population PK models", two levels of random effects can be estimated: one that accounts for inter-individual and a second one that accounts for intra-individual variability. In particular, the inter-individual variability provides the basis for understanding differences in the PK between subjects through the identification of covariates [48-50, 54]. The ways in which covariates are incorporated into models, depend on the type of the covariate. In theory, covariates can be continuous, categorical or dichotomous variables. For continuous covariates, linear, power or exponential relationships are generally applied whereas for categorical or dichotomous covariates, additive, fractional change or exponential relationships are applied as shown in Table 1.3 [54].

Table 1.3 Mathematical equations for incorporation of covariates into the model using clearance as an example of PK parameter, age as an example of continuous covariate and sex as an example of categorical covariate

Covariate type	Relationship	Equation
Continuous	Linear	$CL = \theta_1 + \theta_2 \cdot Age$
	Power	$CL = \theta_1 \cdot (Age)^{\theta_2}$
	Exponential	$CL = \theta_1 \cdot \exp(\theta_2 \cdot Age)$
Categorical	Additive	$CL = \theta_1 + \theta_2 \cdot Sex$
	Fractional	$CL = \theta_1 \cdot (1 + \theta_2 \cdot Sex)$
	Exponential	$CL = \theta_1 \cdot \exp(\theta_2 \cdot Sex)$

Θ are the estimated model parameters; male is coded as 0 and female as 1

The data-driven approach used when incorporating covariates into the models hampers extrapolation beyond the observed ranges. As a result, identification of covariates in regular populations cannot be used to predict variation in the PK of special populations, without assumptions on the relationship between the values of the covariates and physiological functions. In this respect allometric equations are commonly used in combination with population PK models.

Allometric scaling principles are based on the concept that mass (i.e., size) is the prime determinant of variation in physiological function [55] and typically uses an allometric equation of the form

$$Y = Y_0 \cdot \left(\frac{M}{M_0} \right)^b \qquad \text{Equation 1.1}$$

where M is the mass of the organism, M_0 is the mass of a typical subject, b is the power scaling exponent, Y is a biological variable and Y_0 is the value of a biological variable in a typical subject. When predicting the PK in children, allometric scaling has been applied to predict clearance and volume of distribution as displayed in Equation 1.2 [56].

$$CL_{children} = CL_{adults} \cdot \left(\frac{W_{children}}{W_{adults}} \right)^{0.75}$$

$$V_{children} = V_{adults} \cdot \left(\frac{W_{children}}{W_{adults}} \right)^{1} \qquad \text{Equation 1.2}$$

where $CL_{children}$ and $V_{children}$ are the clearance and the volume of distribution in children; CL_{adults} and V_{adult} is the average clearance in adults; W_{adults} is the average body weight in adults and W_{child} is the body weight in children. For other PK parameters of which the physiological determinants are less clear (e.g. inter-compartmental clearance and/or absorption parameters), it is unknown how the principles of allometric scaling can be applied. Therefore, allometric scaling alone often does not suffice for prediction of concentration time profiles using a population PK model [57].

For prediction of clearance as a basis to understand differences in elimination between adults and children, allometric scaling has been applied with reasonable accuracy from adults to children >5 years [58]. However, especially in children ≤5 years, the accuracy of allometric scaling using the 0.75 power exponent has been widely debated. Here, it has been proposed that for every drug a unique allometric exponent should be established based on (a subset of) paediatric data [59, 60]. Although descriptive, this approach has been shown suitable for description of the data and dosing recommendations in clinical practice.

Alternatively, it has been hypothesized that inaccuracy of clearance predictions using the 0.75 power exponent in children ≤5 years is due to developmental changes that are more prominently present in younger children and sometimes by (patho-)physiological variation and/or organ function affecting the elimination of the drug (Equation 1.3) [61, 62]. In this situation, the use of the following equation has been proposed

$$CL_{children} = CL_{adults} \cdot \left(\frac{Weight_{children}}{Weight_{adults}} \right)^{0.75} \cdot MF \cdot OF \qquad \text{Equation 1.3}$$

in which the allometric term $(Weight_{children}/Weight_{adults})^{0.75}$ accounts for the effect of size, MF is the maturation function representing the ontogeny of the enzyme activity defined based on paediatric data from a prototype compound with similar elimination route and OF is a constant factor to

account for organ function and/disease which is often unknown thereby limiting its applicability. Organ function is most often applied in the case of renal elimination where it is standardized to creatinine clearance values in the reference population [61-65].

In summary, scaling of clearance from adults to young children requires either the use of one size descriptor, e.g. body weight, with an adapted exponent or the use of additional descriptors, i.e. age and organ function. In both cases, the applicability of these approaches is reduced as the additional descriptors are drug-specific which complicates the extrapolation beyond the age and body-weight ranges that have actually been studied. Such additional descriptors are likely to be different between drugs which differ in elimination pathway, liver perfusion and cellular uptake [66]. In addition, for the other PK model parameters, such as volume of distribution and half-life, the scaling from adults to young children remains unknown, thereby hampering the prediction of concentration time profiles. Similarly, it remains unknown how to scale PK from pivotal study population to disease patients using an empirical covariate model.

Clearly, the empirical properties of compartmental PK models are less well-suited for scaling between different populations as it relies on the availability of PK data and ignores the underlying physiological processes. In this respect, better understanding of the physiological determinants of PK in special populations and how to reflect those physiological changes into mathematical functions provides the basis for future predictions.

Physiologically-based pharmacokinetic models

A PBPK model is also a compartmental model, but differs from the classical population PK models in that the compartments are usually representative for (grouped) organs and/or tissues with model parameters being a reflection of physiological parameters, such as organ volumes and blood flows [46, 47]. The compartments in PBPK models are arranged and interconnected by the circulation based on anatomical/physiological considerations and described in a mathematical framework in order to predict the disposition of the drug in the body [46, 67, 68]. To this end, the PBPK model strives to provide for a physiological foundation by which drug-specific along with system-specific parameters can be used to predict the time course of drug concentrations in the different tissues/organs, including plasma.

In the PBPK model as illustrated in Figure 1.2, all organs/tissues compartments are connected in parallel between the arterial and venous blood flows. In each compartment, mass balance equations are developed to describe the fate of the drug within the compartment. These equations are combined in a system of interdependent differential equations and parameterized in terms of system-specific and drug-specific parameters. In the compartmental structure, system-specific properties are the volumes of tissues and organs the expression and function of transporters and metabolising enzymes. The drug-specific properties are, for example, the molecular weight, the lipophilicity, the partition and permeability across pertinent barriers, , and the affinities to specific transporters and drug metabolising enzymes [46, 47, 67-69] .

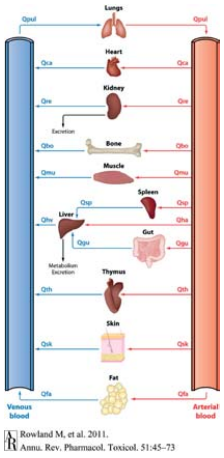

Figure 1.2 Schematic representation of a PBPK model.
Q refers to blood flow: to the lungs (Qpul), the heart (Qca), the kidneys (Qre), the bones (Qbo), the muscles (Qmu), the spleen (Qsp), the liver (Qha), the hepatic vein (Qhv), the gut (Qgu), the thymus (Qth), the skin (Qsk), and the fat (Qfa). Reproduced from Rowland et al 69

The physiological basis of the PBPK models enables prediction of PK in special populations by solely considering the known changes in the values of the system-specific parameters [69]. Using this approach, PBPK models have been successfully applied for prediction of the changes in PK as result of genetic factors [70], hepatic impairment [71, 72], renal impairment [73, 74] and age [75, 76]. Prediction of the inter-individual variability is also possible when using PBPK. There, a virtual population is defined by using demographic databases containing individual information on age, weight, height, gender and race. These demographics are then used to calculate system-specific parameters by means of anthropometric equations. This, however, often needs the inclusion of user-defined information on the inter-individual variability to account for all the variation observed [75, 77]. The downside of this practice is that it is not always possible to account for all the correlation between system-specific parameters as some of these correlations may not be known. As a result, over-estimation of the variability may be observed.

When using a PBPK model, predictions of the time course of PK in the different tissues/organs are used to derive PK parameters as outlined below:

Absorption upon oral administration

The prediction of the rate and extent of intestinal absorption depends on various system-specific properties such as (i) the volume and perfusion, the radius, length, the effective surface area and the pH of the gastro-intestinal tract; (ii) the gastric emptying time; (iii) the small intestinal transit time; (iv) the passive permeability of the intestinal epithelium; (v) the expression and function of influx and efflux active transporters and; (vi) the expression and function of metabolising enzymes in the intestines. In addition various drug-specific properties affect the absorption such as solubility, pK_a, volume/size of the drug and the drug affinity to specific transporters and drug metabolising enzymes [78, 79].

One of the first absorption models incorporated into PBPK is the compartmental absorption and transit (CAT) model where the small intestine is described as a series of seven compartments *plus*

two compartments corresponding to the stomach and colon [80]. The second model is the advanced dissolution absorption and metabolism (ADAM) model, which is based on the CAT model but contains a different dissolution model and expressions to describe distribution and the interaction with cytochrome P450 enzymes and saturable efflux transport (e.g. P-gp, MRP2 and BCRP) in the gastro-intestinal tract [81-83]. More recently, a third absorption model has been developed which includes a series of compartments representing the anatomical parts of the gastro-intestinal tract, such as the gastro-intestinal-sections stomach, duodenum, upper and lower jejunum, upper and lower ileum, caecum, colon ascendens, transcendent and descendens, sigmoid and rectum [84, 85].

Distribution

The distribution of a drug in the body reflects its distribution into different tissues/organs which are consequence of system and drug. The drug-specific properties are the binding affinities to plasma proteins and red blood cells, which in concert determine the red blood cell over plasma concentration ratio whereas the system-specific properties are blood flow rate, volume and composition of the organ and the permeation from the vascular space, including protein binding, transporters and partitioning between blood plasma and organ tissue. The calculation of organ-plasma partition coefficients is dependent on tissue composition in terms of its fractional content of water, lipids, and proteins with physicochemical properties of the substance (mainly lipophilicity) [86-95]. The volume of distribution at steady state (V_{ss}) can be calculated as shown in Equation 1.4 [96].

$$V_{ss} = V_{plasma} + V_e \cdot E/P + \sum_{i=1}^{n} k_{p_i} \cdot V_{tissue_i} \qquad \text{Equation 1.4}$$

where V_{plasma} is the volume in plasma, V_e is the volume in the erythrocyte, E/P is the erythrocyte-to-plasma coefficient, $k_{p,i}$ is the organ-plasma partition coefficients and $V_{tissue,i}$ is the physical volume of the i^{th} out of n organs/tissues

The level of detail in the model structure can vary significantly between PBPK models in terms of number of tissue/organ compartments but also the number of compartments within tissues/organs leading to very complex models. In practice very often these complex models can be reduced by lumping tissues with similar properties in a single compartment while maintaining separate compartments for tissues/organs with distinct properties, such as the liver compartment [97]. The distribution into each compartment is then described using blood flow limitation where equilibrium is instantaneous and determined by blood flow rates. Alternatively, as for example in organs protected by efflux transporters, the distribution models are assumed permeation limited [67, 68].

Clearance

Within the context of PBPK, different models for the prediction of clearance have been proposed. This is important since in mechanistic terms the value of the clearance is influenced by various physiological processes including perfusion, binding, cellular uptake and intrinsic clearance. In return, the physiological determinants of the drug clearance are known to change due to disease, growth and/or developmental changes and therefore provide a mechanistic basis for the prediction of clearance under specific (patho)physiological conditions for the prediction of the first dose. The most well-known physiological clearance models are i) the “well stirred model”, ii) the “parallel tube model” and iii) the dispersion model [98-100]. The well-stirred model assumes that the drug undergoes infinite mixing as soon as it enters the organ, whereas the parallel-tube model assumes that the drug

travels undispersed trough the organ. Finally, the dispersion model contains a parameter (the dispersion number) that quantifies the axial spreading of a drug as it passes along the liver length. Previous findings have shown contradictory results regarding the predictive power of these three models [101-104]. However, in most cases the difference among models was small and considered irrelevant for small molecules. Therefore, the use of the well-stirred models is recommended because of its mathematical simplicity [101, 102].

In summary, PBPK models are a powerful tool for the prediction the time course of drug concentration in special populations. The prediction of the associated inter-individual variability is, however, not yet optimal as it often requires inclusion of a user-defined inter-individual variability to the system-specific parameters. Also, the complexity of the PBPK models makes it difficult to use this approach in combination with non-linear mixed effect models that allows application of optimal design and population data analysis techniques.

Semi-physiological pharmacokinetic models

The application of PBPK models further underlines that PK models that are built upon physiological principles are of large importance for accurate prediction of PK in special populations. However, an important question that remains is how to integrate PBPK often applied for predictions with the population PK models often applied for optimisation of the design and evaluation of the data in the first clinical study in special populations.

Prediction of the inter-individual variability in drug concentration is crucial for optimal design of the first clinical studies in special populations (including optimisation of PK sampling strategy). As abovementioned, PBPK model predictions can under- or over-predict the inter-individual variability. For under-prediction, an insufficient number of patients might be recruited and for over-prediction, an unnecessary number of patients might be recruited. Both situations are undesirable especially from an ethical point of view. In addition, the complex structure of the models limits the application of optimal design techniques. One of the most often applied techniques (i.e., clinical trial simulations) requires the generated data to be back-fitted into the model so that the precision of the model parameter estimates can be determined. Such handling is very limited when using PBPK as the complexity of the model makes it impossible to be used for fit purposes unless the majority of the fixed and random-effect parameters are fixed.

On the other hand, population PK models are embedded in a rigorous statistical framework to account for estimation of fixed and random effects based on individual drug concentration time profiles. Although the population PK models are empirical, the compartmental structure allows the creation of a mechanistic foundation based on physiological principles. This foundation allows key physiological parameters to be incorporated into a framework that has the optimal properties to overcome issues related to the use of optimal design techniques. Such framework can also provide the solution for integrating PBPK models used for prediction with the population PK models used for evaluation of the data. Thereby, this framework ensures that knowledge is not lost in the transition from prediction to data analysis techniques and, at the same time, increases the power of the data analysis techniques which is often based on a limited amount of data.

Hence, the use of semi-physiological PK models is proposed as a framework. When using the semi-physiological PK models, one would encounter a situation where the optimal design and data analysis techniques can be maximised and where the physiological foundation to maintain predictive power is

preserved. The semi-physiological PK model interfaces (i) a population PK model that mechanistically considers protein binding (Figure 1.3) and; (ii) physiological equations, including key system-specific parameters, for the description of the changes in the absorption, distribution and clearance (as shown hereafter) that could be result of changes in the physiological status.

Absorption

For prediction of the bioavailability, the semi-physiological framework considers the a similar approach as applied by Johnson *et al* [75] where first-pass and gut wall metabolism are the determinants of the bioavailability (F_{obs}) as shown in Equation 1.5.

$$F_{obs} = f_a \cdot f_{gut} \cdot f_H \qquad \text{Equation 1.5}$$

where f_a is the net fraction of dose absorbed, f_{gut} is the fraction escaping gut wall metabolism and f_H is the fraction escaping the hepatic first pass effect. These can be calculated based on well-stirred principles as shown in Equation 1.6.

$$f_H = \frac{Q_H}{Q_H + \left(fu \cdot CL_{int\,rinsic}\right)/RB}$$

$$f_{gut} = \frac{Q_{gut}}{Q_{gut} + fu_{gut} \cdot CL_{int\,rinsic_{gut}}} \qquad \text{Equation 1.6}$$

where , $CL_{intrinsic}$ is the intrinsic clearance in the liver and considers liver enzyme activity and liver weight, Q_H is the liver blood flow, fu is the free fraction in plasma, RB is the blood-plasma ratio, $CL_{intrinsic,gut}$ is the intrinsic clearance in the gut, fu_{gut} is the free fraction of the drug at the enzyme site and Q_{gut} is a hybrid parameter reflecting drug absorption rate from the gut lumen, drug transfer to the enterocyte blood supply and volume of the enterocytes[75].

Distribution

The volume of distribution at steady state can be also described as in Equation 1.7[105].

$$V_{ss} = V_{plasma} + V_{water} \cdot \left(\frac{fu}{f_{tissue}}\right) \qquad \text{Equation 1.7}$$

where V_{plasma} is the volume of plasma; V_{water} is the is the aqueous volume outside of the plasma into which the drug distributes and; f_{tissue} is the free fraction in tissue. V_{plasma} and V_{water} are calculated by using anthropometric equations [106].

Clearance

The semi-physiological framework should separately consider hepatic and renal clearance. For the hepatic clearance, the well-stirred model is considered as shown in Equation 1.8[107].

$$CL_{hepatic} = \frac{Q_H \cdot fu \cdot CL_{int\,rinsic}}{Q_H + (fu \cdot CL_{int\,rinsic})/RB} \qquad \text{Equation 1.8}$$

where $CL_{hepatic}$ is the hepatic clearance and Q_H is the liver blood flow. If necessary, this model could be extended to accommodate specific uptake and efflux transporters.

The renal clearance model considers the contribution of glomerular function rate, tubular secretion and re-absorption as displayed in Equation 1.9 [96].

$$CL_R = Q_R \left[\frac{fu_b \cdot GFR}{Q_R} + \left(1 - \frac{fu_b \cdot GFR}{Q_R}\right) \cdot \left(\frac{Q_R \cdot fu_b \cdot CLu_{sec,int}}{Q_R + fu_b \cdot CLu_{sec,int}} \right) \right] \cdot \left(1 - F_{Re-abs}\right)$$ Equation 1.9

where CL_R is the renal clearance, Q_R is the renal blood flow, fu_B is the free fraction in blood, CLu_{sec} is the intrinsic clearance related to the active secretion and $F_{Re\text{-}abs}$ is the fraction reabsorbed.

The semi-physiological population models are designed as a physiological fit-for-purpose model, implying that the features included in the model should be decided on a case-by-case basis depending on its relevance for allowing the model to suit for its purpose. As a result, the complexity of the model is reduced but the predictive power is retained. Figure 1.3 illustrates an example of a semi-physiological population model where the PK of the compound can be characterised using a two-compartment model and the volume of central compartment is not equal to plasma volume. The physiological equations applied to the PK parameters are as described above.

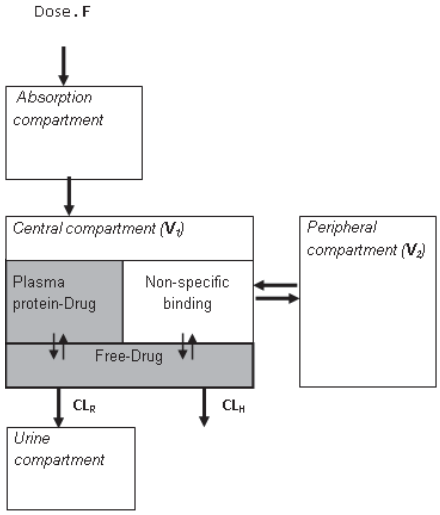

Figure 1.3 Schematic representation of a semi-physiological population model for a two drug with a two-compartment kinetics. F, CL_R and CL_H represent total bioavailability, renal and liver clearance. These parameters and volume of distribution at steady state (V_1 + V_2) are derived using physiological equations

Conclusions

The diversity of special populations and their potential differences in drug response requires the performance of dedicated clinical studies in drug development. The execution of these studies is not easy due to many ethical and practical barriers, which makes it a challenge to transform the limited data that can be collected into critical knowledge to drive safe and effective dosing. In this perspective, the switch from a less evidence-based to a more model-informed drug development becomes a necessity. Particularly, the use of model-based approaches is necessary i) to leverage knowledge for design of a study in order to increase the chances of gathering informative data and ii) to empower the data analysis of the study results. Traditionally used model-based approaches for

prediction of (variation in) the PK in special populations are: compartmental PK models and PBPK models.

The compartmental PK models are a powerful basis for the application of optimal design and data analysis techniques, but their empirical properties hamper their use for predictions of the PK in special populations. The opposite holds true for PBPK models which are powerful for predictions of the PK but less suitable for the application of optimal design and evaluation techniques. Hence, a third type of compartmental model called semi-physiological PK models is proposed. The proposed framework is constituted of a "physiological fit for purpose" model which combines the physiological equations for prediction of the PK in special populations with the statistical basis of the population PK models. To this end, the semi-physiological PK models preserve the physiological foundation to maintain predictive power and maximise the application of optimal design and data analysis techniques.

References

1. Weilert,D.K. Special Population Studies (Healthy Patients Studies) in *Clinical Trials Handbook* 531-562 (Willey, 2009).

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Ethnic Factors in the Acceptability of Foreign Clinical Data E5 (CPMP/ICH/289/95). 1998. 22-12-2014.

3. U.S.Department of Health and Human Services *et al.* Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials. 2005. 22-12-2015.

4. Committee for Medical Products for Human Use. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function(CPMP/EWP/2339/02). 2005. 22-12-2014.

5. U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, & Center for Biologics Evaluation and Research. Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. 2003. 22-12-2014.

6. Committee for Medicinal Products for Human use. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Decreased Renal Function (EMA/83874/2014). 2014. 22-12-2014.

7. U.S.Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research. Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling . 2010. 22-12-2014.

8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Studies in Support of Special Populations: Geriatrics E7. 1993. 22-12-2014.

9. Committee for Medicinal Products for Human use. Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (EMEA/CHMP/EWP/147013/2004). 2007. 22-12-2014.

10. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Clinical Investigation of Medicinal Products in Pediatric Population E11 . 2000.

11. Committee for Medicinal Products for Human use. Guideline on the Investigation of Medicinal Productes in the Term and Preterm Neonate (EMEA/267484/2007) . 2007. 22-12-2014.

12. U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, & Center for Biologics Evaluation and Research. Guidance for Industry: Exposure-Response Relationships - Study, Design, Data Analysis, and Regulatory Applications. 2003. 22-12-2014.

13. U.S.Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research. Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products . 2014. 22-12-2014.

14. Huang,S.M. & Temple,R. Is this the drug or dose for you? Impact and consideration of ethnic factors in global drug development, regulatory review, and clinical practice. *Clin. Pharmacol. Ther.* 84, 287-294 (2008).

15. Yasuda,S.U., Zhang,L., & Huang,S.M. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. *Clin. Pharmacol. Ther.* 84, 417-423 (2008).

16. Cawello,W. *et al.* Pharmacokinetics, safety and tolerability of rotigotine transdermal patch in healthy Japanese and Caucasian subjects. *Clin. Drug Investig.* 34, 95-105 (2014).

17. Allen,A., Bal,J., Cheesbrough,A., Hamilton,M., & Kempsford,R. Pharmacokinetics and pharmacodynamics of intravenous and inhaled fluticasone furoate in healthy Caucasian and East Asian subjects. *Br. J. Clin. Pharmacol.* 77, 808-820 (2014).

18. Hamberg,A.K. *et al.* A pharmacometric model describing the relationship between warfarin dose and INR response with respect to variations in CYP2C9, VKORC1, and age. *Clin. Pharmacol. Ther.* 87, 727-734 (2010).

19. Schelleman,H., Limdi,N.A., & Kimmel,S.E. Ethnic differences in warfarin maintenance dose requirement and its relationship with genetics. *Pharmacogenomics.* 9, 1331-1346 (2008).

20. Ingelman-Sundberg,M. Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy. *J. Intern. Med.* 250, 186-200 (2001).

21. Iitsuka,H. *et al.* Pharmacokinetics of mirabegron, a beta3-adrenoceptor agonist for treatment of overactive bladder, in healthy Japanese male subjects: results from single- and multiple-dose studies. *Clin. Drug Investig.* 34, 27-35 (2014).

22. Poggesi,I. *et al.* Pharmacokinetics in special populations. *Drug Metab Rev.* 41, 422-454 (2009).

23. Pugh,R.N., Murray-Lyon,I.M., Dawson,J.L., Pietroni,M.C., & Williams,R. Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.* 60, 646-649 (1973).

24. Nolin,T.D., Naud,J., Leblond,F.A., & Pichette,V. Emerging Evidence of the Impact of Kidney Disease on Drug Metabolism and Transport. *Clin Pharmacol Ther* 83, 898-903 (2008).

25. Levey,A.S. *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med.* 130, 461-470 (1999).

26. Cockcroft,D.W. & Gault,M.H. Prediction of creatinine clearance from serum creatinine. *Nephron* 16, 31-41 (1976).

27. Department of Economic and Social Affairs Population Division of the United Nations. World Population Ageing 2013. ST/ESA/SER.A/348. 2013. 22-12-2014.

28. European Medicines Agency. EMA geriatric medicines strategy (EMA/CHMP/137793/2011). 2011. 22-12-2014.

29. Shi,S. & Klotz,U. Age-related changes in pharmacokinetics. *Curr. Drug Metab* 12, 601-610 (2011).

30. Hubbard,R.E., O'Mahony,M.S., & Woodhouse,K.W. Medication prescribing in frail older people. *Eur. J. Clin. Pharmacol.* 69, 319-326 (2013).

31. Bartelink,I.H., Rademaker,C.M., Schobben,A.F., & van den Anker,J.N. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin. Pharmacokinet.* 45, 1077-1097 (2006).

32. Kearns,G.L. *et al.* Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N. Engl. J. Med.* 349, 1157-1167 (2003).

33. European Parliament & Council of the European Union. Medicinal Products for Paediatric Use. REGULATION (EC) No 1901/2006. 2006.

34. European Parliament & Council of the European Union. Medicinal Products for Paediatric Use. REGULATION (EC) No 1902/2006. 2014.

35. One Hundred Eighth Congress of the United States of America. Pediatric Research Equity Act of 2003. S. 650. 2003.

36. One Hundred Tenth Congress of the United States of America. Food and Drug Administration Amendments Act of 2007. H. R. 3580. 2007.

37. One Hundred Twelfth Congress of the United States of America. Food and Drug Administration Safety and Innovation Act. S. 3187. 2012.

38. Lalonde,R.L. *et al.* Model-based drug development. *Clin. Pharmacol. Ther.* 82, 21-32 (2007).

39. Zhang,L., Allerheiligen,S.R., Lalonde,R.L., Stanski,D.R., & Pfister,M. Fostering culture and optimizing organizational structure for implementing model-based drug development. *J. Clin. Pharmacol.* 50, 146S-150S (2010).

40. Milligan,P.A. *et al.* Model-based drug development: a rational approach to efficiently accelerate drug development. *Clin. Pharmacol. Ther.* 93, 502-514 (2013).

41. Sheiner,L.B. & Steimer,J.L. Pharmacokinetic/pharmacodynamic modeling in drug development. *Annu. Rev. Pharmacol. Toxicol.* 40, 67-95 (2000).

42. Sheiner,L.B. Learning versus confirming in clinical drug development. *Clin. Pharmacol. Ther.* 61, 275-291 (1997).

43. Jadhav,P.R., Zhang,J., & Gobburu,J.V. Leveraging prior quantitative knowledge in guiding pediatric drug development: a case study. *Pharm. Stat.* 8, 216-224 (2009).

44. Jadhav,P.R. & Kern,S.E. The need for modeling and simulation to design clinical investigations in children. *J. Clin. Pharmacol.* 50, 121S-129S (2010).

45. Fleishaker,J.C. & Smith,R.B. Compartmental model analysis in pharmacokinetics. *J. Clin. Pharmacol.* 27, 922-926 (1987).

46. Shargel,L. & Yu,A.B.C. Introduction to Biopharmaceutics and Pharmacokinetics in *Applied Biopharmaceutics & Pharmacokinetics* 29-45 (McGraw-Hill, New York, 1999).

47. Nestorov,I. Whole-body physiologically based pharmacokinetic models. *Expert. Opin. Drug Metab Toxicol.* 3, 235-249 (2007).

48. Ette,E.I. & Williams,P.J. Population pharmacokinetics I: background, concepts, and models. *Ann. Pharmacother.* 38, 1702-1706 (2004).

49. Duffull,S.B., Wright,D.F., & Winter,H.R. Interpreting population pharmacokinetic-pharmacodynamic analyses - a clinical viewpoint. *Br. J. Clin. Pharmacol.* 71, 807-814 (2011).

50. Kiang,T.K., Sherwin,C.M., Spigarelli,M.G., & Ensom,M.H. Fundamentals of population pharmacokinetic modelling: modelling and software. *Clin. Pharmacokinet.* 51, 515-525 (2012).

51. Ette,E.I., Williams,P.J., & Lane,J.R. Population pharmacokinetics III: design, analysis, and application of population pharmacokinetic Studies. *Ann. Pharmacother.* 38, 2136-2144 (2004).

52. Aarons,L. & Ogungbenro,K. Optimal design of pharmacokinetic studies. *Basic Clin. Pharmacol. Toxicol.* 106, 250-255 (2010).

53. Ogungbenro,K. & Aarons,L. Design of population pharmacokinetic experiments using prior information. *Xenobiotica* 37, 1311-1330 (2007).

54. Bonate,P.L. Non-linear mixed effect models:theory in *Pharmacokinetics-Pharmacodynamic Modeling and Simulation* 233-304 (Springer, New York, 2011).

55. West,G.B., Brown,J.H., & Enquist,B.J. A general model for the origin of allometric scaling laws in biology. *Science* 276, 122-126 (1997).

56. Anderson,B.J. & Holford,N.H. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu. Rev. Pharmacol. Toxicol.* 48, 303-332 (2008).

57. Mahmood,I. & Goteti,K. Prediction of Drug Concentration-Time Profiles in Children From Adults: An Allometric Approach. *Am. J. Ther.*(2013).

58. Edginton,A.N. & Willmann,S. Physiology-based versus allometric scaling of clearance in children; an eliminating process based comparison. *Paediatr Perinat Drug Ther* 7, 146-153 (2006).

59. Mahmood,I. Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. *Clin. Pharmacokinet.* 53, 327-346 (2014).

60. Knibbe,C.A., Krekels,E.H., & Danhof,M. Advances in paediatric pharmacokinetics. *Expert. Opin. Drug Metab Toxicol.* 7, 1-8 (2011).

61. Holford,N. Dosing in children. *Clin. Pharmacol. Ther.* 87, 367-370 (2010).

62. Tod,M., Jullien,V., & Pons,G. Facilitation of drug evaluation in children by population methods and modelling. *Clin Pharmacokinet.* 47, 231-243 (2008).

63. Rhodin,M.M. *et al.* Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr. Nephrol.* 24, 67-76 (2009).

64. Allegaert,K., Anderson,B.J., van den Anker,J.N., Vanhaesebrouck,S., & de,Z.F. Renal drug clearance in preterm neonates: relation to prenatal growth. *Ther. Drug Monit.* 29, 284-291 (2007).

65. Anderson,B.J., Allegaert,K., van den Anker,J.N., Cossey,V., & Holford,N.H. Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *Br. J. Clin. Pharmacol.* 63, 75-84 (2007).

66. Rowland,M., Benet,L.Z., & Graham,G.G. Clearance concepts in pharmacokinetics. *J. Pharmacokinet. Biopharm.* 1, 123-136 (1973).

67. Nestorov,I. Whole body pharmacokinetic models. *Clin. Pharmacokinet.* 42, 883-908 (2003).

68. Jones,H.M., Mayawala,K., & Poulin,P. Dose selection based on physiologically based pharmacokinetic (PBPK) approaches. *AAPS. J.* 15, 377-387 (2013).

69. Rowland,M., Peck,C., & Tucker,G. Physiologically-based pharmacokinetics in drug development and regulatory science. *Annu. Rev. Pharmacol. Toxicol.* 51, 45-73 (2011).

70. Vieira,M.D. *et al.* PBPK model describes the effects of comedication and genetic polymorphism on systemic exposure of drugs that undergo multiple clearance pathways. *Clin. Pharmacol. Ther.* 95, 550-557 (2014).

71. Johnson,T.N., Boussery,K., Rowland-Yeo,K., Tucker,G.T., & Rostami-Hodjegan,A. A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. *Clin Pharmacokinet.* 49, 189-206 (2010).

72. Edginton,A.N. & Willmann,S. Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. *Clin Pharmacokinet.* 47, 743-752 (2008).

73. Hsu,V. *et al.* Towards quantitation of the effects of renal impairment and probenecid inhibition on kidney uptake and efflux transporters, using physiologically based pharmacokinetic modelling and simulations. *Clin. Pharmacokinet.* 53, 283-293 (2014).

74. Sayama,H., Takubo,H., Komura,H., Kogayu,M., & Iwaki,M. Application of a physiologically based pharmacokinetic model informed by a top-down approach for the prediction of pharmacokinetics in chronic kidney disease patients. *AAPS. J.* 16, 1018-1028 (2014).

75. Johnson,T.N., Rostami-Hodjegan,A., & Tucker,G.T. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin. Pharmacokinet.* 45, 931-956 (2006).

76. Edginton,A.N., Schmitt,W., & Willmann,S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. *Clin. Pharmacokinet.* 45, 1013-1034 (2006).

77. Willmann,S. *et al.* Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. *J. Pharmacokinet. Pharmacodyn.* 34, 401-431 (2007).

78. Agoram,B., Woltosz,W.S., & Bolger,M.B. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. *Adv. Drug Deliv. Rev.* 50 Suppl 1, S41-S67 (2001).

79. Sugano,K. Introduction to computational oral absorption simulation. *Expert. Opin. Drug Metab Toxicol.* 5, 259-293 (2009).

80. Yu,L.X. & Amidon,G.L. A compartmental absorption and transit model for estimating oral drug absorption. *Int. J. Pharm.* 186, 119-125 (1999).

81. Darwich,A.S., Neuhoff,S., Jamei,M., & Rostami-Hodjegan,A. Interplay of metabolism and transport in determining oral drug absorption and gut wall metabolism: a simulation assessment using the "Advanced Dissolution, Absorption, Metabolism (ADAM)" model. *Curr. Drug Metab* 11, 716-729 (2010).

82. Neuhoff,S. *et al.* Application of permeability-limited physiologically-based pharmacokinetic models: part I-digoxin pharmacokinetics incorporating P-glycoprotein-mediated efflux. *J. Pharm. Sci.* 102, 3145-3160 (2013).

83. Neuhoff,S. *et al.* Application of permeability-limited physiologically-based pharmacokinetic models: part II - prediction of P-glycoprotein mediated drug-drug interactions with digoxin. *J. Pharm. Sci.* 102, 3161-3173 (2013).

84. Thelen,K. *et al.* Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part 1: oral solutions. *J. Pharm. Sci.* 100, 5324-5345 (2011).

85. Thelen,K., Coboeken,K., Willmann,S., Dressman,J.B., & Lippert,J. Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part II: extension to describe performance of solid dosage forms. *J. Pharm. Sci.* 101, 1267-1280 (2012).

86. Schmitt,W. General approach for the calculation of tissue to plasma partition coefficients. *Toxicol. In Vitro* 22, 457-467 (2008).

87. Rodgers,T., Leahy,D., & Rowland,M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J. Pharm. Sci.* 94, 1259-1276 (2005).

88. Rodgers,T. & Rowland,M. Mechanistic approaches to volume of distribution predictions: understanding the processes. *Pharm. Res.* 24, 918-933 (2007).

89. Rodgers,T., Leahy,D., & Rowland,M. Tissue distribution of basic drugs: accounting for enantiomeric, compound and regional differences amongst beta-blocking drugs in rat. *J. Pharm. Sci.* 94, 1237-1248 (2005).

90. Rodgers,T. & Rowland,M. Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *J. Pharm. Sci.* 95, 1238-1257 (2006).

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

92. Poulin,P. & Theil,F.P. Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution. *J. Pharm. Sci.* 91, 129-156 (2002).

93. Poulin,P. & Theil,F.P. Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetic models of drug disposition. *J. Pharm. Sci.* 91, 1358-1370 (2002).

94. Poulin,P., Schoenlein,K., & Theil,F.P. Prediction of adipose tissue: plasma partition coefficients for structurally unrelated drugs. *J. Pharm. Sci.* 90, 436-447 (2001).

95. Berezhkovskiy,L.M. Volume of distribution at steady state for a linear pharmacokinetic system with peripheral elimination. *J. Pharm. Sci.* 93, 1628-1640 (2004).

96. Rowland,Y.K., Aarabi,M., Jamei,M., & Rostami-Hodjegan,A. Modeling and predicting drug pharmacokinetics in patients with renal impairment. *Expert. Rev. Clin. Pharmacol.* 4, 261-274 (2011).

97. Nestorov,I.A., Aarons,L.J., Arundel,P.A., & Rowland,M. Lumping of whole-body physiologically based pharmacokinetic models. *J. Pharmacokinet. Biopharm.* 26, 21-46 (1998).

98. Pang,K.S. & Rowland,M. 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. Biopharm.* 5, 625-653 (1977).

99. Roberts,M.S. & Rowland,M. A dispersion model of hepatic elimination: 1. Formulation of the model and bolus considerations. *J. Pharmacokinet. Biopharm.* 14, 227-260 (1986).

100. Roberts,M.S. & Rowland,M. A dispersion model of hepatic elimination: 2. Steady-state considerations--influence of hepatic blood flow, binding within blood, and hepatocellular enzyme activity. *J. Pharmacokinet. Biopharm.* 14, 261-288 (1986).

101. Ito,K. & Houston,J.B. Comparison of the use of liver models for predicting drug clearance using in vitro kinetic data from hepatic microsomes and isolated hepatocytes. *Pharm. Res.* 21, 785-792 (2004).

102. Yamamoto,T., Itoga,H., Kohno,Y., Nagata,K., & Yamazoe,Y. Prediction of oral clearance from in vitro metabolic data using recombinant CYPs: comparison among well-stirred, parallel-tube, distributed and dispersion models. *Xenobiotica* 35, 627-646 (2005).

103. Roberts,M.S. & Rowland,M. Correlation between in-vitro microsomal enzyme activity and whole organ hepatic elimination kinetics: analysis with a dispersion model. *J. Pharm. Pharmacol.* 38, 177-181 (1986).

104. Hallifax,D., Foster,J.A., & Houston,J.B. Prediction of human metabolic clearance from in vitro systems: retrospective analysis and prospective view. *Pharm. Res.* 27, 2150-2161 (2010).

105. Rowland,M. & Tozer,T.N. Distribution in *Clinical Pharmacokinetics* 137-155 (Lippincott Williams & Wilkins, Philadelphia, 1995).

106. Price,P.S. *et al.* Modeling interindividual variation in physiological factors used in PBPK models of humans. *Crit Rev. Toxicol.* 33, 469-503 (2003).

107. Yang,J., Jamei,M., Yeo,K.R., Rostami-Hodjegan,A., & Tucker,G.T. Misuse of the well-stirred model of hepatic drug clearance. *Drug Metab Dispos.* 35, 501-502 (2007).