Chapter 7

Optimisation of first clinical studies in special populations – summary conclusions and perspectives

Introduction

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. To support dose labelling, drug regulators require dedicated clinical studies in special populations. Frequently, these clinical studies in special populations are studies into the pharmacokinetics (PK), of which the results are then be used to extrapolate efficacy and safety data from pivotal study populations into special populations. The conduct and analysis of these clinical PK studies is difficult due to practical and ethical barriers which often lead to small sample sizes and sparse data, and is further complicated by the inherent heterogeneity of these patient groups. In this thesis, the concept of semi-physiological PK modelling is introduced as an alternative approach to obtain the critical knowledge needed for optimisation of the design and the analysis of the clinical studies in special populations.

In the context of drug development, the application of model-based approaches is widely used for the prediction of (variation) in PK. Traditionally used model-based approaches include compartmental PK modelling and physiologically-based PK (PBPK) modelling. These modelling approaches have distinctly different strengths and weaknesses. Table 7.1 summarises the pertinent properties of these approaches.

Table 7.1 Properties, advantages and limitations of compartmental and PBPK models for prediction of variation in PK in children and other special populations

Compartmental PK models	Physiologically-based PK models
Data-driven descriptive approach	Knowledge-driven, mechanistic approach
Description of inter-individual variation on the basis of co-variates with limited possibilities for extrapolation beyond the observed range	Physiological approach to describe and explain variation enabling extrapolation outside observed range
Statistical basis enables the application of optimal design and population data-analysis techniques	Model complexity limits the application for optimal design and population-analysis techniques
Has been used successfully in combination with allometric scaling to predict exposure in healthy children (>5 years) to account for differences in size [1,2].	Can in principle be used to predict exposure in children of all ages [3–8]
Has not been evaluated in combination with allometric scaling to predict exposure in healthy children (<5	

years) to account for differences in size and maturation.	
Cannot be applied for the prediction of the variation in exposure in special populations other than children	Can be applied for the prediction of exposure in special populations in general if knowledge on the physiological differences is available [9–13]

Briefly, compartmental PK modelling is a data-driven approach with a sound statistical basis for determination of the optimal design of a study and for analysis of the data, but without a mechanistic basis for extrapolation outside the ranges of physiological function that have actually been studied. This hampers the prediction of PK in the various special populations without taking into consideration descriptive scaling factors. A frequently applied method for prediction of clearance is the allometric scaling, but its application seems to be limited to children [1,2]. On the other hand, PBPK modelling is a knowledge-driven approach with a physiological basis that enables prediction of the PK outside the ranges of physiological function that have been studied. The increased complexity of these models, however, limits the use of advanced optimal design and data-analysis techniques. The utility of PBPK concepts for the prediction of changes in the PK has been demonstrated in numerous studies in special populations[3–13]. In principle, PBPK modelling is applicable to every special population as long as quantitative information is available on how genetic, (patho-) physiological and/or environmental factors impact the physiology.

The intrinsic properties of the traditionally used model-based approaches have led to the current practice where PBPK models are used for prediction and compartmental PK models for data analysis [14,15]. One of the pitfalls of this practice is that PBPK modelling concepts are rarely used for optimisation of the design of clinical studies. Moreover information acquired by using PBPK models is disregarded when analysing the data of a clinical study with a compartmental PK model. As a result, physiological insights are not used when commencing with clinical drug development in special populations. An approach that integrates PBPK and compartmental PK modelling concepts is of considerable interest for clinical studies in special populations, to optimise the “learn and confirm” cycles of model-informed drug development.

In this thesis we aimed to develop a semi-physiological PK framework that combines properties of PBPK models with the statistical basis of the compartmental PK models. This framework was designed (i) to preserve the physiological foundation in order to maintain the predictive power and to allow prediction of the PK to various special populations and; (ii) to diminish model complexity in order to maximise the possibilities for the application of advanced optimal design and population data-analysis techniques.

Section 2: development of a semi-physiological pharmacokinetic framework

One of the most important objectives of developing a semi-physiological PK framework is the accurate prediction of clearance as this PK parameter is a major determinant of the changes in drug plasma concentration driving the efficacy and safety. In order to predict clearance, traditionally used approaches are allometric scaling and PBPK modelling. The research described in **section 2** of this thesis aimed i) to investigate the interchangeability and ii) to compare the accuracies of the allometric scaling and the PBPK approaches for the prediction of clearance. Focus was on the

prediction of clearance in children since allometric scaling principles are widely applied in this population. Also, an alternative mechanistic approach for the prediction of clearance was proposed and evaluated for accuracy.

Traditionally used approaches

Allometric scaling in combination with maturation functions is a relatively straightforward approach for the prediction of changes in the PK on the basis of a compartmental PK model. This approach has been introduced to predict the clearance in children when the processes involved in the elimination route are known to undergo maturation. The maturation functions are typically derived based on paediatric data from a prototype compound with similar elimination route, whereby it is implicitly assumed that the maturation functions solely represent the ontogeny of the liver enzyme activity. It remains to be established how well these hypothesised pathway-specific maturation functions can be applied across different compounds sharing similar elimination pathways.

In **chapter 3**, PBPK and allometric scaling in combination with a maturation function were compared in order (i) to provide insight into their interchangeability and; (ii) to provide insight into the physiological meaning of the maturation functions. Interchangeability was assessed using hypothetical compounds with similar elimination pathways but otherwise different PK properties. Maturation functions derived on the basis of clinical PK data from paracetamol and morphine as paradigm drugs were used. These drugs were of interest because of the differences in the extraction ratio, while sharing the same route of elimination (glucuronidation). The accuracy of the predictions using PBPK modelling for paracetamol and morphine was evaluated using the estimates of developed compartmental PK models in combination with allometric scaling as a reference.

The predictions of clearance using allometric scaling and PBPK were shown to be comparable in children > 1 year. In children < 1 year, predictions were only comparable for hypothetical compounds with an extraction ratio and a lipophilicity (log P) that are similar to the corresponding values of the paradigm drug used for derivation of the maturation function. In addition, the maturation functions using the prototype compounds were shown to solely represent ontogeny of the liver enzyme activity for the compound with a low extraction ratio (i.e., paracetamol). Further, predictions of clearance using the PBPK model were accurate for paracetamol but slightly biased for morphine. Predictions of the inter-individual variability were under-estimated by the PBPK models for both compounds and over-estimated by allometric scaling for morphine. Under-estimation of the PBPK prediction is likely to be due to the unknown sources of variability while the over-estimation by allometric scaling suggests that fixing allometric scaling exponents into the model requires the model to compensate for potential biases using random-effects.

In summary, the results of this investigation indicated that interchangeability between PBPK and allometric scaling in combination with maturation function cannot be assumed for the prediction of clearance. Although no conclusions with regard to the superiority of one approach over the other can be derived from this investigation, the application of the allometric scaling approach was shown to be restricted by the drug-specific properties of the selected maturation function. Also, the inadequacy of both model-based approaches to predict inter-individual variability is a potential limitation in the context of the application of optimal design and data analysis . These results re-inforce the need for developing a framework that contains (i) expressions for system-specific properties and; (ii) allows adequate prediction of inter-individual variability.

The "well-stirred model" as an alternative approach

The investigation presented in **chapter 4** aimed to further evaluate the accuracy of allometric scaling in combination with a maturation function for the prediction of clearance in children**.** In this investigation, the maturation functions were derived using *in vitro* data that solely represent the ontogeny of the liver enzyme activity. In addition, the investigation presented in **chapter 4** also aimed to evaluate an alternative mechanistic approach based on the well-stirred model of hepatic clearance to predict clearance in children. The well-stirred model contains specific expressions for system-specific properties and its reduced complexity compared to a PBPK model allows combination with compartmental PK models for more accurate prediction of the inter-individual variability.

For this investigation, a literature database was compiled including 203 clearance values of 18 compounds derived from subjects in the age range from term-neonates to adults. All selected compounds were CYP3A-metabolised compounds since future application of the proposed semi-physiological PK framework was based on CYP3A-metabolised compounds (**section 3**).

CYP3A metabolism is complex due to the involvement of at least three isoforms (i.e., CYP3A4, CYP3A5, and CYP3A7) each with different substrate-specificities and ontogenies. This complexity probably explains the wide variation in the information on CYP3A-ontogeny. In this investigation, three maturation functions, previously reported to adequately predict clearance in children were evaluated [4,16,17].

In children >3 months, both allometric scaling in combination with maturation function and the well-stirred model were shown to predict clearance in paediatric patients reasonably well. Some bias was observed in children in the age range between 6 months and 5 years where the CYP3A4 activity was not considered to be above adult levels in the maturation function. In children <3 months: (i) biased predictions were obtained when allometric scaling was used independent of the maturation function that was applied; (ii) unbiased predictions were observed when the well-stirred model was used in combination with maturation functions representing the overall CYP3A activity (yet with high individual percentage errors and relatively low 2-fold percentage error) and; (iii) biased predictions were observed when the well-stirred model was used in combination with a maturation function solely representing the CYP3A4 activity. A sensitivity analysis using various maturation functions indicated that the activity of CYP3A7 is only relevant in children <3 months and that in term-neonates it accounts for up to 86% of the overall CYP3A metabolism.

In summary, the results of this investigation showed the inadequacy of allometric scaling in combination with maturation function(s) to predict clearance in paediatric patients where the system is not yet fully matured. These results can be explained by the results presented in **chapter 3** which indicated that maturation functions were not always solely representative for the ontogeny of the liver enzyme activity. On the other hand, the well-stirred model of hepatic clearance was shown to be adequate for the prediction of clearance in paediatric patients. Yet, the high individual percentage errors and relatively low 2-fold percentage error of the well-stirred model underlined the need for considering inter-individual variability in the predictions.

Section 3: applications of the semi-physiological pharmacokinetic framework

Although clearance is often the driving PK parameter for efficacy, predictions of full PK profiles are required for application of optimal design and data analysis techniques. Hence, a semi-physiological PK framework is proposed. The research described in this section aimed at the application of the semi-physiological PK framework by illustrating its value in predicting the PK in a variety of special populations, i.e., hepatic and renal impaired patients and paediatric patients.

The semi-physiological PK framework was designed to integrate the physiological basis of the PBPK models with statistical aspects of the compartmental PK models. The proposed semi-physiological PK framework interfaces (i) a compartmental PK model that contains expressions to accommodate variation in plasma protein binding as a cause of variation in clearance and volume of distribution and; (ii) physiological equations, such as the well-stirred model of hepatic clearance for the description of the changes in the first-pass effect and clearance. The exact features of the model are decided on a case-by-case basis depending on their relevance for allowing the model to suit for their purpose (i.e., the proposed models are so-called "physiological fit-for-purpose models"). This enables the semi-physiological PK model to accommodate mechanistic functions that capture changes of the key physiological parameters in the target population.

In the semi-physiological PK framework, the inter-individual variability is estimated using two components: one defined by anthropometric equations, which estimate the variability in the key physiological parameters by considering the patient demographics and; a second component defined by estimation of the remaining inter-individual variability (i.e. the variation that cannot be explained by the use of the anthropometric equations). The statistical framework of the compartmental PK models also allows for correlation between parameter estimates to be considered and thereby, to avoid over-prediction of the inter-individual variability.

Based on the abovementioned properties, the semi-physiological PK framework should (i) allow adequate prediction of the PK in various special populations (not only children); (ii) maximise the value for the optimisation of clinical study designs and the application of population data analysis techniques (including better prediction of inter-individual variability) and; (iii) ensure that knowledge is not lost in the transition from prediction to evaluation (i.e., data analysis).

In **chapter 5** and **chapter 6**, semi-physiological PK models were developed for two model drugs (i.e. solifenacin and tamsulosin) with similar PK properties. Both solifenacin and tamsulosin are compounds with linear PK that are mainly metabolised by CY3A isozymes where less than 10% of the dose is excreted unchanged in the urine. In plasma, solifenacin and tamsulosin extensively bind primarily to α1-acid glycoprotein (AGP)[18,19]. Data available for model development comprised total plasma and urine concentrations. To quantify protein binding, data on free plasma concentrations were used for solifenacin and data on individual plasma free fractions were used for tamsulosin.

Both semi-physiological PK models were developed using nonlinear mixed-effects modelling and were based on the use of general partitioning framework to account for binding in the central compartment to plasma proteins and to non-plasma tissues (Figure 7.1; left panel). In the tamsulosin model, binding in the central compartment to non-plasma tissues was found negligible (Figure 7.1; right panel). Also, principles from physiology that apply to the main PK process (i.e.,, first-pass effect,

distribution, and elimination) were considered in order to allow quantification of the impact of changes in the key physiological parameters (i.e., body composition, glomerular function, liver enzyme capacity, and liver blood flow) on the PK.

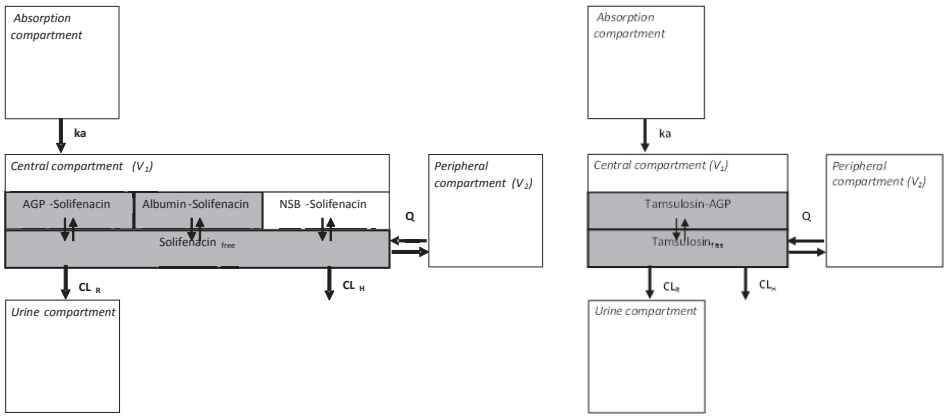

Figure 7.1 Schematic representation of the semi-physiological PK models developed for solifenacin (left panel) and tamsulosin (right panel). The arrows within the central compartment represent instantaneous equilibrium and arrows between compartments represent kinetic processes. Total and free- plasma concentrations as well as plasma-protein concentrations were measured in the compartments indicated by the grey colour. The urine concentrations were measured in the compartment named urine compartment.

The development of the semi-physiological PK models allowed insight into the influence of changes in underlying physiological processes on the PK. For example, for both compounds the agreement between the predicted bioavailability and the observed bioavailability obtained in a clinical study indicated that bioavailability is mainly determined by the first-pass metabolism in the liver. For solifenacin, the 10-fold difference between the measured and estimated *in vitro* clearance reflects the involvement of influx hepatic drug transporters whereas for tamsulosin the agreement between the measured and estimated *in vitro* clearance indicates that there is no involvement of influx hepatic drug transporters. As expected based on the results observed for PBPK (**chapter 3**), the inter-individual variability could not be fully explained by considering the variability predicted from the anthropometric equations. The semi-physiological PK model, however, allowed adequate estimation of the remaining inter-individual variability.

In **chapter 5**, the application of the semi-physiological PK models to predict the PK in hepatic and renal impaired patients was evaluated for solifenacin and tamsulosin. Predictions were obtained solely by adjustment of the physiological parameters that had been reported to change upon hepatic dysfunction [13,20]. Changes upon renal dysfunction for solifenacin considered not only changes in glomerular function rate but also changes in the hepatic transporter in patients with a glomerular filtration rate below 40 mL/min/1.73 m^2. These changes were found to be in the order of approximately 60% based on a literature survey and were expected to be independent of the type of the transporter involved. Recently, a more extensive analysis involving 151 compounds showed this factor to be in the order of approximately 70% and confirmed it to be independent of the type of the transporter. This factor was also shown to be independent of the metabolism of the compound [21].

Predictions using the semi-physiological PK model were close to the observed changes in PK in both hepatic and renal impaired patients. The capability of the semi-physiological PK model to predict inter-individual variability in clearance could not be fully evaluated due the limited number of data points that were available.

Chapter 6 describes the application of the semi-physiological PK models to predict the PK of tamsolusin in paediatric patients (>6 years). The results from this analysis were compared to the results obtained with the traditionally used allometric scaling model as a reference. Predictions using the semi-physiological PK model were obtained by adjustment of the values of physiological parameters for which changes had been reported in the literature. Prediction of the inter-individual variability in children was based on estimates the variability in the physiological parameters sampled from the P3M™ database [22] *plus* the estimated remaining inter-individual variability. For the allometric scaling, prediction of the inter-individual variability considered the weight distribution in the population derived using the P3M™ database [22] *plus* the estimated inter-individual variability.

Predictions obtained using the semi-physiological PK model and the allometric scaling model were very similar, except for more accurate prediction of the terminal half-life when using the semi-physiological PK model compared to the allometric scaling model. These results are in agreement with previous investigations showing that the use of allometric scaling for prediction of reasonably accurate PK profiles is not always possible [23]. On the other hand, it should be emphasized that evaluation of the predictions on the terminal half-life is by some means restricted due to the short sampling time. Predictions of the inter-individual variability were slightly improved by the use of the semi-physiological PK model. As observed in **chapter 3**, allometric scaling slightly over-estimated the inter-individual variability probably because the model compensates for potential biases using random-effects. The over-prediction of the inter-individual variability in paediatric patients is expected to be directly proportional to the increase in the estimated inter-individual variability observed in adult patients after fixation of the allometric scaling exponents.

In conclusion, the semi-physiological PK framework was successfully developed for two model drugs and applied for predictions of the PK in special populations affected by disease or growth related changes. Predictions in paediatric patients using the semi-physiological PK models were not markedly superior to the predictions using the allometric scaling model. Notwithstanding, only the semi-physiological PK model is in principle suitable for predictions upon multiple factors simultaneously impacting the PK (e.g., growth, maturation and disease).

General conclusions

From the traditionally used model-based approaches, only allometric scaling can be combined with compartmental PK models, which enables the application of optimal design and advanced data-analysis techniques. However, the allometric scaling approach was shown to have very low predictive power in paediatric patients where ongoing maturation of physiological processes has an influence on the hepatic clearance (**chapter 3** and **chapter 4**). In addition, allometric scaling is in principle also not suitable to predict the clearance affected by other factors such as disease changes. An alternative approach for allometric scaling was found to be the well-stirred model of hepatic elimination (**chapter 4**) which can be used to predict the hepatic clearance not only in paediatric patients but also in other special populations [3–13]. In addition, the well-stirred model allows combination with compartmental PK models for identification of optimal design in the first clinical studies in special

populations and for more accurate prediction of the inter-individual variability. Hence, the proposed semi-physiological PK framework interfaces the compartmental PK model with expressions to describe variation in plasma protein binding with the well-stirred model of hepatic clearance for the description of the changes in the extent of absorption and clearance (**chapter 5** and **chapter 6**). When using this approach, other features of the model, are to be decided on a case-by-case basis depending on their relevance for allowing the model to suit for its purpose (i.e., the proposed models are so-called "physiological fit-for-purpose models"). In this thesis, two semi-physiological PK models were developed using two model drugs. These models were successfully evaluated for predictions of the PK in special populations affected by disease or growth related changes (**chapter 5** and **chapter 6**).

Future perspectives

The PK in special populations, such as children in the age range below 5 years, is often affected by a combination of factors, such as growth, maturation and sometimes disease[2]. This complicates prediction of the changes in the PK of these patient populations when compared to healthy adults. In this thesis, a semi-physiological framework was evaluated for the predictions of variation in the PK. The utility of this approach was demonstrated in cases where only one single factor has affected the PK. In principle, the semi-physiological framework should also allow predictions of the changes PK when it is affected by a combination of multiple factors.

In this paragraph, some of the preliminary results are presented that were obtained in situations where multiple factors have influenced the PK. In brief, exploratory investigations were performed to evaluate the application of the semi-physiological PK framework (i) to predict the clearance and volume of distribution in pediatric patients < 5 years where the PK is simultaneously affected by growth and maturation and; (ii) to predict the clearance in paediatric patients < 5 years with congenital heart disease (CHD) where the PK is simultaneously affected by disease, growth and maturation. Also, the application of the semi-physiological framework for optimisation of the design (e.g. sample size and sampling schedule) of a first clinical study in special populations is discussed.

Application to pediatric patients below 5 years of age

The semi-physiological PK models developed in **chapter 5** and in **chapter 6** were based on the following physiological equations to predict hepatic clearance (CL_H) [24] and volume of distribution at steady state (V_{ss}) [25]

$$CL_H = \frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H + f_u \cdot {CL_{int}}/{RB}} \qquad \text{Equation 7.1}$$

$$V_{SS} = V_{plasma} + V_{water}\left(\frac{f_u}{f_{tissue}}\right) \qquad \text{Equation 7.2}$$

where in Equation 7.1, Q_H is liver blood flow, f_u is unbound fraction in plasma, RB is the blood to plasma concentration ratio and CL_{int} is the intrinsic clearance which is calculated considering liver weight and enzyme activity; and in Equation 7.2, V_{ss} is the volume of distribution at steady state, V_{plasma} is the volume in plasma, V_{water} is the total volume of body water and f_{tissue} is the unbound fraction in the tissues. The capability of these physiological equations to predict the clearance and volume of distribution when it is simultaneously affected by growth and maturation is evaluated in this subsection.

The model drug used was midazolam, which is a compound with an intermediate extraction ratio which is mainly metabolised by CYP3A isoforms. *In vitro* and *in vivo* evidence suggests that the PK of midazolam is not altered by active transporters, which makes of midazolam a widely used probe for determination of CYP3A4 activity [26,27].

The semi-physiological PK model for midazolam was developed using individual and average PK profiles in adults obtained from two publications [28,29].For the evaluation of the model predictions the clearance and volume of distribution values in children were retrieved from the publication by Bjorkman *et al* [30]. Predictions of midazolam clearance in children were performed by using the values of the model parameters estimates in adults in combination with the changes caused by growth and maturation. In the final model, predictions considered the pertinent changes in volume of plasma, total body water, liver blood flow, plasma protein binding, liver weight and the maturation of the CYP3A activity on the basis of the maturation function that had been derived in **chapter 4**. Predictions using the semi-physiological PK model were also compared to the predictions using the allometric scaling model (maturation function was not considered).

The results depicted in Figure 7.2 show that the well-stirred model of hepatic clearance (Equation 7.1) predicts the clearance reasonably well, but that the prediction of the volume of distribution (Equation 7.2) is inaccurate. Thus, this requires the equation to be adapted. The clearance values that were predicted using the semi-physiological PK model, were shown to be superior to those obtained using the allometric scaling model, whereas predicted values of volume of distribution using the semi-physiological PK model, were similarly biased relative to those obtained using the allometric scaling model.

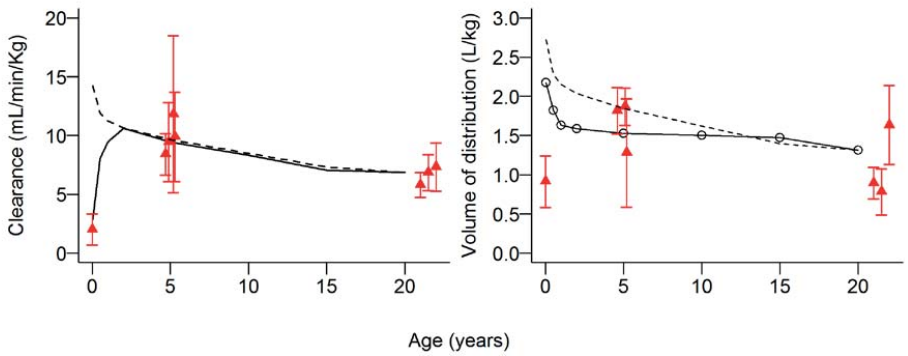

Figure 7.2 Predicted clearance and volume of distribution for midazolam as a functions of age, together with literature data[30]. Solid lines represent the predictions using the semi-physiological PK model and dotted lines the predictions using the allometric scaling model.

The observed favourable properties of the semi-physiological PK model for the prediction of clearance are in agreement with the results presented in **chapter 4** where an extensive evaluation of the well-stirred model was performed. An extensive evaluation of the equation to predict the volume of distribution (Equation 7.2) was not possible, since an accurate estimation of the reference of the volume of distribution in children requires dense data to be collected. In neonates and in young

infants, collection of dense data is often hampered by the maximum allowable blood volume to be sampled.

In the absence of clinical data (as encountered in the paediatric population), prediction of volume of distribution could rely on the physiological basis of PBPK models. In these models volume of distribution at steady state is commonly calculated as follows [31]:

$$V_{ss} = V_{plasma} + V_e \cdot E/P + \sum_{i=1}^{n} k_{p_i} \cdot V_{tissue_i} \qquad \text{Equation 7.3}$$

where V_{plasma} is the volume in plasma, V_e is the volume in the erythrocyte, E/P is the erythrocyte-to-plasma coefficient, $V_{tissue,i}$ is the physical volume and $k_{p,i}$ is the organ-plasma partition coefficients of the i^{th} out of n organs/tissues. The organ tissue to blood partition coefficient is calculated based on fractional content of water, content of lipids, protein binding and physicochemical properties of the compound such as lipophilicity (LogP) and alkalinity/acidity (pKa) [32–40]. Here an approach as outlined in **chapter 3** could be performed, using PBPK to simulate the volume of distribution in children for a range of hypothetical compounds with different LogP, pKa and degrees of plasma of protein binding. The results could be used to either optimise existing physiological equations or to empirically develop a new one.

Examples of equations for prediction of volume of distribution that could be (further) evaluated are the equation derived by Gibaldi and McNamara [25](Equation 7.2) and the mechanistic equation derived by Huisinga *et al* [41](Equation 7.4)

$$V_{SS} = V_{SS,ref}\left((1-R)\cdot\frac{LBW}{LBW_{ref}} + R\cdot\frac{BW-LBW}{BW_{ref}-LBW_{ref}}\right) \qquad \text{Equation 7.4}$$

where BW denotes body weight, LBW, denotes lean body weight and R denotes the adipose to total volume of distribution ratio of the reference individual. Here, R could be calculated for different hypothetical compounds. Theoretically, a relationship between R and the compound properties (e.g. LogP, pKa and protein binding) is likely. If used for predictions, the value of R could also be estimated by applying this equation to the semi-physiological PK models. The use of this equation was shown to accurately predict the volume of distribution in children > 5 years and is expected to require maturation to be considered in children <5 years. Therefore, it is likely that a new equation will need to be developed.

The development of new equation to predict volume of distribution in special populations affected by changes in body composition could be achieved on the basis of models that were designed to identify predictors. Given the PBPK equations to determine tissue distribution (Equation 7.3), possible predictors are the compound's lipophilicity, alkalinity/acidity and protein binding. These predictors alone or combined (to generate indices) may determine the key tissue volumes (e.g., adipose, muscle…) and in what ratios they should be considered in order to predict the volume of distribution in the target population.

Besides, accurate estimation of clearance and volume of distribution prediction of a full PK profile requires potential changes in the inter-compartmental clearance to be adequately predicted. Therefore, a mechanistic interpretation of compartmental PK models is necessary. Pilari *et al* [42] proposed a minimal lumping approach for PBPK models, where lumped models based on similar time

constants for distribution into tissues are further lumped based on visual inspection, to allow direct comparisons with compartmental PK models. Time constants for tissue distribution are calculated by multiplying the volume of the organ tissue by the organ tissue to blood partition coefficient and then dividing it by organ tissue blood flow.

For the drugs investigated, the central compartment in the compartmental PK models were shown to comprise at least blood, lungs, kidneys and liver whereas the peripheral compartment(s) was (were) shown to comprise mainly muscle, adipose and bone tissues. Using this knowledge, mechanistic scaling of inter-compartmental clearance becomes possible by using the ontogeny of the organ blood flows (Q) of the lumped tissues as shown in Equation 7.5.

$$Q = \sum_{tissue} V_{tissue} \cdot k_{tissue} \;\therefore\; Q = \sum_{tissue} Q_{tissue} \qquad \text{Equation 7.5}$$

where Q is the inter-compartmental clearance and Q_{tissue} is the blood flow of the tissue. This knowledge was successfully applied to predict inter-compartmental clearance in children > 5 years using the semi-physiological PK model (**chapter 6**). Its applicability in children < 5 years is yet to be investigated.

This proposed mechanistic interpretation of compartmental PK models applies to compounds with linear PK properties with regard to the distribution. Saturable elimination can be easily incorporated in compartmental PK models, but saturable/delayed protein binding or saturable transporter mediated disposition are more difficult as they may impact the number of compartments in the final compartmental PK model. In this thesis, the semi-physiological PK model was developed for solifenacin (**chapter 5**), tamsulosin (**chapter 6**) and midazolam (**presented here**). For all of these compounds, protein binding was instantaneous relative to other processes and was found to be linear under therapeutic plasma concentrations. A different partitioning framework would be necessary to account for non-linear binding outside the central compartment.

Application to pediatric patients below 5 years with Congenital Heart Disease

In this subsection the capability of the well-stirred model to predict the clearance when it is simultaneously affected by disease, growth and maturation is evaluated. The model drug used was sufentanil, which is an intermediate to high extraction ratio compound that is mainly metabolised by CYP3A isoforms. The well-stirred model equation (Equation 7.1) was evaluated using literature data in adult patients undergoing non-cardiac surgery [43]and in paediatric patients undergoing cardiac [44–46]and non-cardiac surgery [47].

The impact of CHD on the clearance in children was predicted by considering decreased liver blood flow caused by decreased cardiac output. Potential impact of CHD on protein binding was deemed unlikely as sufentanil binds to AGP [48] of which the plasma concentrations were shown comparable in paediatric patients undergoing cardiac and non-cardiac surgery [49]. To our knowledge, CHD has also no impact on the maturation functions of the CYP3A isoforms.

The results for this evaluation are presented in Figure 7.3. It was shown that to account for the effect of CHD a decrease of liver blood of flow to 50% of the reference values in infants, children and adolescents is sufficient to predict clearance values. The assumed change in liver blood flow is in agreement with the changes that have been reported for adult patients with severe chronic heart failure [50]. In neonates on the other hand, 50% change in liver blood flow was insufficient to explain

the observed differences in clearance.

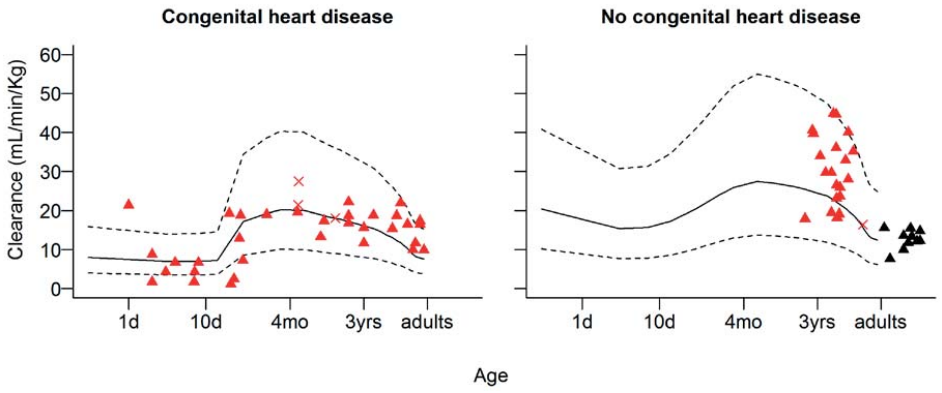

Figure 7.3 Predicted clearance for midazolam as a functions of age, together with literature data [44–47]. Solid line represents the average predictions, the dotted line represents the two-fold prediction error and the symbols represent the literature individual (triangles) and average (crosses) literature data in children (red) and in adults (black).

Decreasing the liver blood flow by 90% is required for adequate predictions in neonates. Differences in the pathophysiology or severity of the disease, or occurrence of comorbidities are possible explanations for the stronger disease impact on clearance observed in neonates. Unfortunately, none of these differences can be derived from the information provided in the original publications [44–46]. Other possible causes for the inadequate clearance predictions could be the result of inadequate predictions of free fractions in plasma and enzyme activity. However, predicted free fractions are in agreement with observed free fractions (0.19 *vs* 0.20/0.19) [51,52] and the maturation function used to predict CYP3A enzyme activity has been extensively evaluated (**chapter 4**).

In general, well-stirred models were shown capable of predicting the clearance when it is simultaneously affected by disease, growth and maturation changes. However, as discussed in the previous section, predictions of full PK profiles would also require quantification of disease related changes in volume of distribution and inter-compartmental clearance. It is expected that CHD would also affect the inter-compartmental clearance by decreasing cardiac output [22] and subsequently the blood flow to various tissues. This hypothesis is supported by the changes in initial and terminal half life observed in paediatric patients with CHD [47]. After establishment of adequate equations to predict variation in volume of distribution in children, prediction of the full PK profiles in paediatric patients with CHD should become feasible using the semi-physiological framework.

Application to inform clinical study designs

The semi-physiological framework constitutes as alternative scientific basis to predict the combined effect of multiple factors on the PK in special populations (**chapter 5**, **chapter 6** and the exploratory results presented in this section). In addition, the underlying statistical basis of this framework allows combination with non-linear mixed effect modelling and thereby, adequate predictions of the inter-individual variability (**chapter 6**). Altogether, the semi-physiological framework constitutes the ideal basis for the optimisation of a first study in special populations.

Optimisation of the first clinical study in special populations is fundamental for estimation of the dose or dose regimen that matches predefined target exposures but also for optimisation of other

design features such as sample size and PK sampling scheme. Poorly designed clinical studies in special populations lead to loss of information, inability to answer specific research questions and are potentially unethical [53]. One should note that repetition of clinical studies in special populations is often not feasible and that, therefore, losing the opportunity to properly investigate the PK of a novel drug in these populations is likely to hamper dose labelling. For the optimisation of clinical studies, optimal design theory can be used. The use of optimal design theory to justify the sample size and to optimise the PK sampling scheme has recently been recommended by the FDA guidance on paediatric investigation [54].

Table 7.2 depicts the background of three different methodologies often applied for optimisation of the design of clinical studies as well as their advantages and disadvantages. The optimal sampling design is the fastest methodology as it utilises an analytical process for optimisation of sample size and sampling scheme. This methodology, however, does not take into account the optimal design necessary to allow the model to, for example, distinguish between one and two compartments [53]. In this respect, optimal sampling design is often used for a pre-selection of the study designs to be further investigated using clinical trial simulations [55]. This methodology involves the use of compartmental PK models to simulate data considering pre-defined study designs and subsequently backfitting the same model to determine the precision with which the model parameters can be determined. A special case for the clinical trial simulations is the posteriori Bayesian simulation where the back-fit makes use of a Bayes theorem. The posteriori Bayesian simulation is applied in clinical studies where sparse sampling is required as for example in clinical studies in neonates and infant patients. This methodology focuses on the ability of a sampling scheme to allow accurate estimation of individual PK parameters (e.g. AUC) rather than to allow model selection [55,56].

Table 7.2 Overview of the methodologies used for optimal design of clinical studies

Optimal sampling theory	**Clinical trial simulations**	**Posteriori Bayesian estimation**
Involves an analytical process using the parameter estimates from the compartmental PK model and a population Fischer information matrix	Involves an interactive simulation and estimation process using the compartmental PK model	Involves an iterative simulation using the compartmental PK model and estimation process using a two-stage Bayesian procedure
Optimisation of dose, sample size and sampling scheme	Optimisation of dose, sample size and sampling scheme	Optimisation of sparse sampling
Targets for accurate estimation of model parameters	Targets for accurate estimation of model parameters	Targets for accurate estimation of PK parameter
Does not consider precision in model parameter estimates	Considers precision in model parameter estimates	Considers precision in PK parameter estimates
Does not consider model selection	Considers model selection	Model selection is not applicable.

The application of all of these optimal design methodologies using semi-physiological PK models is possible because these models have reduced complexity and can easily be combined with the statistical framework of optimal design theories. On the other hand, the complexity of PBPK model predictions restricts the application of optimal design methodology to optimise clinical studies, because of the computational burden. In these cases, it has been proposed that PBPK models are used to simulate PK profiles which are then used to develop a compartmental PK model so that

optimal design can be applied [14,15]. The disadvantage of this approach is that it is time consuming since it involves the development of a PBPK model and subsequently of a compartmental PK model. Also, using the dense data simulated using a PBPK model to develop a compartmental PK model can be quite challenging. Further, this approach fully relies on the capability of the PBPK model to predict parameter and variance estimates while in **chapter 3** of this thesis, PBPK models were shown to under-predict inter-individual variability.

Although theoretically possible, the semi-physiological framework has not yet been evaluated to inform clinical study designs. It is anticipated, however, that optimisation of clinical studies using the semi-physiological PK could benefit from improvement of the existing anthropometric equations or from the development of novel anthropometric equations. This should also be of benefit for PBPK models in which anthropometric equations are also keys determinants of the predicted inter-individual variability.

Anthropometric equations make use of patient demographics to estimate variation in physiological parameters. The various anthropometric equations available have been reviewed by Price *et al* and were selected for the development of the P3M™ database [22] which is a source of data for human physiological parameters in adults and children. The physiological parameters in P3M™ have been calculated using the NHANES database which only contains information of US citizens. In this respect, future applications of the semi-physiological approach for the optimisation of clinical trials in special populations requires:

i. the availability of demographic databases for various populations as the NHANES database may not be representative for a specific special population or for populations in different regions/countries where the clinical study will be performed.
ii. a comprehensive meta-analysis using the data collected over the years to determine key physiological parameters. The proposed meta-analysis has increased power to identify key demographics to be considered in the anthropometric equations and is likely to provide better insight into the expected differences between populations. Having one equation for various subpopulations will also avoid physiological implausible shifts. Further, this meta-analysis could be used to identify knowledge gaps and streamline the collection of new data for further development of the equations.

It should be noted, however, that the improvement/development of anthropometric equations will not lead to the justification of all the observed inter-individual variability, due to the existence of additional unknown sources of variability that cannot be explained by the patient demographics. To circumvent this problem, the semi-physiological PK models estimate the remaining (unexplained) inter-individual variability of the model parameters, whereas the PBPK models separately add variance to the anthropometric equations, thereby mostly neglecting the existent correlation between different physiological parameters. In this respect, the semi-physiological PK model is more likely to adequately predict the inter-individual variability. Yet, when applying optimal designs, it may be reasonable to increase the expected variance in each of the model parameters to compensate for the fact that the variation in the dense data that are normally used for model development in the reference population is unlikely to be representative for the variation observed in the special populations in the clinical settings.

Conclusions

Physiological equations used in the semi-physiological framework seem capable of predicting the combined effect of different factors on clearance. The impact of maturation on the volume of distribution is not well captured by the common equations used to predict the value of this key PK parameter. Hence, future research on the presented framework must focus on the optimisation/evaluation of existent physiological equations to predict volume of distribution in special populations with different body compositions. In addition, the semi-physiological framework is yet to be applied to predict full PK profiles in special populations impacted upon simultaneous factors and to optimise the first clinical studies in special populations.

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