Expectations from PK-PD modelling and simulation in the evaluation of medicinal products in children

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The new European Regulation on medicinal products in children (2006) is a large stimulation for a proper evaluation of medicinal products in children and the availability of formulations adapted to age. A specific evaluation of these products in children is requested due to the PK and PD differences between children and adults precluding a direct extrapolation from adults to children using a proportionality rule based on body size. The evaluation of medicinal products in children is more difficult, takes longer and is more costly than in adults. Among the major difficulties are the invasiveness of the procedures of the evaluation (pain, blood loss related to blood sampling) and the difficulties in recruiting patients. A linear back-extrapolation from adults to children is solely possible down to the age of full maturity of the physiological functions of interest (PK or PD). Beyond these age-limits a specific evaluation is requested.

The main expectation from the modelling of the influence of maturation on the various physiological systems involved in the PK and the PK-PD relationship is to estimate the value of the PK and PK-PD parameters and to predict the optimal dose regimen as a function of age without any new investigation. The validation of these mathematical predictions could be performed using sparse samples therefore dramatically alleviating the burden of clinical studies on children and accelerating drug evaluation in this population.

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Introduction to population PK-PD modelling in paediatric clinical pharmacology

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Oscar Della Pasqua, Meindert Danhof

During the introduction lecture on population PK-PD modelling in paediatric clinical pharmacology, with the use of examples the advantages of the population approach while studying the PK-PD relationship of drugs in children are discussed:

1. Applicable to sparse and unbalanced data sets allowing for studies in neonates and young infants
2. Scientific basis for study/trial simulations, dose adjustment or labeling extensions in other populations
3. Co-variate analysis for identification of predictors of variability in PK and PD (genetics, body weight, age, interactions etc)

While these advantages are applicable during drug development as well as clinical use (change of indication or different age group), proper validations of the final (covariate) models are of utmost importance. In the presentation examples are presenting highlighting the need for properly validated PK as well as PD models. It is concluded that

1. Population PK-PD modelling using non linear mixed effects modelling should be the *primary* analysis method in paediatric drug development and dosing studies
2. Population PK-PD models can be also be developed based on data from previous clinical studies (retrospective studies/meta analyses)
3. Dosing regimen based on validated population PK-PD models should be included in the *label* of drugs

Regulatory experience of paediatric applications - focusing on modelling aspects

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Drug development for paediatric patients is a challenging area and the new paediatric EU regulation highlights the need for proper documentation of paediatric drug treatment. Modelling of pharmacokinetic (PK) and pharmacodynamic (PD) data has been suggested as a useful tool for analysing paediatric data. PK data alone can be used to extrapolate efficacy from adults to paediatric patients and between paediatric patients of different ages, if similar systemic exposure can be assumed to produce similar efficacy in those sub-groups. However, if such assumption cannot be made; PD and/or clinical efficacy data needs to be collected.

Due to the usually limited size of the safety data base in the paediatric population, extrapolations from adult data or paediatric data in different age groups may be needed. If the exposure safety relations could be assumed to be similar, PK data could be useful to identify sub-groups at risk.

Evaluation of collected PK and/or PK/PD data and further predictions can be performed via model- and simulation-based techniques. Regulatory authorities appreciate such approaches but it should be emphasised that the requirements on modelling and simulation methods are dependent on the intended use of the model, e.g., the demands on model evaluation increase with the relative importance of the analysis. For example, models used for simulations of relevance for dose adjustments in the paediatric population require rigorous model evaluation including assessment of the predictive properties of the model. In paediatric applications relying on PK and/or PK/PD models, the quality of the report and analysis may be critical.

The presentation will include some aspects of PK (and possibly PKPD) modelling of paediatric data in recent applications within different therapeutic areas. Identified problems and specific topics related to these applications will be discussed.

References

CPMP/ICH/2711/99. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population

CHMP/EWP/147013/04 Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population

CHMP/EWP/185990/06 Reporting the Results of Population Pharmacokinetic Analyses

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Dose Selection in Early Paediatric Development

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Dose recommendation for paediatric indications remains a major challenge in early clinical development. The rationale for dose selection and dosing regimen in clinical trials is often determined by a trial and-error approach. Most importantly, medical practice assumes linear, direct relationships between body size, physiological function and response.

Generally, paediatric trials are conducted after the exposure–response relationship for a given drug has been determined in adults. These data can be used to routinely guide selection of a reference range of doses for paediatric trials. In these circumstances, dose selection is driven by the goal of emulating drug exposure levels which yield the desired safety and efficacy profiles in adults. Yet, clinical scientists must decide on whether to scale doses for differences in function (e.g., clearance, pharmacodynamics) or whether differences in body size suffice as a surrogate for function.

Even though doses are often normalised to body mass (mg/kg), surface area (mg/m^2), age, or other descriptor of body size, it is important to realise that dose adjustment may not be required for some drugs. In addition, the use of a fixed dose (mg) across the continuum of age and weight may provide more accurate information about pharmacokinetics and pharmacodynamics in children.

In this presentation, different pharmacostatistical methodologies will be presented for identifying descriptors of developmental changes, which can subsequently be treated as covariates for dose adjustment in children. Of particular relevance are the differences in dosing rationale for small molecules, biologicals and vaccines. Implementation procedures, such as the use of population stratification, titration algorithms and flexible study protocols will also be discussed briefly. Given the variation in weight observed in paediatric studies that span the spectrum of age, we show that the use of a fixed dosing regimen results in a dynamic range of exposures. Thus, fixed dosing may be preferred initially in lieu of a dose escalation approach to allow for a more complete evaluation of relevant covariates for pharmacokinetics and pharmacodynamics than might be afforded in studies where only two or three normalised doses are investigated.

In conclusion, we show that the use of integrated PKPD modelling of adult and paediatric data is essential in early paediatric trials. However, additional implementation steps must be considered to ensure accurate dose selection in this vulnerable population. Nonlinear mixed-effects modelling and Bayesian statistical methods should therefore be used in conjunction with an interim evaluation of drug exposure.

Evaluating Study Design and Conduct Efficiency of Event-Driven Clinical Trials via Discrete Event Simulation: Applications in Paediatric Oncology

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Previous exploration of oncology study design efficiency has focused on Markov processes alone (probability-based events) without consideration for time dependencies. Barriers to study completion include time delays associated with patient accrual, inevaluability (IE), time to dose limiting toxicity (DLT) and administrative / review time. Discrete event simulation (DES) can incorporate probability-based assignment of DLT and IE frequency, correlated with cohort in the case of DLT, with time-based events defined by stochastic relationships. A SAS-based solution to examine study efficiency metrics and evaluate design modifications that would improve study efficiency is presented. Virtual patients are simulated with attributes defined from prior distributions of relevant patient attributes. Study population datasets are read into SAS macros which select patients and enroll them into a study based on the specific design criteria if the study is open to enrollment. Waiting times, arrival times and time to study events are also sampled from prior distributions; post processing of study simulations is provided within the decision macros and compared across designs in a separate post-processing algorithm. This solution is examined via comparison of the standard 3+3 decision rule relative to the "rolling 6 design", a newly proposed design construct for the phase I paediatric oncology setting. For twelve completed historical studies the median (range) time to study completion was 452 (220-606) days, the number of evaluable subjects enrolled was 22 (11-33), and the number of DLTs per study was 3 (0-5). In 1000 study simulations where the average time to new patient accrual was 10 days, the average (± standard deviation) time to study completion was 294 ± 75 days for the rolling six design *vs.* 350 ± 84 days for the 3+3 design, while the number of DLTs per study was the same (3 ± 1). The rolling six method may significantly decrease the duration of paediatric phase 1 studies without increasing the risk of toxicity. The design will be tested prospectively in upcoming Children's Oncology Group (COG) phase 1 trials.

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Voriconazole paediatric dose: an example

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Voriconazole is a potent triazole with broad-spectrum antifungal activity against clinically significant and emerging pathogens. The present population pharmacokinetic analysis evaluated voriconazole plasma concentration-time data from three studies in paediatric patients 2 to <12 years of age, incorporating a range of single or multiple intravenous (IV) and/or oral (PO) doses. An appropriate pharmacokinetic model for this patient population was created using the nonlinear mixed effects modelling approach. The final model described voriconazole elimination by a Michaelis-Menten process and distribution by a two-compartment model. It also incorporated a statistically significant ($P < 0.001$) influence of CYP2C19 genotype and of alanine aminotransferase levels on clearance. The model was used in a number of deterministic simulations (based on various fixed, mg/kg, and individually adjusted doses) aimed at finding suitable intravenous and oral voriconazole dosing regimens in paediatric patients. As a result, 7 mg/kg BID IV or 200 mg BID PO, irrespective of bodyweight, were recommended for this patient population. At these doses, the paediatric area-under-the-curve (AUC) distribution exhibited the least overall difference from the adult AUC distribution (at dose levels used in clinical practice). Loading doses or individual dosage adjustments according to baseline covariates are not considered necessary when administering voriconazole to children.

K-PD models: principles and applications

Prof Pascal Girard

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Prof Michel Tod

Some pharmacodynamic models, called K-PD models, have been developed for the description of drug action kinetics in the absence of drug concentration measurements. Because blood samples for drug measurements are not needed, these models may be very useful in pediatric studies, by reducing their invasiveness. In addition, a number of PD measurements are also non invasive and specific devices exist for measures in children. Therefore, the kinetics of drug action may be characterized with minimal invasiveness. A brief description of the key features of these models will be given, and a number of examples of application will be presented. K-PD models are expected be most useful when the drug kinetics is simple (i.e. when the one-compartment model is a reasonable description), or when the response kinetics is slow compared to drug kinetics. K-PD models have already demonstrated their usefulness in animal and adult studies. They are very attractive for pediatric studies and they should facilitate the assessment of drug efficacy and safety.

Sparse sampling design in population PK/PD studies

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Population pharmacokinetics / pharmacodynamics analyses often involve a limited sampling strategy in the data collection, mainly due to financial but also ethical and physiopathological concerns such as in paediatric studies. To decrease the risk of unreliable results in such limited samples studies, efforts have been devoted since a decade to the development of a methodology for population designs evaluation and optimisation based on the expression of the Fisher information matrix for nonlinear mixed effects models [1, 2].

We present the methodology used for population design evaluation and optimisation as well as software available. An illustration is given using the freely available R function PFIM [3] on a real example, which is the design for simultaneous population modelling of the time course of warfarin concentration and its effect on the prothrombin complex activity after single dose administration.

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2. Retout S, Mentré F, Bruno R. Fisher information matrix for non-linear mixed-effects models: evaluation and application for optimal design of enoxaparin population pharmacokinetics. *Statistics in Medicine*, 2002; 21(18): 2623-39.
3. www.pfim.biostat.fr

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Designing paediatric studies: scaling from adult populations

Prof Leon Aarons

Centre for Applied Pharmacokinetics Research, School of Pharmacy and Pharmaceutical Sciences, The University of Manchester

Kayode Ogungbenro, Ivan Matthews, Leon Aarons

A case study will be presented in which a population pharmacokinetic model for famciclovir/penciclovir in adults was used to recommend an appropriate dose for paediatrics. Furthermore, a limited sampling design based on sampling windows for 4 different paediatric age groups (1 month - 1 year, 1 - 2 years, 2 - 5 years and 5 - 12 years) using an adequate number of subjects for future pharmacokinetics experiments was developed. Penciclovir plasma data from 6 different adult and paediatric studies were analysed using nonlinear mixed effects modelling. Simulations were used to select a paediatric dose that gives similar exposure to 500mg in adults. Optimal sampling times and sampling windows were obtained using purpose built software and simulations were used to select adequate sample sizes for future paediatric studies.

A two compartment first order absorption model with absorption lag time with allometric size models on volume parameters and an allometric size model, age and creatinine clearance functions as covariates on CL adequately describe the pharmacokinetics of famciclovir/penciclovir in adults and paediatrics. A dose of 10mg/kg body weight in paediatrics gives similar exposure to 500mg in adults. A single sampling windows design (0.25 - 0.4, 0.5 - 1, 1.25 - 1.75, 2.75 - 3.5 and 7.25 - 8 hrs) for 5 samples per subject and 30 subjects in each of the paediatric age groups is suggested for future studies.

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Regulatory experience in application of modelling in dose selection

Dr Elisabeth Rook

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Modelling and Simulation (M&S) supporting dose selection is commonly applied in applications for medicinal products new in pediatrics, for an extension of the intended age-group, and new formulations. Two examples are presented where M&S was applied for development of new formulations. In the fist example, a fixed combination product of two NRTI's (nucleoside reverse transcriptase inhibitors) was developed for children. The challenge was the posology of one of the active agents (ZDV) was 3 times daily dosing (TID), based on BSA, whereas the other active substance (LMV) is dosed twice daily (BID) per kg BW. Clinical experience of the separate product learned that BID dosing of 3TC was equally effective as TID dosing. Based on a general population growth chart, BSA ranges corresponding with BW values were calculated. M&S was applied to evaluate a new BID dose recommendation, using a prior model on the regular TID regimen. Based on M&S data and supportive clinical experience with the BID dose regimen, pediatric labelling for the fixed combination product was accepted by the EMEA, whereas the tablet itself was not tested in either clinical or PK studies. As high Cmax levels were predicted for ZDV (due to reduced dose frequency), close post-marketing safety surveillance was warranted.

For another HIV product, a Protease Inhibitor, a child-friendly oral solution was developed reducing pill-load. A 5-arm dose-finding study was performed in three age groups, and both sparse and rich sampling was applied. Based on M&S, and supported by (limited) clinical data, doses were selected that gave the best fit to adult reference values. Good fits were achieved for the highest age groups (>6 y). For the youngest age group, according to the model, significant higher doses were needed than tested. As the clinical data were very limited and failing for this age group, additional studies are required. For safety reasons, the Applicant preferred to continue studies with a lower dose than required according simulations.

These examples show that regulatory assessors see the benefit of M&S in this field and are willing to accept dose-recommendations based on M&S, even if that dose is not tested in-vivo, provided that there is sufficient evidence that the new dose regimen would be safe and effective.

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Statistical modelling issues arising from PK/PD bridging in paediatrics

Dr Jerry R. Nedelman

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PK/PD bridging refers to selecting a dose for the paediatric population as one that produces systemic drug concentrations that in adults are associated with an efficacious pharmacodynamic response. According to the FDA Paediatric Study Decision Tree, PK/PD bridging can be used to support use in paediatrics of a drug previously approved for adults provided similar disease progression and similar response to treatment may be assumed in the paediatric and adult populations, and provided the paediatric and adult populations may be assumed to have similar PK/PD relationships. Demonstrating similarity of PK/PD relationships may require estimating those PK/PD relationships from dose-controlled clinical trials, i.e., clinical trials where patients are randomized to assigned doses, not to assigned concentrations. In such dose-controlled trials, systemic drug concentrations are uncontrolled outcomes of the dose/PK relationship as well as inputs to the PK/PD relationship. Therefore, inferences about the PK/PD relationship are at risk of being confounded, i.e., biased, if the relationship of PD to PK is not independent of the relationship of PK to dose. Such a risk of confounding was confronted in seeking the approval of Trileptal as monotherapy for paediatrics. Although the absence of confounding can never be definitively proven, diagnostics can be brought to bear that increase confidence in the assumption that confounding is absent. This presentation will discuss the concerns about confounding and the diagnostics that were used for Trileptal.

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Clinical trial design optimization in paediatrics using prior knowledge combined with modelling and simulations

Eric Snoeck

Exprimo NV

Historically, about 75% of drug products used in paediatric populations have had insufficient labelling information for paediatric dosing, safety or efficacy [1]. In nearly half of the drugs studied by the FDA since 1997, substantive differences have been found in dosing, safety or efficacy in children when compared with adult programs [2]. Poor dose selection, lack of acknowledgement of differences between adult and paediatric populations, and lack of paediatric formulations were found to be associated with paediatric antihypertensive trial failures [3].

Model based drug development is evolving and modelling and simulation (M&S) is increasingly used as a key decision-making tool within individual drug development programs. Exposure-response modelling using available data in adults and children combined with prior knowledge to perform clinical trial simulations of paediatric studies is particularly appealing as these studies have a number of practical and ethical constraints [4]. The invasiveness of the procedures and the obstacles to paediatric patient recruitment are the main difficulties to circumvent. Drugs behave differently in children compared to adults with potential differences in absorption, distribution, metabolism and elimination. The effects of drugs may be different in children as the magnitude and nature of the response may be different. Also adverse events and diseases may differ between children and adults. Infants and children should therefore not be considered to be “little adults”.

My presentation will briefly discuss three of our paediatric M&S projects taking into account the above-mentioned differences between adults and children. The first example shows the use of simulations proposing a dose adaptation rule for intravenous levetiracetam in children based on adult intravenous data and paediatric oral data [5]. In the second example, it will be shown that a well-founded informed decision could be made about the design of a planned paediatric study using M&S on the basis of relatively limited data combined with literature information. Lastly, M&S based on a pharmacodynamic endpoint to aid in proposing a dose adaptation rule in children and optimising the design of a planned paediatric study will be presented in the third example.

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Modelling and simulation in support of adaptive designs in paediatric populations

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The use of paediatric patients in clinical trials requires an efficient design in order to maximise the information from the minimum number. In this respect they are a scarce resource. There is also a requirement to protect paediatric patients from over exposure to unsafe and ineffective treatment. Adaptive designs enable both of these objectives, by allowing changes in the design based on accumulating data.

This talk will outline how adaptive trials can be used in a paediatric population, and will explain how this contributes to a good understand of the dose response curve. This in turn will show how patients are protected from unsafe doses, whilst gaining the most information in the trial using the minimum resource. Where applicable, real examples will be used to illustrate.

Leveraging prior knowledge in guiding pediatric drug development

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Pediatric drug research is essential to providing children with safe and effective therapies, but until about 10 years ago drug studies in children were uncommon. Several factors contributed to the lack of pediatric studies, but one of the major factors was the limited financial incentive to do the research. With the growing realization that pediatric treatment decisions based on adult data could put the health of children at risk[1], Congress added section 505A to the Food, Drug, and Cosmetic Act in 1997, creating a program to encourage drug manufacturers to conduct studies in children. This program allowed industry to receive a six-month extension of marketing exclusivities and patent protections for an active ingredient if they conducted pediatric studies requested by the FDA in a "Written Request." This incentive is commonly referred to as "pediatric exclusivity." The exclusivity program has been successful and was reauthorized as the Best Pharmaceuticals for Children Act of 2003, and again under the Food and Drug Administration Amendments Act of 2007. Since the beginning of the exclusivity program, over 830 studies have been requested in 356 Written Requests for pediatric studies. Over 140 medication labels have been updated with pediatric use data from these studies.

Antihypertensive drug products are managed by the Division of Cardiovascular and Renal Products (DCaRP), one of 15 review divisions of the Office of New Drugs in CDER. As of January 2008, DCaRP has authored more than 35 Pediatric Written Requests, 24 of which were in antihypertensives. About 50% of pediatric effectiveness trials lead to inconclusive results. The availability of patient demographic, disease progression, placebo effects, dropout and drug effect data from previous adult and pediatric trials for the same molecule and/or similar molecules provide a rich database. This information can be leveraged to develop drug/disease models that can be applied to design more efficient and informative pediatric drug development programs. The latest pediatric legislation and the potential benefit of employing modeling/simulation methods during development of protocols for written requests will be presented along with a case study.

Briefly, clinical trial simulations were conducted to support dosing regimens and trial design, as well as to estimate sample size for the pediatric study. Data from adult patients for drug X, placebo data from Corlopam study[2] and experience in developing anti-hypertensive for immediate blood pressure (BP) control in pediatric population were used. The simulation experiment allowed us to design a powerful and informative study for pediatric patients, more specifically, it allowed us to

- Study the effect on sample size, if the pediatric patients were less responsive and less sensitive compared to adult patients.
- Study the impact of missing data and guide the choice of powerful statistical method for primary analysis.
- Study the factors affecting the success of a given study.

[1] http://www.fda.gov/cber/gdlns/ichclinped.pdf
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Introduction to PBPK

Neil Parrott

Hoffmann La Roche

Thierry Lave

The fundamental difference between physiologically based pharmacokinetic models (PBPK) and other models is that the PBPK models start with a model structure representing the physiology of the body with model parameters corresponding to actual blood flows and tissue and organ volumes. In addition to parameters describing the physiology, PBPK models quantify the processes of absorption, distribution, metabolism and elimination (ADME) for each drug based on in vitro data relevant to each of these processes. This presentation will mention some recent advances in ADME techniques which make the practical application of PBPK for drug discovery a reality and will review how such models are now being used in our company to support pre-clinical and early clinical projects. Finally, the benefits of the PBPK indicate that they should be considered as a key component in approaches for pediatric dose estimation.

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Using Size and Age to Predict Clearance and Volume

Prof. Nick Holford

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Dose individualisation is one of the major challenges for clinical pharmacology. The science based principles of pharmacokinetics and pharmacodynamics have identified clearance (CL), volume of distribution (V), maximum drug response (Emax) and potency (EC50) as the key parameters determining the time course and intensity of drug effect.

Dose individualisation in clinical practice is largely based on empiricism and prescriber convenience with little attention to the scientific basis for the dose-response relationship. This is especially true for paediatric dosing because it is obvious that a standard dose that might work for many adults would be too large for a child. Empirical methods based on simple per kilogram or predicted surface area guided models are widely used but provide a poor basis for dissecting the separate roles of size and age to explain and predict differences in dose requirements.

There is strong theoretical and experimental evidence to support the use of allometric scaling methods across species and within the human species (1). Body weight can be used as the primary explanatory factor for differences in parameters such as CL, V and, when appropriate, Emax. With this sound foundation using weight to explain a large fraction of between subject variability it is then reasonable to search for other models to account for the remaining differences e.g. based on differences in age. Models for maturation of metabolic and renal function are currently still empirical but have been shown to be applicable across the human age span from very premature neonates to adults. With the main factors of size and maturity accounted for the next step is to consider factors unrelated to weight and age e.g. genotype determined differences in metabolism.

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Blood brain barrier maturation: implications for drug development

Rob Webster

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This presentation briefly summarizes the available data on the maturation of the blood brain barrier in animals and humans, discussing the impact of age on blood brain barrier permeability in human infants. This presentation discusses species differences in blood brain barrier maturation and the impact this has on pre-clinical experimention into age related changes in blood brain barrier permeability. The available blood brain barrier penetration data in the pediatric population is discussed along with examples of attempts to model pediatric blood brain barrier permeability. Finally, based on all of these data a strategy is proposes by which risks of differences in CNS penetration in the pediatric population can be considered during drug development.

Using the Knowledge of Biology in the Prediction of Clearance as the Main Determinant of Drug Exposure in Paediatric Populations

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In 1984 Les Benet and colleagues wrote “At any point in the history of health care, our knowledge was considered to be quite extensive; however, in perspective, the knowledge of yesterday seems to have been very limited, just as today’s knowledge can be expected to seem one day as such”. They extended their comments by advocating an appreciation of physiologic constraints when applying basic scientific and mathematical concepts to pharmacokinetics. Since then, efforts to predict ADME characteristics from *in vitro* data with the aid of modelling and simulation (M&S) have been on the rise and have formed a significant part of the new move towards quantitative pharmacology. The techniques involved enable the researcher to take full advantage of investigating parts of the systems (human body) and interaction of drugs with these parts in isolation and then re-assembling them within models. This approach can incorporate some individual attributes for interaction between the drug and parts of the system (e.g. metabolism by each enzyme) with known changes in the system under different conditions (e.g. abundance of enzymes and liver size with age) and inform us un most likely outcome of using drugs under these conditions *prior* to administration of drugs.

The application of population pharmacokinetics in the later stages of drug development has enables us to recogniose the most relevant covariates of drug PK and PD (including the effects of age) for many drugs. However, many of these co-variates can be easily identified at earlier stages; thus, POPPK studies are “confirmatory” rather than being the first step in our “learning” curve about paediatric pharmacokinetics. Although our understanding of how the human body works may not be extensive, available knowledge is nevertheless predictive of PK in many cases. In this context, and with the ever increasing accessibility of automated tools that incorporate the known complexities of human physiology and biology, generalisations such as “children are small adults - babies are young children” do not provide specific solutions to the assessment of PK in paediatric populations, especially in babies and infants.

Use of PBPK in simulating drug concentrations in pediatric populations:
Case studies of Midazolam and Gabapentin.

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Objectives: To evaluate the possibility of predicting drug absorption and bioavailability in pediatric population from pure *in silico* inputs or from available adult *in vivo* data. The significance of clearance and gastrointestinal tract scaling to the appropriate age for accurate predictions was assessed.

Methods: GastroPlus™ 5.3 with the PBPKPlus™ Module (Simulations Plus, Inc., Lancaster, CA) was used to simulate adult human plasma concentration time profiles (Cp vs. time) observed for Midazolam and Gabapentin after oral administration of each drug. Simulations were compared to corresponding literature data in order to validate the dose dependence. The built-in Population Estimates for Age-Related (PEAR) Physiology™ was used to calculate organ weights, volumes, perfusion rates, and tissue-plasma partition coefficients for an average human male adult and the pediatric patients. *In vitro* values for gut distribution and *in vitro* K_m and V_{max} values for CYP3A4 were used along with *in silico* estimation of biopharmaceutical and pharmacokinetic properties for Midazolam simulations. The Gabapentin renal secretion was estimated from glomerular filtration rate. For the simulations of a pediatric population, the gut parameters and the clearances were scaled from adults to pediatric patients. The resulting pediatric simulations were compared to the clinical data from the literature.

Results: Using the default ACAT model and the observed expressions of CYP3A4 in liver and gut, GastroPlus PBPK simulations accurately reproduced the nonlinear dose dependence for Midazolam bioavailability and Cp vs. time profiles for po administration of Midazolam solution from 7.5 mg to 30 mg in adult patients. Using the default ACAT model and estimate of Gabapentin renal secretion based on glomerular filtration rate accurately reproduced the nonlinear dose-dependent pharmacokinetics in adult population. Using a purely *in silico* calculation of pediatric physiology, and scaling the gastrointestinal tract parameters and clearance to a pediatric population, the pediatric C_{max}, and T_{max} were accurately simulated for both compounds.

Conclusions: *In vitro* data or *in vivo* Cp vs. time profiles from adult populations can be successfully used to predict the midazolam and gabapentin Cp vs. time profiles in pediatric patients if the organ physiology for given age is accompanied by scaling of the gastrointestinal tract parameters to the same age.

PBPK/PD modeling with PK-Sim & MoBi in support of the PIP

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Mechanistic physiology-based modeling of pharmacokinetics offers a rational approach to pediatric scaling and challenges of the PIP. Available information about growth and maturation of physiological processes and the ontogeny of enzymatic processes during life can directly be used to predict the pharmacokinetics in children. Whenever mechanistic pharmacodynamics models are available as in blood coagulation ontogeny information for target proteins and whole target systems can also be employed to develop optimal dosing strategies in children.

Major advantages of the mechanistic approach are

- the explicit representation of all available data and crucial assumptions,
- the early identification of conflicts between assumptions and data,
- the possibility to extrapolate beyond already studied scenarios,
- the gain of information and new insight into pharmaceutics and pharmacology.

Today's modeling tools like PK-Sim/MoBi support the application of mechanistic modeling in pharmaceutical applications as ready to use representations of current knowledge integrated into graphical user interfaces suited for non-modelers also. They cover the whole workflow of pediatric scaling from the establishment and validation of adult reference models to the prediction and analysis of applications to virtual pediatric populations. The standardization of routines ensures constantly high quality of projects and allows comparison between different projects.

Physiology-based approaches will gain further importance when more high quality raw data for physiological properties and processes like transport and binding proteins is available. The level of regulatory acceptance will largely benefit from standardized study protocols and evaluation criteria for adult reference models that are currently under development. Applied to individualization tasks physiology-based methodologies are expected to contribute to an improved understanding of pharmaceutics and pharmacology and will hopefully support the development of new treatment optimization strategies for both children and adults.

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Alternative methods in risk assessment and kinetics in paediatric pharmacology: A common need for PBPK modelling.

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After briefly setting the scene of Chemicals and Cosmetic ingredients risk assessment (REACH, 7th Amendment to the Cosmetics regulation), a parallel will be drawn between the situation of Chemicals risk assessment, Cosmetics ingredients risk assessment, and the development of pediatric medicines, in terms of pharmacokinetic information needs. All three situations are characterised, for different reasons, by the scarcity of animal and human kinetic data. The need for extrapolation of information from experimental situations to unknown situations relevant for risk assessment is therefore shared by all three regulatory contexts. Various forms of modelling: data-based and physiologically based kinetic modelling (PBPK), population kinetics, pharmacokinetic – pharmacodynamic (PKPD) modelling are key instruments to build a useful picture of the available information, generated by various in silico, in vitro and in vivo techniques. The methodology to evaluate PK prediction techniques will be discussed. The major recommendations of the ECVAM / IHCP workshops on PBPK and in vitro kinetic modelling will be presented.

Advantages and challenges of mechanism-based modeling approach to drug development and testing

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The mechanism-based modeling approach is illustrated by means of the example of insulin absorption from subcutis. The idea of this approach is to represent the relevant biological and pharmacological processes as realistically as possible. This has the advantage that the model parameters have clear physiological or biochemical interpretations. Hence, parameter values can be imported from other studies, and knowledge can be accumulated from study to study as the model becomes increasingly comprehensive. This also makes the approach a better tool for interpolation/extrapolation between groups. We illustrate how different insulin variants call for different model structures, depending on the role of polimerization, protein-binding, crystal formation, etc. We also illustrate how nonlinearities in the various biotransformations lead to dose-nonlinearity and limited bioequivalence between different concentrations. Mechanism-based modeling requires a different approach to drug testing where repetition of esentially the same trial for many animals/persons to some extent is replaced by accurate determination of specific physiological parameters and their variation across populations.

Modeling & simulation in pediatric drug development and regulation

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Efficient development and regulation of drugs in pediatrics can be achieved using best practices of the learn-confirm paradigm (1), coupled with model-based drug development practices (2,3). Several pharmacometrically enhanced model-based learn-confirm cycles are employed in adult drug development to acquire knowledge of (a) mechanism of action, (b) therapeutic principle, (c) exposure-response and (d) clinical safety and effectiveness. In pediatric drug development, fewer learn-confirm cycles are required (4-7). With the full knowledgebase of drug action in adults, pediatric safety and effectiveness may be inferred by a pharmacokinetic learning trial in pediatric patients to establish the dose-exposure relationship (including influential demographic and disease related covariates) and customizing the pediatric dosing regimens to match the adult exposure pattern associated with safety and effectiveness [8]. A limited confirmatory investigation of safety or effectiveness may be employed when uncertainty of the pediatric exposure-response relationship warrants confirmation of effectiveness and safety [9].

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Modeling and Simulation Opportunities to Support Pediatric Investigation Plans.

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The recent Paediatric Regulation in the European Union to improve the availability of information on the use of medicines in children provides significant challenges to developers of pharmaceutical agents in meeting the obligations of this regulation. Central to the obligation is the submission of a Pediatric Investigation Plan (PIP) which outlines the studies a developer will undertake to address the Regulation. The Regulation requires that this plan be submitted early in the development of a new agent (after initial pharmacokinetic studies – phase I) with the understanding that revision and modifications will occur as development progresses. At this stage of initial PIP submission, the developer has available preclinical pharmacology and toxicology data with limited exposure/safety information and pharmacokinetic data from dose escalation studies, generally conducted in healthy adult human volunteers. In addition, historical information from compounds that are similar in chemistry and pharmacology may be useful if pediatric experience has been documented in clinical literature. From this information, the sponsor must integrate knowledge about the compound's pharmacodynamics, likelihood of similar response between adults and pediatric subpopulations, the impact of child development on this relationship, and the ability to bridge knowledge about the pharmacokinetics of the agent in healthy adults to a treated population of children to develop an adequate study plan for the PIP. These challenges create an opportunity for using modeling and simulation methods to support decision making for agreement on PIPs. For this effort to be successful, all parties in the drug development endeavor - sponsors, health authorities, and clinical investigators - will need to fully understand and utilize knowledge gained from modeling and simulation, supported by available experimental data, and prospectively validated in efficacy studies to move this effort forward. If successful, this could alter the way drug development proceeds in the future, not only for pediatrics but for adults as well.

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Population PK/PD in paediatrics; a perspective on the way forward

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Model based drug development in adults generally relies upon a series of sub-models that describe the PK/PD/clinical endpoint relationship, the underlying disease, adherence and drop-out. The various sub-models are developed as needed to answer a particular question, such as what dose to study in Phase III.

The situation in paediatrics is no different, but in this case the starting dose is often unknown and so bridging from adult pharmacokinetic data is performed, making the assumption that exposure should be the same in the children as in adults. Predictions of the pharmacodynamics and clinical endpoints follow subsequently. However, the assumption that the PK/PD/clinical endpoint relationship is the same in children as in adults is an uncertain assumption, as is also that the underlying disease is the same in children as in adults. The creation of paediatric specific disease models is desirable but very challenging due to the paucity of subjects and data that usually typify paediatric clinical trials. In the future regulatory authorities could play a large role in developing disease models in children, since they have the largest repository of data available and which could be used to support the development of such models. Once specific paediatric disease models exist (or can be scaled appropriately from adult versions) better predictions can be made of what dose to give to children.

Model based drug development is increasingly used in adult drug development, but even when performed, the details of such analyses may be omitted totally or watered down in documentation submitted to the regulatory authorities; the same can be expected to occur in paediatric submissions. The reasons behind this are not clear cut. One way forward could be for regulatory authorities to further increase their visibility in handling such model based data; the present workshop is an excellent activity in this respect. Increased visibility might also come from developing a paediatric PK/PD guideline, or even publishing collections of submitted examples where model based drug development has been used in paediatrics, citing what was good and bad about the analyses from a regulatory perspective. Increased visibility on the part of the regulatory authorities should encourage increased use and submission of model based drug development in paediatrics, which will hopefully result in better therapy without subjecting children to unnecessary trials.

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Regulatory vision of paediatric applications

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We envisage that current and improved modelling and simulation (M&S) techniques enable a more efficient evaluation of the collected data. We believe that employment of M&S in the paediatric area will aid in optimisation of drug use and result in minimisation of the number and size of studies needed.

A model will never be perfect but efforts should be made to make models predictive over a large age span including important developmental stages, e.g. increased use of physiology-based models. It would be in everyone's interest to share pharmacokinetic data and common basic information. Thus, it would be beneficial if confidentiality regarding paediatric data was agreed to be less strict and collaborations could be possible between companies, academia and regulatory bodies within this field.

We foresee that the implementation of the new paediatric EU regulation will increase the use of M&S and therefore increased regulatory resources in this area of expertise will be required.

To ensure an adequate quality of the M&S activities, training in and knowledge about M&S needs to be expanded within industry and regulatory authorities. Moreover, the utility and possible gain of M&S must be spread among disciplines, e.g. pharmacokineticists, pharmacologists, statisticians, physicians and upper management.