Whole-Body Physiologically-Based Pharmacokinetic Modeling of Moxifloxacin to Support a Translational Approach in Pediatric Study Design

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Introduction

At present, many medicines are not developed for children or available in suitable dosage forms. Therefore, the FDA and the EMEA have launched initiatives that request pediatric assessment of new drugs. For antibiotics development strategies for dosing recommendations in order to maintain efficacy and safety in different age groups are required.

Objective

Since the ADME properties of moxifloxacin are fully investigated and age dependencies of the processes involved are available, a pediatric whole-body physiology based (WB-PBPK) model for moxifloxacin paying attention to developmental changes is applied to design clinical studies in children.

Methods

The Bayer standard workflow using PBPK modeling with the software PK-Sim®[1] for extrapolation from adults to pediatric populations is used to describe moxifloxacin concentration-time profiles, as shown in Figure 1:[2,3]

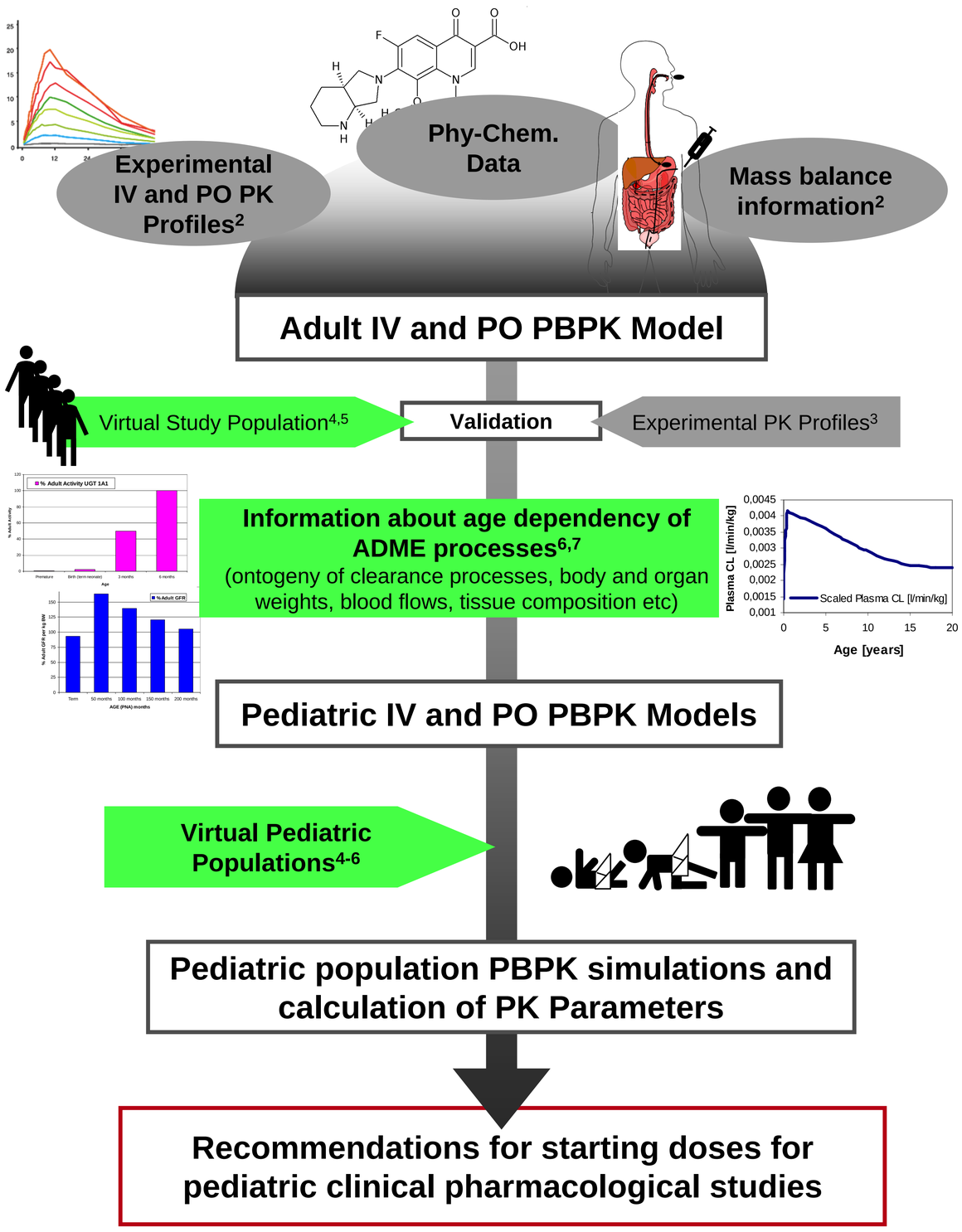

Figure 1: Bayer Standard Workflow for extrapolation from adults to the pediatric population

Results

The WB-PBPK model provided an accurate description of the experimentally measured concentration-time profiles in the adult validation population[4-6], as shown in Figure 2. The model was scaled to children and used for predictions of different doses and dosing intervals.

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In an exemplary way, the simulated plasma concentration time profiles of 6 month old children following multiple administration of 50 mg moxifloxacin once daily are shown in Figure 3.

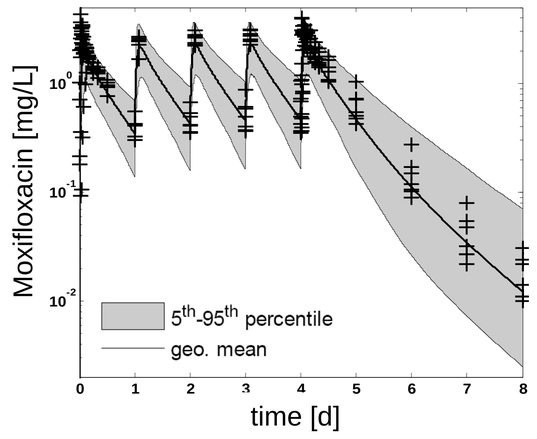

Figure 2. Validation of the adult PBPK model for multiple (OD) oral administration.[4-6]

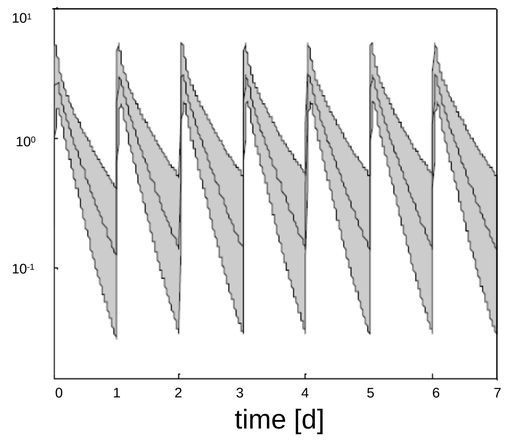

Figure 3. Plasma concentration time profiles following oral administration of 50 mg to 0.5 year old children

Based on the WB-PBPK simulations for children over the pediatric age range the age dependency of the PK parameters relevant for safety and efficacy were calculated, as shown in Figure 4.

Recommended starting doses based on the PBPK Model:

Age	Dose
Adolescents 18 – 12 yrs	5 – 6 mg/kg (maximum 400 mg) OD
School children ≤ 12 yrs – 6 yrs	
Preschool children ≤ 6 yrs – 2 yrs	7 – 8 mg/kg OD
Infants & Toddlers ≤ 2 yrs – 0.3 yrs	9 – 10 mg/kg OD

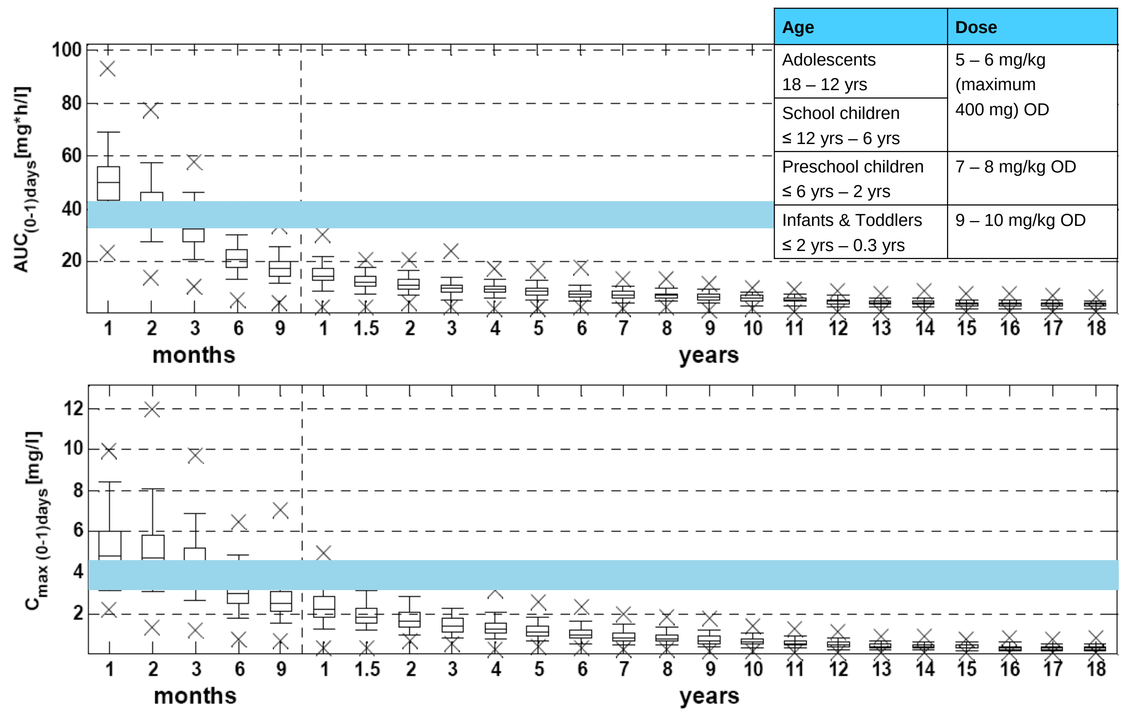

Figure 4 Relevant PK parameters over the complete age range including the adult reference intervals (blue shaded corridor)

The evaluation of the relevant PK parameters, as shown in Figure 4, suggests that preschool children and infants require between 25 to 80% higher doses and/or shorter dosing intervals than those recommended in adults to achieve equivalent exposure. The results obtained from the pediatric PBPK model are used to plan first studies in pediatric patients.

Conclusion

The WB-PBPK approach uses drug-independent prior information about developmental differences between the pediatric populations and adults. It enables development of study designs suited for iterative validation and refinement when clinical data of the drug first tested in pediatric patients becomes available. This knowledge-driven approach strengthens the scientific basis of the pediatric development and is well suited for continuous trial support.

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