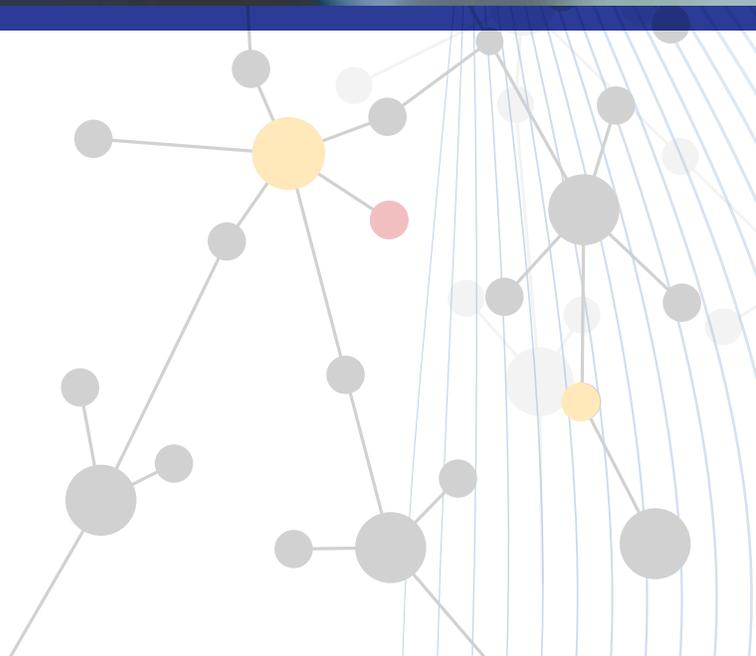# CERTARA

Advancing Pediatric Drug Development and Regulatory Acceptance Using Simcyp PBPK: from Birth to Young Adult

Case studies for dose selection, neonate exposure, drugs for children's rare diseases, DDI for pediatrics, and developing child-specific formulations

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PBPK allows you to ask many 'what if' questions and elucidates the distribution, metabolism and absorption mechanisms of drugs to determine the important factors for predicting exposure in neonates, infants and children of all ages.

As encouraged by global regulators and bolstered by requirements for sponsors to develop pediatric study plans (PSP in the US), or pediatric investigation plans (PIP in the EU), model informed drug development (MIDD) has demonstrated distinct advantages in pediatric drug development. MIDD, specifically physiologically based pharmacokinetics (PBPK), is an invaluable and proven tool that can help avoid unnecessary pediatric studies, ensure clinical trial dose selection is based on science, and minimize clinical trial enrollment while delivering relevant treatment data.
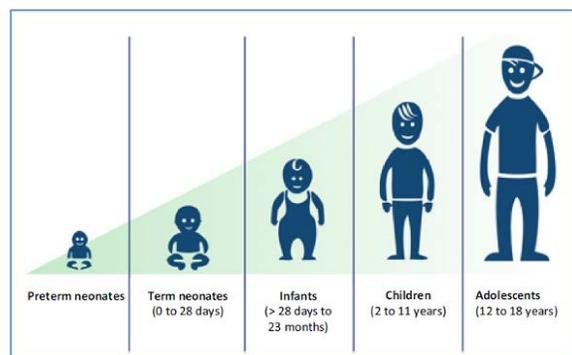
To be clear, PBPK can predict clinical outcomes in all age groups—neonates, infants, children, and adolescents.

ASSESSING DRUG EFFECTS IN CHILDREN

Children are not small adults, and not all children are the same. Children may need different doses of medicine, different sizes of devices, or different types of therapy at each stage of growth. Growth, maturation, and environmental factors, along with disease and genetic factors, directly affect drug performance in children.

For example, a premature baby's body is composed of 80% water and 5% fat, while at one year old that composition changes to 61% water and 20% fat. Factors such as kidney function, brain volume, blood flow, and absorption, distribution, metabolism, and excretion (ADME) are non-linear during the neonate to small child period. Finally, organ maturation has a significant effect on drug metabolism and excretion. Children have relatively larger livers, lower glomerular filtration rates, and less renal tubular absorption and excretion compared to adults.

Figure 1.

Developing and prescribing drugs to children is a scientific, ethical and logistical challenge

Preterm neonates | Term neonates (0 to 28 days) | Infants (> 28 days to 23 months) | Children (2 to 11 years) | Adolescents (12 to 18 years)

MIDD ADDRESSES THE MANY CHALLENGES IN PEDIATRIC DRUG DEVELOPMENT

Pediatric drug development cannot be defined as one process; it is an expansive endeavor with much variation, especially for dosing recommendations. And while there has been tremendous progress, the ethical, logistical, and physiological issues remain significant, including:
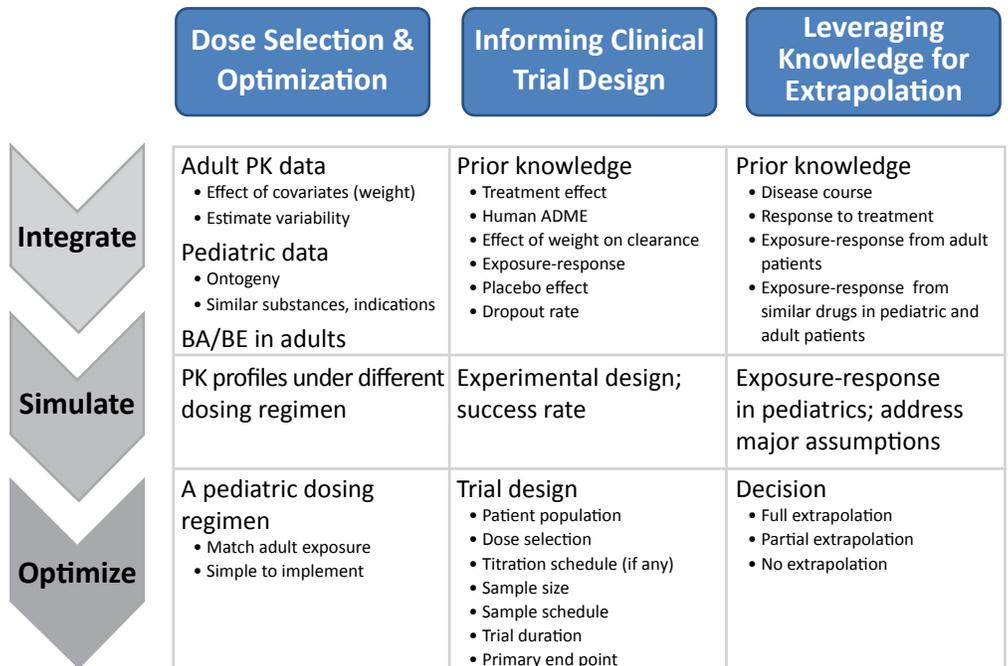
• Enrollment and optimization of clinical trials

• Trial protocols for children, such as sampling frequency and placebo effect

• First-in-human dose prediction

• Impact of ontogeny and other age-dependent factors

• Age- and population-related physiological differences

• Disease-related changes

• Biomarkers and endpoints

• Distribution, metabolism, and absorption issues specific to children

Pediatric drug–drug interactions (DDIs) can be life threatening, and a plan for assessing the potential interactions should form part of every pediatric drug development program, according to the FDA. PBPK modeling can be leveraged for both DDI factors related to the drug and also for the potentially age-dependent DDI liability across different pediatric age groups.

FDA recently published a suggested "Integrate-Simulate-Optimize" workflow for applying MIDD (Figure 2). The understanding of the pathophysiology or the expression of the disease is the main driver for leveraging existing knowledge, as well as extrapolation of information from other populations (adults or other pediatric populations). We present case studies that demonstrate the application of PBPK modeling in each of the key areas shown below.

Figure 2.

Suggested workflow of applying MIDD in pediatric drug development: bioavailability; bioequivalence; pharmacokinetic, pharmacodynamic.

	Dose Selection & Optimization	Informing Clinical Trial Design	Leveraging Knowledge for Extrapolation
Integrate	Adult PK data • Effect of covariates (weight) • Estimate variability Pediatric data • Ontogeny • Similar substances, indications BA/BE in adults	Prior knowledge • Treatment effect • Human ADME • Effect of weight on clearance • Exposure-response • Placebo effect • Dropout rate	Prior knowledge • Disease course • Response to treatment • Exposure-response from adult patients • Exposure-response from similar drugs in pediatric and adult patients
Simulate	PK profiles under different dosing regimen	Experimental design; success rate	Exposure-response in pediatrics; address major assumptions
Optimize	A pediatric dosing regimen • Match adult exposure • Simple to implement	Trial design • Patient population • Dose selection • Titration schedule (if any) • Sample size • Sample schedule • Trial duration • Primary end point	Decision • Full extrapolation • Partial extrapolation • No extrapolation

PBPK IS A POWERFUL TOOL FOR PEDIATRIC DRUG DEVELOPMENT

One of the advantages of PBPK models is that they make optimal use of available data by marrying the complex interplay of physiological parameters with drug characteristics.

Pediatric PBPK models integrate additional information regarding organ development and ontogeny of pathways involved in drug disposition and are frequently used for dose prediction in different age groups based on equivalent adult exposure in both clinical and drug development settings.

PBPK modeling enables extrapolation of relevant endpoints from in vitro and in vivo data and the answering of myriad 'what if' drug development questions. Simcyp PBPK models describe the drug concentration in different organs behavior across different body tissues and thus help to inform clinical trial design, first-in-human dosing, formulation design, dose differentiation for special populations, and predictions related to potential drug-drug interactions (DDI).

A recent paper identified 181 publications and available regulatory reviews that used PBPK for pediatrics, representing a 33-fold increase between 2005 and 2020. As shown in figure 3, 50% were classified under clinical, 18% under drug development, and 33% under model development (defined as generating data for use in the pediatric model). Covariate identification (47% of clinical), dose selection (75% of drug development), pharmacokinetic prediction, and model parameter identification (68%) were identified as the main secondary applications (figure 4).

Figure 3.

Use of pediatric PBPK in clinical, drug development, and model development settings
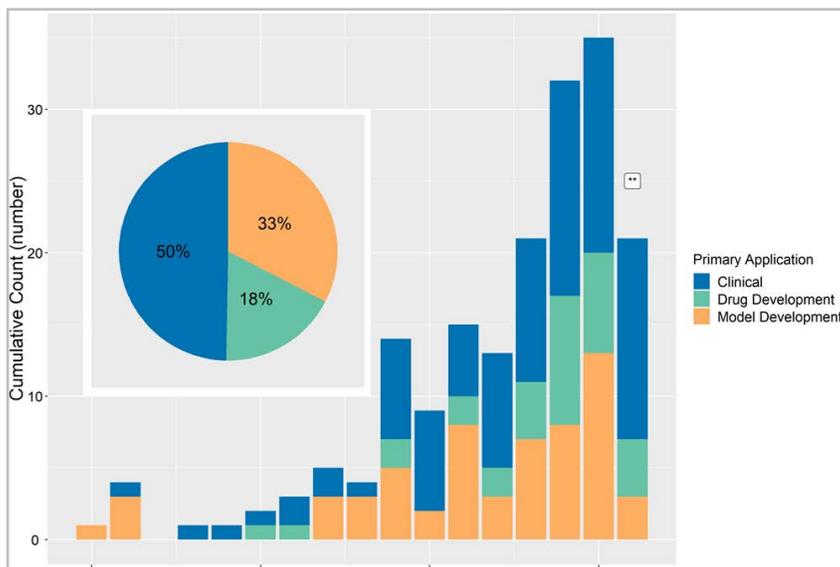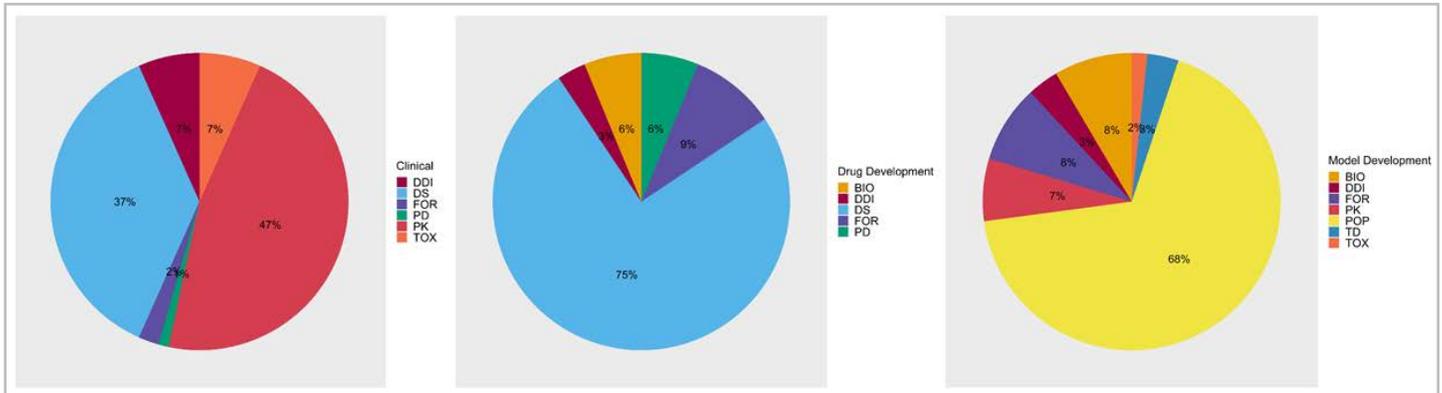
Figure 4.

Secondary applications for pediatric PBPK highlight dose selection, population development, and trial design as modeling outputs

Biologics (BIO); Drug-drug interaction (DDI); Dose selection (DS); Formulation (FOR); Pharmacodynamics (PD); Pharmacokinetics (PK); Population file development (POP); Trial design (TD); Toxicology (TOX)

SIMCYP PEDIATRIC

Simcyp Pediatric is a module within the Simcyp Simulator that allows for the modeling of pharmacokinetic behavior in neonates, infants, and children. This provides valuable information relevant to dosing decisions, analysis of DDI and other safety issues, design and formulation of drugs for children, and the design of pediatric clinical studies to minimize the number of required subjects.

With Simcyp Pediatric, researchers can:

- Determine and optimize dose selection for children, from neonates to age 2, 2-6 years, 6-12 years, and adolescents;
- Predict pharmacokinetics based on in vitro drug data or from adult in vivo data by retrograde modeling;
- Quantify potential DDIs for any age range;
- Assess the impact of formulation changes for pediatric dosing;
- Simulate pharmacokinetic variability over any pediatric age range;
- Support development of small molecules and biologics
- Inform clinical trial design for pediatrics.

CASE STUDIES DEMONSTRATE SIMCYP PEDIATRIC APPLICATIONS

The Simcyp Simulator includes a full PBPK model together with extensive libraries on demographics, developmental physiology, and the ontogeny of drug elimination pathways. It links in vitro data to in vivo ADME and pharmacokinetic/pharmacodynamic (PK/PD) outcomes to help explore potential clinical scenarios and support decision-making in drug development.

The adult and pediatric (including neonate to age 2) versions of the Simcyp Simulator have been used in the 10 applications in this paper, categorized as:

- Drugs developed specifically for children diseases or children's conditions as varied from adults;

- Dosing in children. In infants and neonates, PBPK models incorporating pediatric ontogeny can more accurately predict the drug PK as compared to allometry, when there is a sufficient understanding of the ADME process of the drug and the ontogeny is well-characterized for those processes;

- Formulation/bridging for children. Liquid versus oral, extended release, transdermal delivery, topicals, and other options have been achieved via PBPK bridging analyses;

- DDI in children. Aligned with organ development, the DDI liability may vary widely from the adult data;

- Scaling from adult to adolescents;

- Optimizing of combination therapy for children.

PEDIATRIC CASE STUDY #1 – DEFLAZACORT—RARE CHILDREN'S DISEASE

Duchenne Muscular Dystrophy (DMD) is a severe type of muscular dystrophy that primarily affects boys. Muscle weakness usually begins around the age of four and worsens quickly. Muscle loss typically occurs first in the thighs and pelvis, followed by the arms, which can result in trouble standing up. Scoliosis is also common. Females with a single copy of the defective gene may show mild symptoms.

Deflazacort (Emflaza®) was fast-tracked, given orphan status and approved by the US FDA in February 2017 for patients 5 years and older. Emflaza is a corticosteroid that works by decreasing inflammation and reducing the activity of the immune system. It is also a pro-drug, which undergoes conversion in the plasma by esterases, taken to the liver, and metabolized by CYP3A4 enzymes. Not only did this raise a concern about the drug's DDI liability, but DMD patients typically take multiple other medicines to support the heart, breathing muscles, bone health, gastrointestinal symptoms, hormone levels, common antibiotics, and to manage pain.

Simcyp Pediatric Simulator was used to model exposure in children and adolescents, simulate DDI and provide dose recommendations. Dose adjustments for moderate to severe CYP3A4 inhibitors and inducers were determined using the PBPK modeling as shown in the label below.

FDA writes in a recently published paper, *"Approximately 60% of the intended uses of PBPK in regulatory decision making are related to drug-drug interaction. The PBPK predictions for the drug drug interaction in children and adolescents, such as the interaction with concomitant administration of CYP3A modulators, have been accepted as supportive evidence for the proposed dosing recommendations on the deflazacort label."*

Figure 5.

Language from the drug label for Emflaza as determined by Simcyp PBPK simulations

CASE STUDY #2 – QUETIAPINE—FORMULATION BRIDGING FOR CHILDREN

Early onset schizophrenia and bipolar disorder can occur in children as young as 12. As with many mental illnesses, adherence to drug regimen is a challenge, especially for teenagers. Quetiapine is an atypical antipsychotic for the treatment of schizophrenia, bipolar depression, bipolar mania that works by helping to restore the balance of certain natural substances (neurotransmitters) in the brain.

Originally approved as an immediate release (IR) formulation, given twice/day, changing the formulation to a daily extended release (XR) delivery to improve patient adherence was undertaken. The Simcyp ADAM module was used to compare exposure between the two formulations. The modeling showed differences in regional distribution, with most of drug in the IR formulation being absorbed in the duodenum and jejunim, while the XR formulation releasing further down the intestine and being absorbed in the colon (Figure 6). Although not relevant for quetiapine, using a modified release formulation that avoids release in the proximal intestine is an approach that can be used for drugs with low bioavailability due to significant intestinal metabolism.
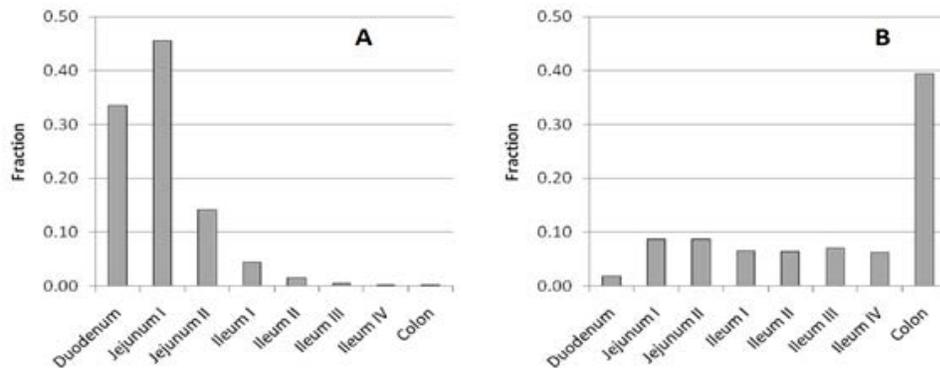

Figure 6.

Simcyp's ADAM module shows the regional distribution of the predicted fraction of dose across the GI tract in IR (A) and XR (B) formulations of quetiapine

PBPK models using the Simcyp Simulator employing in vitro ADME and physicochemical data, clinical PK data of quetiapine IR/XR in adults, and clinical PK data of quetiapine IR in children were developed. These models predicted the effects of CYP3A4 inhibition and induction on the PK of quetiapine, the PK profile of quetiapine IR in children and adults, and the PK profile of quetiapine XR in adults (Figure 7). Most important, the PBPK model predicted that children and adolescents are likely to achieve a similar exposure following administration of either the XR formulation once daily or the IR formulation twice daily at similar total daily doses. This was a high impact use of pediatric PBPK modelling in that a clinical study was avoided, and approval was given for the pediatric labelling of Quetiapine XR.

Figure 7.

Strategy for application of Simcyp Pediatric module to assess differences in exposure after dosing of XR and IR formulations
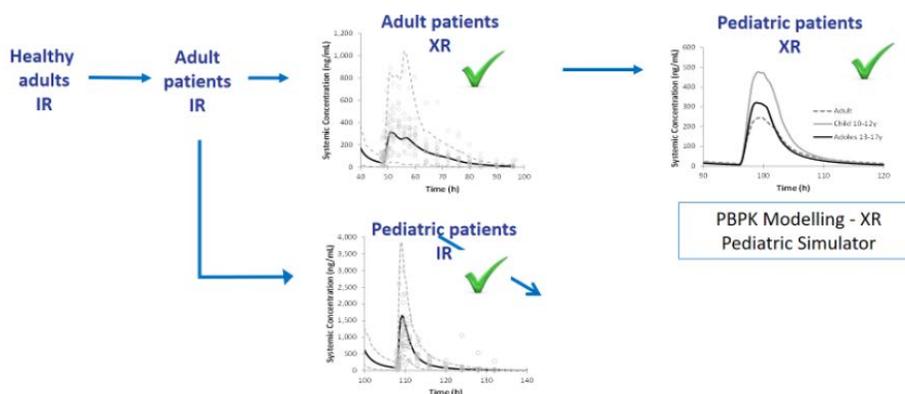
CASE STUDY #3: VOXELOTOR—DOSING FOR CHILDREN IN A COMPLEX DISEASE

Sickle Cell Disease (SCD) is a group of inherited red blood cell disorders in which there are not enough healthy red blood cells to carry oxygen throughout the body. In SCD, the red blood are shaped like sickles or crescent moons versus round blood cells. These cells can easily get stuck and tend to die early, causing a shortage of red blood cells.

In November 2019, the US FDA granted accelerated approval for Voxelotor (Oxbryta®) tablets for the treatment of SCD in adults and children 12 years of age and older. A small molecule that binds to hemoglobin and increases the protein's affinity for oxygen, Voxelotor also inhibits hemoglobin polymerization, thus preventing red blood cells from becoming deformed.

The Simcyp Simulator was used to build and verify a model in healthy adults and integrate the disease-related factors (Figure 8). By incorporating binding changes and changes in hematocrit, we are able to capture that significant change in blood-plasma ratio and recover exposure we would expect to see in sickle cell adults. Next, we integrated age-related changes based data in children and adolescents with SCD.

In pediatrics, the physiological changes are significant. As this drug is highly protein bound, any change in ontogeny for albumin will have an impact on the binding of the drug, as well as hematocrit changes that will impact blood exposure of the drug. The simulations validated the dosing in older children and provide dosing recommendations for children 9 months to 12 years old. Further clinical studies and PBPK simulations are ongoing.
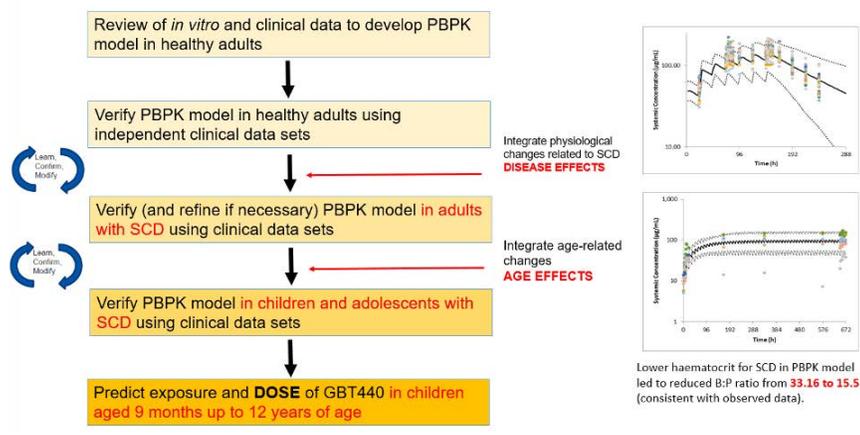
Figure 8

Strategy to predict appropriate dose of Voxelotor in children with SCD

CASE STUDY #4: RADIPRODIL—PBPK-PD RECEPTOR OCCUPANCY MODEL FOR NEONATES

Infantile spasm syndrome, also called West syndrome, is a rare type of epilepsy that affects babies. There is no cure for the disease, and the standard of care has limited success in treating symptoms. The drug Radiprodil, originally developed for chronic neuropathic pain conditions, was assessed as a potential treatment. Radiprodil is a selective allosteric modulator of the NR2B N-methyl-D-aspartate receptor GluN2B-NMDA.

Alongside clinical trials, a Radiprodil PBPK-PD model was built based on in vitro data in the Simcyp Simulator. The model was expanded to incorporate our understanding of the developmental physiology and ontogeny of elimination to predict PK in the age-appropriate pediatric population for this disease (2 to 14 months). We then linked the PBPK model to a receptor occupancy (RO) PD model in the Simcyp Simulator.

In vitro experiment based on hepatocyte data was used to further assess our understanding of the ontogeny, first for CYP1A2/acetaminophen and then for Radiprodil. Based on those results, which strongly suggested a lack of ontogeny effect, a dosing decision tree was developed (Figure 9), recommending a low RO and low dose escalation approach. To our knowledge, this is the first time a PBPK model linked to RO has been used to guide dose selection and escalation in the live phase of a pediatric clinical trial.

Because the disease is rare and potentially life threatening, there was the need for trial doses to be efficacious from the start while paying attention to limiting the upper level of RO to avoid unwanted potential side effects associated with high levels of NMDA receptor antagonism. In this case, the use of a PBPK-PD model allowed a potentially more robust dosing strategy to be developed compared to simple allometry alone, which tends to overestimate doses in neonates and infants. The final Simcyp model was used to determine initial doses with age and to guide dose escalation for three individual subjects in the live phase of a clinical trial, predicted and observed data was in close agreement.

Figure 9.

Decision tree for Radiprodil dose escalation in clinical trial
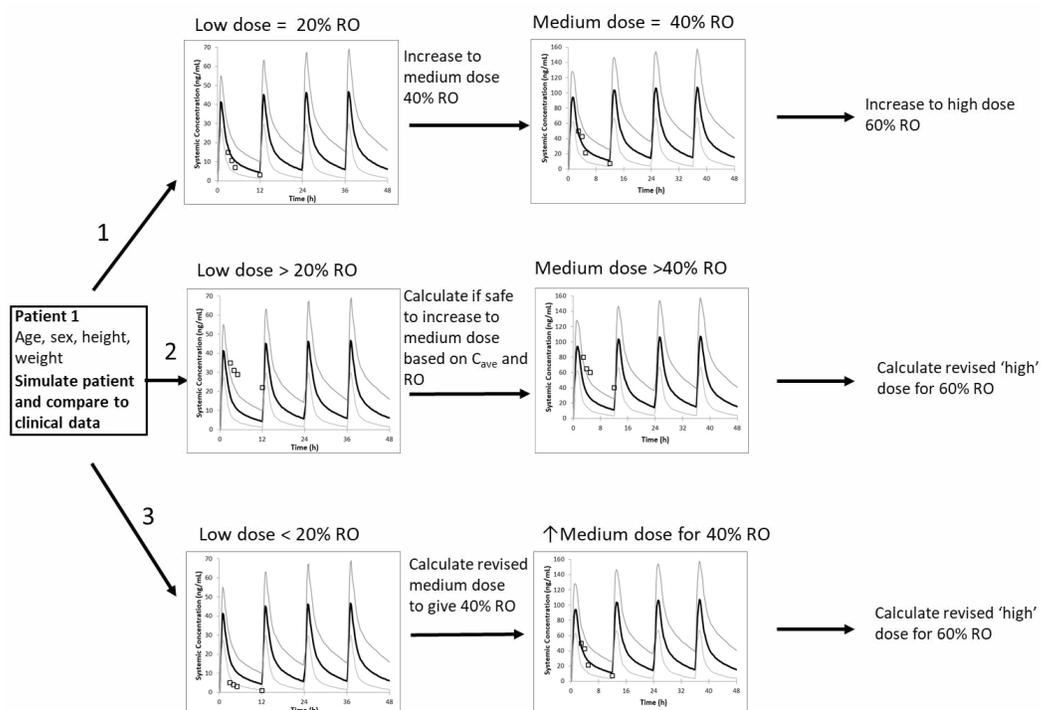
CASE STUDY #5: EVEROLIMUS—SIMCYP'S AGE DEFINING FEATURE FACILITATES DOSING IN NEONATES

Tuberous sclerosis complex (TSC) is a rare genetic disorder resulting in benign tumours in various organs, including the brain, eyes, heart, kidney, skin, and lungs. The majority of patients with TSC develop epilepsy, and approximately two-thirds become refractory to antiepileptic drugs (AEDs).   Everolimus (Afinitor®) was recently approved as adjunctive therapy for TSC-associated partial seizures in ages 2 and older. Unlike many other therapies for treating TSC-associated seizures, Everolimus addresses the underlying pathophysiology of TSC.

As TSC-associated seizures can also affect children aged between 6 months and 2 years, a modeling and simulation approach that incorporated Population PK, Population PD, and PBPK was used to extrapolate exposure. The PBPK model, built and qualified in the Simcyp Simulator, predicted Everolimus exposure in 200 patients, ages 6 months to 1 year. The PBPK data was incorporated into a Population PD model to simulate the reduction in seizure frequency.

As certain enzymes, specifically CYP3A4, are ontogeny-specific, the unique 'age redefining feature' in the Simcyp Pediatric Simulator was used for this program. Everolimus is both a CYP3A4 and PgP substrate. This feature accounts for the time variance in very young subjects by simulating the aging elements over time (physical growth, non-linear organ development, age factors, blood flows, ontogeny kicking in). In short, Simcyp Pediatric can simulate the combination of changes resulting from both physiology and ontogeny factors as children age.

Final dosing determination required the prediction of the Cmin to stay within 5–15ng mL for efficacy. By using the age defining feature in Simcyp, the model showed the dose recommendation of 6 mg/m2 is expected to be effective over the target range of 6 months to 2 years in both the short term (12 weeks of exposure) and long term (up to 2 years of exposure).

PBPK predictions and ontogeny impacts using Simcyp's age redefining feature
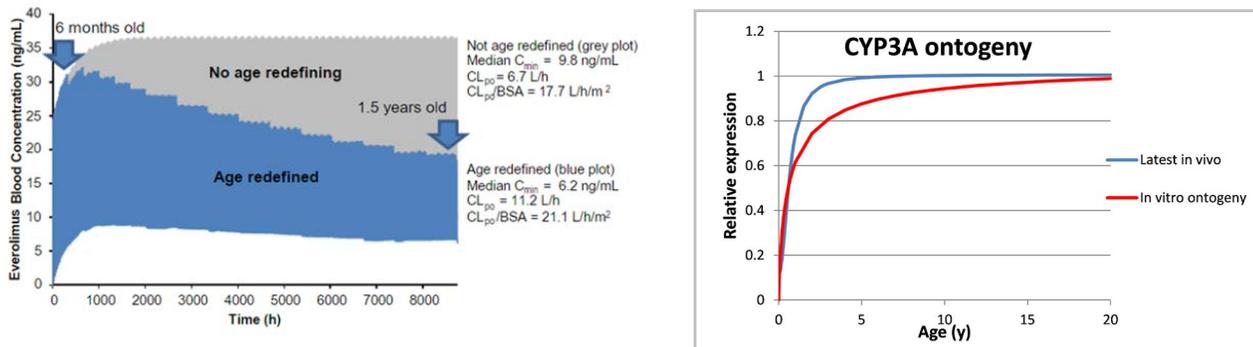
CASE STUDY #6 – GUANFACINE – DDI LIABILITY IN CHILDREN

Attention deficit/hyperactivity disorder (ADHD) is a common childhood diagnosis. The average age of diagnosis for ADHD is 8 years old and 10 years for ADD. Guanfacine (Intuniv® XR) extended release (GXR) is an orally administered, selective alpha2A-adrenergic receptor agonist, non-stimulant treatment for children and adolescents with ADHD.

Guanfacine is primarily metabolized by the CYP3A4 enzyme; thus, it was important to evaluate the DDI liability perpetrated by strong inhibitors and inducers of CYP3A4. Using data from clinical PK studies in which GXR was administered as a monotherapy or co-administered with strong CYP3A4 inhibitors or inducers, PBPK modeling using the Simcyp Simulator was employed for DDI evaluation. Based on these predictions, dosing recommendations for GXR were approved by the US FDA without the need to conduct further clinical studies.

The dosing recommendations on the label are to (1) decrease GXR to 50% of the usual target dose when it is co-administered with strong or moderate CYP3A4 inhibitors and (2) consider titrating GXR up to double the usual target dosage over 1–2 weeks when it is co-administered with strong or moderate CYP3A4 inducers. As pharmacological treatment of ADHD may be needed for extended periods, healthcare providers should periodically re-evaluate the long-term use of GXR and adjust weight-based dosage as needed. The majority of children and adolescents reach optimal doses in the 0.05-0.12 mg/kg/day range. Doses above 4 mg/day have not been evaluated in children (ages 6-12 years), and above 7 mg/day have not been evaluated in adolescents (ages 13-17 years).

Table 1: Recommended Target Dose Range for Therapy with INTUNIV®

Weight	Target dose range (0.05 - 0.12 mg/kg/day)
25-33.9 kg	2-3 mg/day
34-41.4 kg	2-4 mg/day
41.5-49.4 kg	3-5 mg/day
49.5-58.4 kg	3-6 mg/day
58.5-91 kg	4-7 mg/day
>91 kg	5-7 mg/day

Doses above 4 mg/day have not been evaluated in children (ages 6-12 years) and doses above 7 mg/day have not been evaluated in adolescents (ages 13-17 years)

Figure 12.

Dose selection for Guanfacine based on child's body weight

CASE STUDY #7 – TRIKAFTA – COMBINATION THERAPY FOR CYSTIC FIBROSIS IN CHILDREN

Cystic fibrosis is an inherited condition that causes sticky mucus to build up in the lungs and digestive system. This causes lung infections and problems with digesting food. Symptoms usually start in early childhood and vary from child to child, but the condition gets slowly worse over time, with the lungs and digestive system becoming increasingly damaged.

In 2012, FDA approved Ivacaftor (Kalydeco®) for treatment of the underlying cause of CF in a small subset of the patient population. In 2015, a combination treatment of Ivacaftor and Lumacaftor (Orkambi®), followed by a combination of Ivacaftor and Texacaftor (Symdeko®) in 2018. In 2019, the first triple combination of Elexacaftor/Texacaftor/Ivacaftor (Trikafta®) for patients 12 and up, accounting for about 90% of patients with CF was approved.

Many CF patients that take modulator regimens of the above dual combinations will need to transition to the triple combination. An assessment of whether adequate exposures to achieve clinical efficacy are maintained during this transition was needed, as this has not been directly addressed in clinical trials. PBPK modeling using Simcyp was used for this analysis, specifically to understand the CYP3A4 during the cystic fibrosis transmembrane conductance regulator process. Individual models for each drug were developed, followed by simulations of various combination to assess exposure.

The PBPK modeling demonstrated that immediate transfer from the three dual combinations to the triple combination resulted in sustained CFTR in patients 12 years and higher. Clinical trials on younger patients are ongoing.

Figure 13.

Dose adjustments for combination therapy

2.3 Dose Adjustment for Patients Taking Drugs that are CYP3A Inhibitors

Table 2 describes the recommended dosage modification for TRIKAFTA when co-administered with strong (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) or moderate (e.g., fluconazole, erythromycin) CYP3A inhibitors. Avoid food or drink containing grapefruit during TRIKAFTA treatment *[see Warnings and Precautions (5.3), Drug Interactions (7.2), Clinical Pharmacology (12.3), and Patient Counseling Information (17)].*

Table 2: Dosing Schedule for Concomitant Use of TRIKAFTA with Moderate and Strong CYP3A Inhibitors

Moderate CYP3A Inhibitors				
	Day 1	Day 2	Day 3	Day 4*
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet
Evening Dose^	No dose			

* Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet on alternate days.
^ The evening dose of ivacaftor should not be taken.

Strong CYP3A Inhibitors				
	Day 1	Day 2	Day 3	Day 4#
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	No dose	No dose	Two elexacaftor/tezacaftor/ivacaftor tablets
Evening Dose^	No dose			

Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart.
^ The evening dose of ivacaftor tablet should not be taken.

CASE STUDY #8 – TRIFAROTENE CREAM – FIRST NEW RETINOID-BASED ACNE TREATMENT IN 20 YEARS FOR ADOLESCENTS

Acne is the most common skin disease in the United States, affecting up to 50 million Americans annually and approximately 85% of young people. As an inflammatory disease, acne occurs when a combination of sebum and dead skin cells clog pores, allowing the bacteria associated with acne to grow. Acne can trigger feelings of depression, poor body image, and low self-esteem.

In October 2019, Galderma announced that the U.S. FDA approved AKLIEF® (trifarotene) Cream, 0.005% for the topical treatment of acne. It is the only topical retinoid that selectively targets retinoic acid receptor gamma and is also the first new retinoid molecule to receive FDA approval for the treatment of acne in more than 20 years.

The use of the Simcyp Simulator allowed Galderma to expedite and inform its drug development program while also providing safety label claim and pediatric dosing information without the need for testing in clinical patients. Specifically, Simcyp's Mechanistic Dermal Absorption (MechDermA) model was used to predict the outcome of specific drug interactions and provide dosing guidance for pediatric patients aged nine to 17.
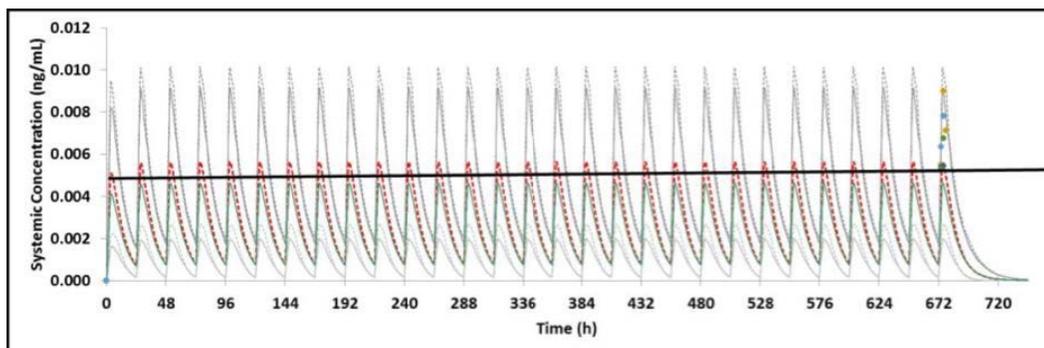

Figure 14.

Simcyp used to bridge clinical gaps in pediatric populations

The Simcyp Simulator's MechDermA model mimics the diffusion of the drug from the skin epidermis into deep tissue. It enables researchers to estimate local and systemic exposure resulting from either topical or transdermal absorption of different drug doses. It allows a drug ADME and potential interactions to be tested in virtual patient populations of different demographics (ages, sexes, weights, ethnicities, etc...) and with specific skin conditions. This approach helps to overcome the ethical and operational challenges associated with conducting pediatric drug trials and, in general, to avoid unnecessary drug exposure to both patients and healthy volunteers.

# CASE STUDY #9 – RISDIPLAM – DDI IMPACT FOR RARE DISEASE IN NEONATES

Spinal muscular atrophy (SMA) is a genetic disease that progressively destroys motor neurons—nerve cells in the brain stem and spinal cord that control essential skeletal muscle activity such as speaking, walking, breathing, and swallowing, leading to muscle weakness and atrophy. It typically begins in infancy or childhood and affects about 1 in 11,000 babies.

Risdiplam (Evrysdi®) was approved by the US FDA in 2020 as the first orally administered drug for SMA treatment for patients ≥2 months old, followed by the European Medicine Agency. Risdiplam addresses the underlying cause of SMA: a reduced amount of survival motor neuron (SMN) protein.

As Risdiplam exhibits time-dependent inhibition of CYP3A in vitro, DDI were a concern, but a clinical study in pediatric patients with SMA was not feasible. Therefore, a novel PBPK strategy involving the Simcyp Simulator was used to extrapolate DDI risk from healthy adults to children with SMA. As shown in figure 15, model-based prediction of in vivo CYP3A inhibition of Risdiplam using PBPK models for healthy adults and patients with SMA, including pediatric populations, were conducted.

Figure 15.

Model-based CYP3A inhibition risk assessments for pediatric patients with SMA
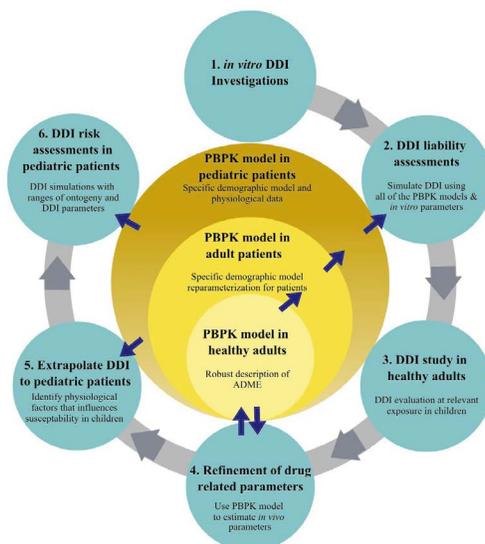
Validation of the Risdiplam and midazolam PBPK model for healthy adults using the observations of the clinical DDI study followed, included refinement of the in vivo data, facilitating the extrapolation and DDI risk assessments using the pediatric Risdiplam PBPK model. Different ontogeny functions of CYP3A enzyme predicted different susceptibility to CYP3A modulations in children, and thus various functions were considered. The Risdiplam PBPK model was validated with independent data for each population. The PBPK-predicted Risdiplam CYP3A inhibition risk in pediatric patients with SMA aged 2 months–18 years was negligible and included in the prescribing information.

This case study demonstrates that pediatric PBPK modeling performed iteratively with well-designed clinical study in adults' enables prospective DDI risk assessments in children. Further, proper selection of intestinal and hepatic ontogeny models based on sensitivity to enzyme modulation facilitates the DDI extrapolation to children.

CASE STUDY #10 – CHRONOCORT-NEW FORMULATION DEVELOPMENT FOR RARE DISEASE IN ADOLESCENTS

Congenital adrenal hyperplasia (CAH) is an orphan condition caused by deficiency of adrenal enzymes needed to produce the adrenal steroid hormone cortisol. The block in the cortisol production pathway causes the over-production of male steroid hormones (androgens), which are precursors to cortisol. The condition is congenital (inherited at birth) and affects both sexes. The cortisol deficiency and over-production of male sex hormones can lead to increased mortality, infertility, and issues during sexual development. Sufferers, even if treated, remain at risk of death through an adrenal crisis. Current therapy for CAH, which affects about 400,000 patients worldwide, uses a variety of generic glucocorticoid (steroids including hydrocortisone, dexamethasone, prednisolone, and prednisone in the US) with no standard treatment regimen.

In July 2021, the European Commission (EC) approved the marketing authorization for Efmody® (hydrocortisone modified-release hard capsules – development name Chronocort®) as treatment of adult and adolescent patients (12 years and older) with CAH. Efmody contains the active substance hydrocortisone and is a 'hybrid medicine, which means that it has a different use and is available in different strengths as capsules formulated to release the active substance over a prolonged period (modified release).

To facilitate clinical development, a PBPK model for the endogenous hormone cortisol (hydrocortisone) in healthy adults and children and adults with adrenal insufficiency was built in the Simcyp Simulator. The model predicted immediate-release hydrocortisone pharmacokinetics in adults across the dose range 0.5 to 20 mg, with predicted/observed AUCs within 0.8 to 1.25-fold. The model also accuarately predicted pharmacokinetic parameters for modified-release formulations, with AUCs within 0.8 to 1.25-fold after single and multiple dosing. Predicted modified-release formulation pharmacokinetics (PK) in 12 to 18-year olds showed PK to be similar to adults (figure 16).

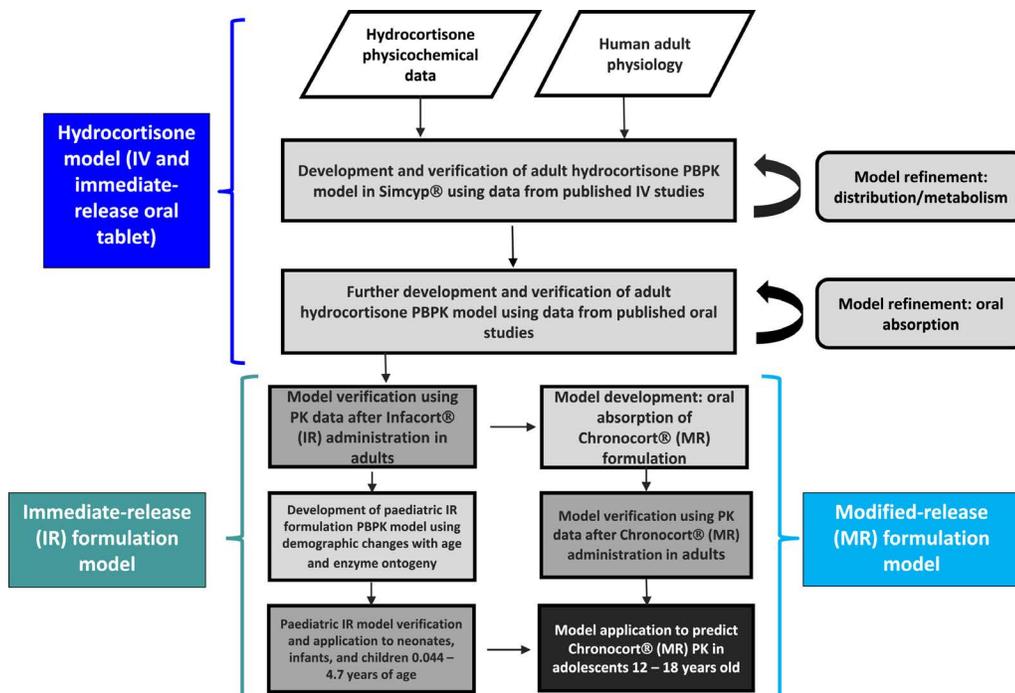PBPK assisted in determining the final dosing regimen.

Figure 16.

Workflow of hydrocortisone model development, verification, and application

Summary

One size does not fit all when it comes to pediatric drug development. The variation in disease type, drug characteristics, age and maturity of patients, ability to conduct clinical trials, and formulation/dosing options must drive the process. Fortunately, drug developers and regulators have recognized that while challenging, innovative approaches can greatly facilitate our ability to overcome the many ethical, logistical, and physiological challenges inherent in pediatric drug development. PBPK is a proven approach to respond to this opportunity, and the Simcyp Simulator has played a pivotal role in guiding that progress.

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Case Study Label Documentation

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Oxbryta:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf

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