



Learning From Failure: Leveraging Modeling and Simulation for Pediatric Drug Development Success

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The changing landscape of pediatric drug development

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We have evolved a view that we must protect children from research to a view that we must protect children through research.

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– Robert Nelson, FDA Pediatric Ethicist

Historically, clinical trials have not examined most pediatric medications. This is due to the ethical and practical challenges of conducting pediatric drug trials. Children are 40% of the world's population. Yet, regulatory agencies have approved only 10% of the drugs on the market for pediatrics.¹ Without a proper clinical process, pediatricians are stuck with inaccurate dosing and therapeutic approaches. The result is a continuation of off-label, experiential drug prescribing.

To address this urgent need, both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) now require pediatric trial plans for new drugs. These trial plans are known as the Pediatric Study Plan (PSP) and the Pediatric Investigation Plan (PIP), respectively. The combination of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) and these new regulatory requirements are moving the pendulum towards safer, more effective medicines for children. Between 2007 and 2013, 469 pediatric studies were completed under BPCA and PREA. And by August 2014, 526 labeling changes were made.² Since 2007, around 300 products have had label changes approved for safety, efficacy or dosing for pediatrics in the European Union.²

These requirements have spurred growth in pediatric drug development. Still, there are major barriers to successful pediatric drug development. Almost half of the trials conducted in recent years have failed to show either safety or efficacy. A total of 44 products submitted to the FDA between 2007 and 2014 had failed pediatric drug trials.³ An analysis by Gilbert J. Burckart, PharmD, and his FDA colleagues revealed several factors that contributed to the widespread failures. These factors include suboptimal dosing, differences between adult and pediatric disease processes, and problematic study designs. Suboptimal dosing often contributed to the failure to show efficacy. The inability to show a drug's effectiveness was linked to two issues: not testing a range of doses and limiting pediatric drug exposure to that which was shown to be effective in adults. Testing a range of doses is critical to understanding dose-response relationships for a drug.

Also, the disease process may differ between children and adults. In this case, matching drug exposure to that observed in adults may not be effective and may result in trial failure. An understanding of pediatric disease progression is crucial for selecting the primary efficacy endpoint. Finally, problematic study designs are a significant contributing factor in clinical trial failures. The design issues included lack of a control group, problems in the design of the efficacy studies, and inadequate assay sensitivity.

A modeling and simulation framework to support strategic decision-making

The nature of human growth and maturation makes predicting pharmacokinetics in children challenging. Drug disposition in children differs from that of adults in many ways. For example, the expression of drug transporters and metabolizing enzymes changes during development.⁴

Thus, drug absorption kinetics are different in children versus adults. Likewise, drug distribution changes with age. Neonates have much higher total body water compared to adults. Finally, organ maturation has a significant effect on drug metabolism and excretion. Children have larger livers, lower glomerular filtration rates, and less renal tubular absorption and excretion compared to adults.⁵ This distinct physiology means that traditional approaches such as allometry risk over- or under-predicting drug clearance in pediatric patients. These risks in prediction errors are especially high for patients less than one year old.⁶

How can drug developers meet regulatory requirements and maximize drug safety and effectiveness while minimizing children's exposure to experimental medications? Modeling and simulation (M&S)—also known as model-based drug development—includes both empirical pharmacokinetic/pharmacodynamic (PK/PD) as well as mechanistic physiologically-based pharmacokinetic (PBPK) modeling and simulation. It leverages prior information from pre-clinical studies, adult trials, peer-reviewed literature, and pediatric studies of related indications or drugs. Integrating patient physiology, drug actions, and trial characteristics in models enables sponsors to optimize dosing and trial design. Indeed, a study of well-characterized drugs showed that PBPK models predict drug clearance more accurately than simple allometry. The improved predictions were especially pronounced in children less than two years of age.⁷ The increased certainty in biosimulated outcomes can help sponsors to ensure informative pediatric trials and gain approvals based on a smaller number of pediatric patients.

Opportunities during drug development for applying modeling and simulation techniques

The benefits of M&S are clear. Regulatory agencies advocate its use to double the success rate of pediatric trials from current levels. A 2014 draft guidance from the FDA states that “modeling and simulation using all of the information available should therefore be an integral part of all pediatric development programs.”⁸ At each stage of clinical development, there are specific opportunities to apply modeling and simulation techniques to increase the likelihood of success. Submission of the PIP is required by the end of Phase I clinical studies. M&S methods can support the dosing rationale stated in the PIP. Population pharmacokinetic (PopPK) and PBPK models based on Phase I data from adults can be used to develop a drug model that aids with pediatric dose selection. PopPK or PBPK models can predict drug exposure across a wide range of ages and weights as well as maturation and organ function. The predicted drug exposure in pediatric patients can then be compared against observed values in adult subjects in Phase I to confirm the models and optimize the safety of treatments. This approach can also be used to develop a sparse sampling strategy. This strategy optimizes the assessment of pharmacokinetic (PK) parameters while minimizing the number of blood draws and other invasive procedures.

Pediatric PBPK and PopPK models can be used synergistically during drug development. The former aids optimizing dosing and sampling times for PopPK.⁹ Conversely, the results from PopPK models can further optimize pediatric PBPK models.

PBPK models are also used to determine the risk of drug-drug interactions (DDIs). DDIs are a primary threat to the safety and efficacy of clinical practice. Clinically relevant drug interactions are primarily due to drug-induced alterations in the activity and quantity of metabolic enzymes and transporters. Indeed, DDIs causing unmanageable, severe adverse effects have led to restricted clinical use, and even withdrawals from the market.

The magnitude of any DDI depends on the fractional importance of the inhibited metabolic pathway. The pattern of CYP metabolic enzymes that contribute to the elimination of a drug may not be the same in children compared to adults. Thus, it is difficult to use information about DDIs in adults to inform the likelihood of pediatric DDIs. And, again, there are practical and ethical problems with evaluating DDIs in pediatric clinical studies. A 2012 Guidance from the EMA states that PBPK simulations may be used to predict the effects of drug interactions in special populations, including young pediatric patients.¹⁰ Use of the Simcyp Pediatric Simulator to simulate DDIs revealed that in certain scenarios, neonates could be more sensitive to a DDI than adults while the opposite might be true in other scenarios involving different CYP enzymes.¹¹ Pediatric PBPK models may help provide information about the risk and size of potential DDIs where there are no existing clinical data.

Pharmacometrics tools are also invaluable in supporting pediatric study plans. The PSP should be submitted at the end of the Phase II meeting, following the availability of exposure-response data in adults. To provide guidance on the conduct of pediatric trials, the FDA has articulated a pediatric study decision tree.¹² The degree of similarity of disease progression and drug response between adults and children determines which of three major pediatric studies should be undertaken: PK only, PK/PD, PK or efficacy. All scenarios require safety studies.

The regulatory path taken determines the strategy for optimizing dosing. In the case that PK studies alone are used, the sponsor should build a PopPK model customized for size and maturation. This model can then be used to perform dose simulations that will result in drug concentrations within the range of those observed in adults. Using the PK/PD approach means creating a PopPK/PD model customized for size and maturation and performing dose simulations that will achieve a target concentration based on the PK/PD relationship. Finally, a PK and efficacy approach involves building a PopPK model and an exposure-response model. Simulations are then performed to find a dose that will produce a drug concentration that results in an adequate response.

Phase III studies in adults are performed to determine whether there is significant evidence of clinical efficacy and safety for an investigational drug. At this point, the PIP and PSP should contain any new insights. This is also the time to develop final pediatric protocols. Clinical trial simulations using Phase II results can be useful for evaluating probability of success in Phase III. Trial simulations using Phase II results can calculate the probability of Phase III success.

Two case studies showing successful use of M&S for pediatric drug development

Learning from one indication to the next: Eculizumab for atypical hemolytic uremic syndrome

Information gained developing a drug for one indication can inform a different indication. PNH (paroxysmal nocturnal hemoglobinuria) is a rare, progressive, and life-threatening disease. It is characterized by rampant destruction of red blood cells (hemolysis) and excessive blood clotting.¹³ Likewise, aHUS (atypical hemolytic uremic syndrome) is an ultra-rare genetic disease. It causes abnormal blood clots to form in small blood vessels throughout the body. The sequelae of aHUS include kidney failure, damage to other organs, and premature death. There were no FDA-approved treatments for this rare disease.

Chronic, uncontrolled activation of the complement system causes both aHUS and PNH. During activation of the complement system, the terminal protein C5 is cleaved to C5a and C5b.

C5a and C5b cause terminal complement-mediated events characteristic of both aHUS and PNH. Eculizumab is a humanized monoclonal antibody (mAb) that binds C5, thereby inhibiting its cleavage. In 2007, this mAb received approval for treating PNH based on clinical study evidence.¹⁴

To help the sponsor get accelerated approval of eculizumab for treating aHUS in both adults and pediatric patients, Certara scientists leveraged previous knowledge gained during its development for PNH. Their starting point was a PopPK model that had been constructed in adult patients with PNH.¹⁵ This model was customized and used to develop optimal dosing strategies for adult and pediatric aHUS patients.

Comparing adults with PNH to pediatric aHUS revealed that children respond differently to intervention. Therefore, a different endpoint was used. The PK/PD relationship in PNH was leveraged to measure the drug's exposure and inform pediatric dosing for aHUS. Knowing eculizumab's mechanism of action for PNH suggested that optimal binding to the pharmacological target (C5) should provide clinical benefit.

Identifying the therapeutic dosing window for a mAb in pediatric patients involved several steps. First, to ensure patient safety, the upper exposure limit needed to be determined. As a safeguard against toxicity, the upper exposure limit was capped at what had been observed in adults. To ensure efficacy, the minimum drug exposure also had to be determined. The predicted concentration of the soluble target and the binding characteristics of the mAb to its target were used to set a minimum concentration threshold. Staying above this minimum threshold would ensure close to full target inhibition. Then, trial simulations using a PopPK model were performed to determine which doses would optimize the probability of obtaining the mAb within the window of target engagement. This enabled the dosing recommendations to be determined for pediatric patients of varying weights.¹⁵



The clinical program for aHUS involved two Phase II studies and a retrospective observational study. A total of 57 patients with aHUS participated in these studies (35 adult, 22 pediatric patients). Two different biomarkers were used to assess the efficacy of treatment. The proximal biomarker, free C5, showed complete suppression upon treatment with the mAb. Likewise, the mAb fully inhibited hemolytic activity (the distal biomarker).¹⁵ The primary endpoint indicated that the response to the intervention exceeded 95%. Patients treated with the mAb experienced several benefits. They showed improvement in platelet counts and other blood parameters and better kidney function. Some patients were even able to end their need for dialysis. Soliris® (eculizumab) received FDA approval to treat aHUS patients in 2011.¹⁶

Using PBPK modeling to assess differing drug formulations for pediatric patients

Quetiapine is an atypical antipsychotic drug. It is prescribed for schizophrenia, bipolar disorder, major depressive disorder and generalized anxiety disorder. The FDA approved an intermediate release (IR) formulation of quetiapine in 1997. This formulation has been studied in adults, children and adolescents. Regulatory approval for the extended release (XR) formulation was granted for use in adults. The approval also required pediatric studies of children over the age of 12.

Many factors influence the bioavailability of different formulations. These factors include the release of the active ingredient, its dissolution and permeability across the gastrointestinal tract, and intestinal metabolism. Furthermore, alterations in PK in children can be due to differences in absorption and transit rate, organ size, blood flow, tissue composition and metabolic capacity at various developmental stages. The challenge was integrating the available *in vitro* ADME, physiochemical and clinical data into PBPK models to predict the effects of age and formulation on the PK of quetiapine.



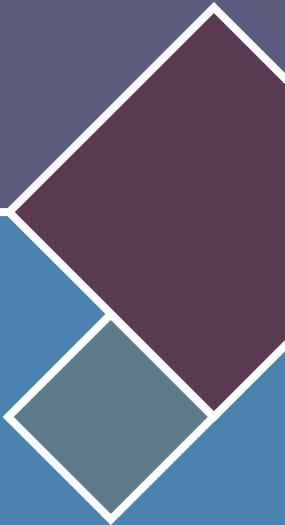
Scientists at Certara and AstraZeneca® developed models that predicted the effects of CYP3A4 inhibition and induction on the PK of quetiapine, the PK profile of quetiapine IR in both children and adults, and the PK profile of quetiapine XR in adults. These validated models were then used to simulate relative exposure following XR formulation in adolescents and children. In both groups, the predicted exposure to quetiapine XR was similar to the IR formulation. Dosing with 300 mg XR once daily was comparable to 150 mg IR twice a day.¹⁷

Meeting the FDA's challenge to double the success rate of pediatric trials

The high rate of trial failures, increasing regulatory demands, and ethical imperatives require reexamining the current approach to pediatric drug development. M&S is a proven approach. It can help optimize trial designs and inform the drug label. This approach can support strategies that increase the likelihood of success for pediatric drug development programs.

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About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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