



Informing Pediatric Drug Development

A Selection from Certara's Best of Blogs

Introduction

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

- Robert Nelson, FDA Pediatric Ethicist

Historically, most medications given to children had not been evaluated in pediatric clinical trials due to logistical and ethical challenges. Without an approved clinical process, physicians are left with inaccurate dosing and therapeutic approaches for children.

Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have legislated that pharmaceutical companies must develop label guidelines for pediatric drug development. These guidelines also must include proper dosing for children of all ages. These agencies have also recommended the use of modeling and simulation (also known as model-informed drug development and discovery) methods. Modeling and simulation leverages information from pre-clinical studies, adult trials, peer-reviewed literature, and pediatric studies of related indications or drug actions.

Certara has developed technologies and strategies for pediatric drug development to inform dose selection. These technologies include pharmacokinetic/pharmacodynamic (PK/PD) simulations using sparse data analysis and our Simcyp Pediatric Simulator. The Simulator captures developmental changes in physiology and enzyme/transporter ontogeny. These changes are particularly prominent in children from birth to two years of age. Certara's solutions provide the most advanced strategy for neonatal drug development.

Certara and our regulatory writing consultancy, Synchronix, also offer regulatory strategy for pediatrics. The strategy includes creation of regulatory documents such as the Pediatric Study Plan (PSP) and Pediatric Investigation Plan (PIP). By helping our clients understand regulatory, scientific, and commercial drug development challenges, we support delivering new therapies to children of all ages.

For more information, please visit:

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The Ultimate Guide to the Biosimulation Revolution

By: Ellen Leinfuss



In my work with biopharmaceutical companies, universities, and regulatory agencies, I fly a lot. Looking out the airplane window, the revolutionary impact of biosimulation on drug development struck me. Unfamiliar with the concept of biosimulation, or modeling and simulation (M&S)? You can think of it as the vast improvements in air travel that have been made in the last half century.

Modeling and simulation gets information about how something behaves without testing it in real life. For instance, say we want to design a plane that has maximum speed. But, we weren't sure what type of wings would improve non-friction. We would use a computer simulation of the plane to estimate the effect of different wing shapes on the coefficient of friction under different conditions. The simulation would provide insights about decisions we could make for the plane without building one. That's what modeling and simulation is.

Imagine this applied to the world of drug development. Biosimulation is transforming our approach to precision medicine and supporting critical decision-making.

Integrating computer-aided modeling & simulation and pharmaceutical science

Biosimulation is widely used by pharmaceutical companies, academic institutions, and regulatory agencies. The pharmaceutical industry uses this tool throughout the drug development process. During drug discovery, M&S helps identify molecules with the highest efficacy and the least toxicity.

For example, we can explore off-target effects as we design candidate drug molecules. Chemists used to build these models from plastic molecules. This work is now done in computers. Computer aided drug design technology can probe specific sites of a molecule to test safety and efficacy predictions.

During pre-clinical development, modeling and simulation provides a scientific rather than intuitive approach to dose selection. Again, this method provides the optimal dose so you achieve the best therapeutic window. This is a stark contrast to the historical approach to drug development. In fact, a significant percentage of the doses for approved drugs are actually wrong. These suboptimal dosing regimens create unnecessary toxicity and lower levels of efficacy.

Biosimulation technology is also used in clinical development to reduce toxicity and potential drug-drug interactions (DDIs). To optimize trial outcomes, sponsors leverage biosimulation technology to model different clinical trial designs.

From "one size fits all" to an individualized approach to treating patients

Twenty years ago, we treated all patients the same. Children. Pregnant women. Patients with different comorbidities. Even individuals from different ethnic groups like Chinese, Indian, Hispanic, and African American. They were all treated in the same way—one size fits all.

Several decades ago, we moved to the concept of patient stratification. You looked at patient body size and weight to inform treatment development and delivery.

Over the last five years, we've started looking at subgroups of patient populations. These subgroups are based on either genetic mutations or genetic polymorphisms, metabolic profiles, or different aspects of their physiology and physiopathology.

Today, the goal of biosimulation is to treat you as an individual, not as a member of a subpopulation. In the not too distant future, we will be able to build avatars of individuals. Before we test or treat a patient, we will treat his avatar and assess how it responds to the drug. Leveraging M&S approaches will be essential to ensure that treatments become as tailored as possible.

Model-based approaches will help make drug development decisions more predictable and reliable

How can sponsors, regulatory agencies, and healthcare providers maximize their use of biosimulation technology? First, the decision-makers in the industry must adopt M&S as an enabler of drug development. We're not saying replace human judgment or technical competency with modeling and simulation. That's not the point. Our mission is to let biosimulation inform drug development and patient care.

Next, we must educate key stakeholders in drug development and patient care on the value of biosimulation. That responsibility falls on the leaders of those organizations and on us. If we don't educate our peers, we will not be able to influence decision-making.

Last, the entire process from discovery to post-marketing has to be an integrated process. Success adopters of biosimulation technology will embrace a culture of information sharing. They will also adopt the "learn/confirm paradigm" as published by Lewis Sheiner in 1997.¹

Ultimately, modeling and simulation will transform the business of drug development and help bring safer drugs to market.

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Using Biosimulation to Support Approvals for Orphan Drugs

By: Suzanne Minton

Rare diseases affect fewer than 1 in 2000 people. Each one affects only a small number of patients. Yet, there are over 7000 rare diseases. And, there are no treatments for 95 percent of them. Thus, many patients suffer from these diseases. The treatments for rare diseases are often referred to as “orphan drugs.” Orphan drug developers face distinct challenges with rare diseases including:

- Heterogeneity in disease progress and treatment outcomes
- Few patients to run new studies
- Uncertain appropriate durations of treatment
- Sparse existing data available from limited populations

Biosimulation methods—also known as model based drug development—include both top-down (empirical) and bottom-up (mechanistic) models. These methods use sparse data from small populations to inform dosing and trial designs. For example, population PK/PD models can test the influence of factors such as age, weight, and disease status on drug exposure and response. Likewise, combining drug and disease models can help distinguish between treatment effects on symptoms vs changes in disease processes. Model based approaches can support accelerated approval pathways that get treatments to patients faster.

Learning from one indication to another

In some cases, information gained developing a drug for one indication can be leveraged to inform its approval for 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.¹ Likewise, aHUS (atypical hemolytic uremic syndrome) is an ultra-rare genetic disease that 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.

Both aHUS and PNH are caused by chronic, uncontrolled activation of the complement system. During activation of the complement system, the terminal protein C5 is cleaved to C5a and C5b. C5a and C5b have been implicated in causing the terminal complement-mediated events that are characteristic of both aHUS and PNH. Eculizumab is a humanized monoclonal antibody (mAb) that binds C5, thereby inhibiting its cleavage. In 2007, Certara Strategic Consulting developed a PK/PD model that supported the approval of this mAb for treating PNH based on evidence of effectiveness from clinical studies.²

Making use of all available data

Diagnosed in only a few thousand patients each year, aHUS proved extremely difficult to study in the clinic due to very low trial recruitment. Though very few patients were available for study, some additional data were available from PNH clinical studies. The drug sponsor needed to optimize dosing of eculizumab for both adult and pediatric aHUS patients, making best use of all available data.

Crafting the model-based development strategy

The sponsor again turned to our scientific consultants. As the sponsor's resource for model-based development strategy for PNH, our scientific experts were already familiar with the drug's pharmacokinetics and safety profile to date. Their starting point was a population PK model that had been previously constructed in adult patients with PNH.³ This model was customized and used to develop optimal dosing strategies for adult and pediatric aHUS patients.

Comparing the case of adults with PNH to pediatric aHUS, it became apparent that children may require lower doses. The PK/PD relationship in PNH was leveraged to measure the drug's exposure and inform pediatric dosing for aHUS. Knowledge about eculizumab's mechanism of action for PNH also suggested that optimal binding to the pharmacological target (C5) should translate into a clinical benefit.

Identification of the therapeutic dosing window for a mAb in pediatric patients with a rare disease 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 previously observed in adults.

To ensure efficacy, the minimum drug exposure also had to be determined. Using the predicted concentration of the soluble target and the binding characteristics of the mAb to its target, a minimum concentration threshold was set to obtain close to full inhibition of the target. Then, trial simulations using a population PK model were performed to determine which doses would optimize the probability of obtaining the mAb within the window of target engagement in neonates, children, adolescents, and adult patients.

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 caused full inhibition of hemolytic activity (the distal biomarker). The primary endpoint indicated that the response to interventions across all age groups was very high.

Crossing the finish line

Using the model-based and observed efficacy and safety profiles, the consultants were able to recommend dosing regimens for adult and pediatric aHUS patients. Patients treated with the mAb experienced several benefits including improvement in platelet counts and other blood parameters and better kidney function, even eliminating the requirement for plasmapheresis in some patients. Soliris® (eculizumab) received FDA approval to treat aHUS adult and pediatric patients.⁴

Note: References for this article are on the following page.

Dosing for Two: How Pharmacometrics Supports Drug Safety in Pregnancy

By: Alice Ke



According to the US Census Bureau, there is a birth every eight seconds in the United States.¹ Women frequently take prescription and over-the-counter drugs during pregnancy. Given the ubiquity of pregnancy and births, you'd think that there would be a robust understanding of the safety and efficacy of drugs in pregnant women. However, the vast majority of drugs are prescribed to pregnant women off-label—often scaling doses from the recommendations set for men or non-pregnant women—because of ethical concerns about performing clinical testing in this vulnerable population.

Physiological and absorption, distribution, metabolism, and excretion (ADME) changes during pregnancy can significantly affect pharmacokinetics (PK). This can lead to under-dosing, with lack of therapeutic effect, or over-dosing, with potential toxicity that endangers both mother and developing fetus. In this blog post, I'll discuss how pharmacometrics and modeling approaches can be leveraged to identify drugs whose PK may be altered during pregnancy, guide rational study design, and support dosing recommendations for pregnant women.

The current landscape for drug safety during pregnancy

Recent moves by the US FDA and European Medicines Agency are requiring that post-marketing studies be conducted into the effects of drugs in pregnancy where there is a high likelihood of use in women of child-bearing age. The challenge for pharmaceutical companies is not only to determine appropriate initial dosing levels—which will vary depending on the stage of pregnancy—but also account for the time-related changes in drug exposure that may occur over an extended study period. As the physiological and biological changes that occur during pregnancy are well-studied, using physiologically-based pharmacokinetic (PBPK) modeling and simulation to study pharmacokinetics is an intuitive solution.

Using modeling and simulation to study maternal-fetal drug disposition

My Certara colleagues developed a full PBPK pregnancy model which has been implemented in the Simcyp Simulator and tested for its ability to simulate how drug concentrations change over time. The model reflects the progression of pregnancy through changes such as body weight, tissue blood flow, blood and plasma volume, fetoplacental volume, CYP450 enzymatic

activity, renal function, and serum albumin levels. In validation studies, good agreement was found between simulated and observed maternal exposure of caffeine, metoprolol and midazolam, three compounds which undergo hepatic metabolism by three different enzyme pathways (CYP1A2, CYP2D6 and CYP3A4).²

Appropriate dosing for drugs with narrow safety windows is critical in order to avoid adverse effects that may occur with only slight alterations in clearance levels. The Simcyp Simulator model is a major advance on previous pregnancy models as it is the first to consider time-dependent factors at any stage of pregnancy. This provides drug developers and the regulatory agencies with a more versatile tool to understand compound-specific changes in drug exposure throughout pregnancy and aid in the planning and design of clinical trials in pregnant women.

PBPK modeling and simulation is increasingly featuring in submissions for regulatory approval, gaining widespread acceptance for its role in optimizing study design, identifying worst-case scenarios for further investigation and informing dosage recommendations and labeling. PBPK models for pregnancy are not only relevant for the development of drugs specifically for pregnancy-related conditions but can also potentially assist with the dose adjustment decisions required to preserve the safety and efficacy of other therapies which are beneficial to expectant mothers. PBPK modeling and simulation also offers the possibility to assess fetal exposure to drugs, one of the major determinants in assessing the benefit versus risk associated with the treatment.

If you'd like a more in-depth look at the issues surrounding applying pharmacometrics approaches for pregnancy, please read the paper that I wrote with Amin Rostami in the *Annual Review of Pharmacology and Toxicology*.³

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Pediatric Drug Dosing: Tackling Big Problems for Little Patients

By: Nastya Kassir



The challenges and complexities of pediatric drug development are well recognized. Pharmacometric modeling and simulation (M&S) leverages prior knowledge to support pediatric drug dosing, trial design and regulatory writing for submissions. As the benefits of pharmacometrics for drug development and regulatory decision-making become increasingly well documented, the FDA has challenged the industry to more rigorously apply modeling and simulation to double the success rate of pediatric trials.¹ To highlight the power of this approach, I'll present a journal article on using population pharmacokinetics (PopPK) and Bayesian methods to develop an optimal sampling strategy to estimate drug exposure.

Organ transplant recipients take immunosuppressants to ensure graft survival

Liver transplantation is a surgical treatment for patients with liver cancer or end-stage liver failure whose disease cannot be managed medically. A wide variety of conditions can lead to whole or "cut-down" liver transplants in children, including biliary atresia, tryosinaemia, North American Indian childhood cirrhosis, and other conditions. After receiving a liver transplant, patients must take immunosuppressive drugs to prevent their immune systems from rejecting the graft.

Dose optimization of tacrolimus is essential to the success of pediatric liver transplants

Tacrolimus is widely used as an immunosuppressant for both adult and pediatric solid organ transplant recipients. Its PK properties have mainly been studied in adults. Tacrolimus has a narrow therapeutic index and significant inter- and intra-individual PK variability. In addition, it has highly variable oral bioavailability due to extensive pre-systemic metabolism by CYP3A and uptake by P-glycoprotein transporters.

To ensure graft survival, it is essential to optimize the dose of tacrolimus for individual patients. The standard of care has been therapeutic drug monitoring wherein trough concentration (C_{trough}) has been used to guide tacrolimus dosing. There is an urgent need for alternative strategies for estimating tacrolimus exposure as the relationship between C_{trough} and organ rejection is controversial.

One alternative would be to use Area Under the Concentration-Time Curve (AUC) as a basis for clinical monitoring. However, AUC-based monitoring requires measuring many concentration-time points over the dosing interval. This is both expensive and time consuming, not to mention impractical and ethically questionable in a pediatric population.

Using PopPK models to develop an optimal sampling strategy

We determined that the best solution was an optimal sampling strategy (OSS) using maximum a posteriori Bayesian estimators (MAP-BE). This

method can predict individual PK parameters, including AUC, using a limited number of samples, which can be taken on a flexible schedule. To establish an OSS using MAP-BE, we developed a PopPK model for tacrolimus in pediatric liver transplant patients using rich sampling.

We analyzed 12-hour intensive PK profiles performed on pediatric liver transplant patients in a retrospective study. While other PopPK studies on this population found that tacrolimus PK followed a one-compartment model, we found that a two-compartment model with first-order absorption and elimination best fit the concentration-time profiles of tacrolimus at steady state. We leveraged the PopPK approach to develop an OSS, which allowed estimation of tacrolimus PK parameters and AUC using a more feasible sampling schedule (three or four time points within four hours).

Despite the high between-subject variability in PK and patient demographics, the combination of PopPK and Bayesian estimation appears to provide an accurate method for predicting tacrolimus exposure in pediatric liver transplant patients. This OSS will support designing prospective clinical trials aimed at determining the drug's therapeutic window in this population. Ultimately, defining optimal pediatric drug dosing guidelines for tacrolimus will be a major step in preventing graft rejection while minimizing toxicity. Getting the dose right will help pediatric patients return to the important work of just being little kids again.

This research was performed with my colleague, Dr. Samer Mouksassi. I encourage you to read our *British Journal of Clinical Pharmacology* article, "Population pharmacokinetics and Bayesian estimation of tacrolimus exposure in paediatric liver transplant recipients."²

Modeling and simulation supports pediatric drug development

There are some major challenges associated with pediatric drug development. While it's crucial to optimize dosing, conducting clinical research in children presents an ethical dilemma. Pharmacometric modeling and simulation is an approach that helps sponsors identify optimal drug doses that balance safety and efficacy while minimizing the exposure of children to experimental therapeutics.

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Using Biosimulation to Quantify the PK of an anti-HIV Drug for Babies

By: Martin Beliveau



As a scientist at Certara and proud Dad to my three kids, pediatric drug development is a topic that is near to my heart. Clearly, children are not just “small adults.” They require special consideration for their distinct physiology during drug development. Likewise, for ethical reasons, it is important to minimize children’s exposure to experimental therapeutics. Biosimulation is an important tool that helps maximize knowledge of drug safety and efficacy in pediatric indications. In this blog post, I’ll discuss how we worked with a sponsor to characterize the pharmacokinetics of a novel long-lasting antiretroviral to help prevent mother-to-child transmission (MTCT) of HIV.

Mother-to-child transmission of HIV remains a global health problem

MTCT of HIV can occur during pregnancy, birth, or lactation. According to the World Health Organization (WHO), without intervention, the rate of MTCT ranges from 15-45%.¹ MTCT is the most common cause of HIV infection in children.²

Antiretroviral prophylaxis can drastically reduce MTCT to less than 5%.³ The most widely used protocol calls for giving the mother a single-dose of the nonnucleoside reverse transcriptase inhibitor, nevirapine (NVP), at the onset of labor and then, giving the infant a single dose shortly after birth.

Breast is best, but what if mom is HIV+?

While this protocol reduces MTCT by almost half,⁴ there is still a significant risk of MTCT in breastfeeding infants during the first six weeks of life.⁵ Thus, the U.S. Centers for Disease Control and Prevention (CDC) recommends that HIV+ mothers do not breastfeed their babies, and use formula instead. Formula feeding is not feasible for most HIV+ mothers in developing countries due to both the cost of formula and a lack of safe drinking water with which to prepare formula. The WHO recommends that babies born to HIV+ mothers, who lack safe alternatives, receive daily oral NVP until four to six weeks of age to prevent MTCT from breastfeeding.⁶

Unfortunately, the success of this recommendation is highly dependent on close adherence to the daily dosing protocol. Previous research shows that it is very difficult for patients to maintain compliance with frequent dosing for long durations.⁷ To address these challenges, a sponsor sought to develop the first injectable, sustained-release NVP formulation that would provide, for six weeks or longer, protective plasma drug levels from a single administration to babies at birth.

A new formulation for long-acting NVP from a single dose

Long-acting NVP consists of large, monodisperse NVP particles coated with biocompatible polymers that control drug release kinetics. *In vitro* assays suggested that these formulations could exhibit burst-free, sustained release of NVP for up to 75 days. Studies in rats showed no toxicity related to the NVP formulation. I used Phoenix NLME to characterize the pharmacokinetics of sustained-release NVP in rats. Then, I used this data to simulate infant NVP exposure from a single injected dose of the long-acting NVP formulation. These data demonstrate preliminary feasibility for this technique to maintain safe, effective NVP plasma levels for six weeks or longer.

Implications for preventing HIV MTCT in breastfeeding infants

Based on these results, the sponsor applied for and received orphan drug designation from the FDA for NVP in preventing pediatric HIV infection. I am excited about the potential of this treatment to save the lives of some of the littlest patients in regions of the world most affected by the HIV epidemic.

This work was recently published in the journal, *Antimicrobial Agents and Chemotherapy*, as “Pharmacokinetics of Injectable, Long-Acting Nevirapine for HIV Prophylaxis in Breastfeeding Infants.”⁸

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About Certara

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