Pharmacometric Modeling to Support Pediatric Clinical Trials

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In the last 10 to 15 years, legislation in the United States and Europe has triggered an increase in pediatric clinical trials, specific label changes, and dosing recommendations.\(^1\) With the reissuance of the Product Research and Equity Act (PREA), trial sponsors are encouraged to plan for pediatric investigations as an essential part of their clinical development program. The significant impediments to conducting trials within this patient population, however, have made success difficult to attain.

A major challenge is identifying, recruiting, and enrolling patients. The available pool of children for target indications is much smaller than adults, and ethical constraints significantly limit the number of participants.

It is also difficult to define pediatric outcomes for many indications in comparison to clinical outcomes for adults, which have already been established or can be evaluated against existing treatment goals. Similar clinical benchmarks may not easily exist in pediatric practice standards.

Differences between children and adults with respect to pharmacokinetics (PK) and pharmacodynamics (PD) are also often influenced by such physiologic factors as body composition, total body water, protein binding, cytochrome P450 ontogeny, gastrointestinal motility and pH, and organ (renal and hepatic) function, all of which can produce significant influences on absorption, distribution, metabolism, and elimination throughout childhood.\(^2\)

The notion that a single study design will be sufficient to extend the data generated in adults to pediatrics is flawed even if the adult and pediatric indications are similar.\(^3\) And unsuitable designs lead to slow enrollment and low retention, as well as higher costs and approval delays. Because of these and other challenges, up to 50% of pediatric effectiveness trials are not interpretable.\(^4\)
Protocols, therefore, need to be designed and customized specifically for the population and not simply reworked from adult protocols. Developmental variability should be considered in inclusion criteria, sample size calculations, and analysis.

Using pharmacometrics
Through novel clinical trial designs, including the use of pharmacometrics, however, researchers in Europe and the United States are beginning to change the drug development pathway and address some of the gaps in pediatric therapeutics.

Pharmacometrics is quantitative clinical pharmacology that affects decision-making throughout the drug development and regulatory review process. It is based primarily on PK and PD modeling and simulation, which can leverage information from such diverse sources as clinical pharmacology, pathophysiology, and statistics. These tools can help in drug efficacy and safety determinations, clinical trial simulations, and disease progression modeling.

Modeling and simulation in pediatric pharmacology research units (PPRU) study designs, for example, were used to determine pediatric dosing for such drugs as actinomycin, pleconaril, lorazepam for sedation, and morphine in infants, among many others. Some of these studies, like lorazepam for sedation, were conducted by children’s hospitals when no alternative data existed and before recent advances in information technology and processes were available.

Simulation and modeling
Pharmacometrics can be applied at all stages of the drug lifecycle. Potential applications range from molecule screening and identification of biomarkers and surrogates to dosing regimen and trial design selection and optimization to prognostic factor and benefit/risk evaluation. These methods have the unique ability to leverage all prior and current information, providing a rational, scientifically sound framework to maximize knowledge and efficiency of drug development programs.

Cost estimates for pharmacometric analyses and modeling—resulting in agency-acceptable simulation reports that can be used to mitigate or complete a PREA requirement and furnish informative product labeling on which pediatric providers can rely—are fractions of the tens of millions of dollars required for pediatric trials, trials which may not yield successful or even usable data.

Clinical trial design
Disease-drug-trial models and clinical-trial simulations can help reduce trial failures. Specific potential benefits include upfront comparison of candidate study designs, dose and safety outcomes selection, sample size and power determination, and evaluation of drug interactions and comorbidities.

Pain studies are one area of drug research where modeling and simulation can be a very good option or offer solutions—given the ethical scenarios in which parents would burden young children in severe pain with participation in double-blind, placebo-controlled studies. Recruiting a statistically valid total number of patients for such studies can be quite daunting. For example, less than 300 children with terminal cancer in the United States each year may experience the kind of pain for which certain types of narcotics could be
appropriate and for which their research participation is sought.

Nevertheless, drug researchers must answer new PREA-generated questions about treating children in pain. Modeling may be the best way to take what we’ve already learned from adult data or older children in hospital settings, and maximize its application to help younger children.

Simulations and models developed to answer the call of PREA can also serve as foundations for future research.

**Covariate/prognostic factor determination**

Simulation and modeling tools can be used in a variety of ways, not just as activities that substitute for actual clinical trials. Simulations can help create clinical trial designs that are more efficient or focused, and therefore, less costly. Apart from dose-ranging studies, the clinical pharmacology characterization of a new drug involves a number of bridging studies to identify influential covariates or prognostic factors, such as body size, age, gender, food intake, comorbidities, comedications, etc.

With data from prior studies and literature, modelers can help protocol designers decide what types of pediatric patients may be screened, what numbers of pediatric patients will be necessary to demonstrate efficacy or safety powered to significance levels, and/or what exclusion/inclusion criteria for pediatric patients might result in a study that is shorter in duration and less prone to failure.

**Regulatory support of modeling/simulation increasing**

The FDA is known to utilize pharmacometric methods to help make regulatory decisions during the Investigational New Drug (IND), Biologics License Application (BLA), and New Drug Application (NDA) review processes.

Moreover, the FDA Modernization Act (FDAMA) allows for “extrapolation from existing studies”—using knowledge from previous clinical trials for approving the same drug for pediatric use, or for establishing equivalence of alternative formulations, as long as the original trial yielded well-defined exposure-response relationships.

In fact, the FDA set a target to design 50% of all pediatric trials using simulations by 2015 and 100% by 2020.⁷

**Filling the knowledge gap**

Since pharmacometric modeling and simulation is a viable option to enhance pediatric drug approvals and satisfy PREA requirements, sponsors will benefit from learning more about whether these tools could be helpful for their PREA activities. Not every product is eligible for simulation and modeling, and some kinds of FDA obligations may not lend themselves to this approach. But for sponsors that can utilize simulation and modeling pharmacometric tools in their pediatrics program, the benefits, including cost savings, are genuine.

Several variables must be considered as sponsors take stock in their pediatric programs and PREA obligations:

*Time.* Fulfilling PREA can be a complicated process. It’s important to be prepared to modify expectations. Many companies think it’s simply “templating” what’s been done before from their adult studies. Depending on the complexity of the models and the
simulations needed, it can take many weeks just to build presets into a modeling program, and several months thereafter to acquire and enter data (from literature or prior studies) that will be used to create the simulation.

Data. Sponsors may need to gather data going back a number of years, which can take time, especially if it’s not in their immediate possession. Previously collected esoteric data and bridging studies, which may not have been considered priority data during a drug’s initial development, may suddenly be important to a simulation-modeling exercise.

Originality. Sponsors may often discover that to accommodate pediatrics they will need to be original in their research approach. Top management may insist on proof that existing adult models and protocol designs won’t work and can’t be “cut and pasted” into pediatric study parameters. It’s a natural response to be skeptical, but taking time to realign thinking and gain management consensus to begin anew has its own challenges.

Conclusion
Increased utilization of modeling and simulation in pharmaceutical development will increase, especially for pediatrics, and regulatory agencies will continue to welcome pharmacometrics in the research process.

Sponsors should dynamically explore the use of models to develop safe and efficacious treatments and to streamline the presentation of knowledge, which will help them capitalize on earlier data, improve trial designs, and strengthen evidence for drug approval and labeling.

Ultimately, the growth and wider use of pharmacometrics will require increased collaboration between industry, academia, and the agencies, including more interactions among clinicians, researchers, and pharmacometric statisticians.

About the Author
Charlene Sanders has more than 15 years of experience in pharmaceutical management and drug development and regulatory affairs, including interactions with both regulators and major pharmaceutical companies.

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