Pharmacometrics:
How PK/PD Modeling and Simulation Are Helping to Advance Pediatric Trials

Highlights:

- Pharmacometrics uses extrapolation data and modeling of biology, pharmacology, disease, and physiology to quantify interactions between a drug and subjects.

- To help streamline pediatric clinical trials, the FDA and EMA have established Pediatric Extrapolation Guidances that permit extrapolation of adult efficacy data to children's trials.

- PK/PD and other approaches to pharmacometrics address challenges of limited availability of suitable patients and parents' inherent reluctance to expose children to unknowns.

Pediatric PK/PD modeling and simulation techniques are cornerstones of pediatric drug development. As identified by the FDA as part of the "Critical Path Initiative," poor dose and dose regimen selection is a frequent reason for trial failure. PK/PD modeling and simulation approaches are particularly useful when existing data is available to support either a full or partial extrapolation of data from other patient populations.

Pediatric PK/PD modeling and simulation is a rapidly-evolving science. Application of these strategies can have an enormous impact on the design of pediatric studies, providing insight and guidance on the rational selection of pediatric doses and dose regimens. Different modeling approaches are used to understand the relationships between drug exposure and response, which in turn are used to build predictive models to guide pediatric dosing.

Physiologically Based Pharmacokinetics

Physiologically based pharmacokinetic (PBPK) modeling offers a unique modality to incorporate multiple levels of information to estimate age-specific pharmacokinetics. In 2012, the US Food and Drug Administration's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology unanimously voted to support the motion that modeling and simulation be considered for all pediatric drug development programs. During the same meeting, the committee also passed a motion that the routine use of physiologically based pharmacokinetic modeling be incorporated, whenever possible, into the pediatric drug development process.

To increase efficiencies surrounding the pediatric drug development process, the FDA introduced the pediatric decision tree (please also see FDA guidance "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products"), which delineates required clinical investigations in pediatric populations in order to comply with current legislation. The framework provides a venue by which adult efficacy data can be extrapolated to pediatrics, subsequently reducing the number of children required to participate in clinical trials. Recognizing that children may display developmentally unique differences in absorption, distribution, metabolism, and excreting (ADME) and, as a result, exhibit variable patterns of drug sensitivity when compared to adults, the decision tree does not permit for extrapolation of PK and safety data between adults and children. As a result, clinical assessments of pediatric PK and safety are required.

Considering the integral role of PK in drug efficacy, use of pediatric PBPK models can serve to integrate multiple levels of information (i.e., in vitro, preclinical, clinical, etc.) to elucidate PK changes among children and function as a complement to pediatric clinical investigations. Estimates of age-specific PK can be utilized to support dose selection and assess the potential for concentration-related toxicities within pediatrics.

Pediatric Extrapolation in Drug Development

Companies are required to provide "substantial evidence" that a drug is effective according to the Federal Food and Drug Cosmetic Act (1962). These requirements are generally met by conducting at least two adequate and well-controlled trials. However, the FDA and EMA have afforded some flexibility to allow (under certain circumstances) the extrapolation of data from adults to pediatric patients. This approach can reduce the number of pediatric patients needed in clinical trials.

If efficacy has not been demonstrated in adults or other pediatric patients, the extrapolation of efficacy cannot be justified and adequate and well-controlled trials in pediatric patients will be needed. However, there are typically a range of options based on the availability of existing data that can help support the decision to adopt a "No Extrapolation," "Partial Extrapolation," or "Full Extrapolation" approach.

PopPK and Sparse Sampling

Population PK/PD analysis (PopPK/PD) is a powerful tool that enables pharmacometricians to integrate complex PK and PD datasets, identify the model parameters, quantify variability and understand the source of variability by seeking correlations between multiple variables (covariates) and the model parameters. For instance, these analyses can reveal how drug clearance (CL) is influenced by factors such as age, gender, race, body weight, body surface area, hepatic function, renal function, concomitant mediations, performance status, disease progression, and so on. These data can then be used to identify subsets of patients (special patient populations) that may need to be excluded from treatment or require dose modification.

PopPK analysis can also be used to estimate pharmacokinetic parameters from very sparse datasets (e.g. one or two samples) collected at random sampling times through the disposition of the drug. This is a particularly valuable tool in pediatric drug development, as it can be used to analyze PK data in children with a minimal number of blood draws. In addition to PopPK strategies, Synteract scientists also make use of computer-based algorithms to design optimized blood-draw schedules to minimize the number of samples that need to be taken from children to obtain PK data. Synteract uses NONMEM for population PK/PD analyses and PFIM to optimize sampling times for pediatric PK studies.

Deep Expertise in Pediatric Extrapolation and Pharmacometrics

Synteract's Pharmacokinetic modeling team has deep industry experience with cutting-edge PK/PD modeling/simulation population PK, sparse sampling, and allometric scaling techniques.

Our key areas of expertise include:

- PK and PK/PD study designs
- Bioavailability/Bioequivalence Studies
- Optimized sparse sampling strategies
- PK/PD Modeling and Simulation
- Allometric scaling
- Physiologically Based PK models (PBPK)
- Pediatric Extrapolation

We have broad therapeutic area experience as well, including oncology, dermatology, neuro degenerative, and rare and orphan diseases with both small molecules and biologics, in neonates, infants, children, and adolescents. We operate under stringent (GLP) data collection and data analysis procedures and build regulatory compliant data sets for submissions within our audit-trailed 21CFR Part 11 PK Database System. Synteract uses PK–Sim® and MoBi® software platforms in performing PBPK modeling for its clients.

Synteract's experienced pediatricians and clinical pharmacologists can help you assess the available data and determine the best approach to minimize the burden of conducting trials in patients. We will help you to proceed with your trial in the most efficient and cost-effective manner, while meeting the regulatory requirements for pediatric labeling.

Contact us to discuss your pharmacometric trial needs: alberto.bryan@synteract.com.

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