Role of Quantitative Clinical Pharmacology in Pediatric Approval And Labeling

Nitin Mehrotra, Atul Bhattaram, Justin C Earp, Jeffry Florian, Kevin Krudys, Jee Eun Lee, Joo Yeon Lee, Jiang Liu, Yeruk Mulugeta, Jingyu Yu, Ping Zhao, Vikram Sinha


Division of Biometrics VII, Office of Biostatistics, Office of Translational Sciences, CDER, US Food and Drug Administration (J.Y.L.)
Running Title: Application of Pharmacometrics in Pediatric Drug Development

Corresponding Author:
Nitin Mehrotra, Ph.D.
Division of Pharmacometrics,
Office of Clinical Pharmacology, Office of Translational Sciences,
CDER, US Food and Drug Administration
10903 New Hampshire Avenue. White Oak Bldg 51, Rm 3199
Silver Spring, MD-20993
E-mail: nitin.mehrotra@fda.hhs.gov
Office: 301-796-0976

Number of text pages: 39 (including figure legends, tables and references)
Number of Tables: 3
Number of Figures: 6
Number of References: 51
Number of words in:
   Abstract: 249
   Introduction: 502
   Discussion: 1544
Abbreviations

- aPTT: activated Partial Thromboplastin Time
- BLA: Biologics License Application
- BPCA: Best Pharmaceutical Children's Act
- CDAI: Crohn's Disease Activity Index
- FDA: Food & Drug Administration
- FDASIA: FDA Innovation and Safety act
- GERD: Gastroesophageal Reflux Disease
- HIV: Human Immunodeficiency Virus
- PCDAI: Pediatric Crohn’s Disease Activity Index
- PREA: Pediatric Research Equity Act
- PWR: Pediatric Written Request
- rCPS: refractory Complex partial seizures
- SAE: Serious Adverse Events
Abstract

Dose selection is one of the key decisions made during the drug development in pediatrics. There are regulatory initiatives that promote the use of model based drug development in pediatrics. Pharmacometrics or quantitative clinical pharmacology enables development of models that can describe factors affecting pharmacokinetics and/or pharmacodynamics in pediatric patients. This manuscript describes some of the examples where pharmacometric analysis was utilized to support approval and labeling in pediatrics. In particular, the role of pharmacokinetic comparison of pediatric PK to adults and utilization of dose/exposure-response analysis for dose selection is highlighted. Dose selection for esomeprazole in pediatrics was based on PK matching to adults while for adalimumab, exposure-response, PK, efficacy and safety data together was useful to recommend doses for pediatric crohn’s disease. For vigabatrin, demonstration of similar dose-response between pediatrics and adults allowed for selection of a pediatric dose. Based on model-based pharmacokinetic simulations and safety data from darunavir pediatric clinical studies with the b.i.d. regimen, different q.d. dosing regimens for treatment-naïve HIV-1 infected pediatric subjects 3 to < 12 years of age were evaluated. The role of physiologically-based pharmacokinetic modeling (PBPK) in predicting pediatric PK is rapidly evolving. However, regulatory review experiences and understanding of the state-of-science indicate that there is a lack of established predictive performance of PBPK in pediatric PK prediction. Moving forward, pharmacometrics will continue to play a key role in pediatric drug development contributing towards decisions pertaining to dose selection, trial designs and assessing disease similarity to adults to support extrapolation of efficacy.
Introduction

Over the past few decades, important legislations have been enacted to foster drug development in children. The Best Pharmaceutical Children's Act (BPCA) of 2002 provides financial incentives (additional exclusivity) for pediatric studies conducted pursuant to request by the Food and Drug Administration (FDA); the Pediatric Research Equity Act (PREA) of 2003 requires clinical research to support pediatric applications for new drugs and biological products. Together, these two legislations have generated information about the efficacy, safety and dosing of approximately 600 products in children. In 2012, the permanent reauthorization of both BPCA and PREA as part of the FDA Innovation and Safety act (FDASIA) indicates that these pediatric research efforts will continue to be an important regulatory and drug development focus.

Despite such significant advances, there are persistent challenges in pediatric drug development. One challenge is the timely initiation and completion of pediatric studies. On average, it takes approximately 8 years from the time a drug product is approved for use in adults until the label is updated to include pediatric data, during which time often products are used off-label. Many studies have shown that off-label drug use in pediatrics is associated with significantly increased risk for developing adverse drug reactions (Neubert et al., 2004; Turner et al., 1999). Drug development in children is further complicated by a relative high trial failure rate. A recent review by the FDA showed that 42% of pediatric trials for drugs that were granted pediatric exclusivity failed to result in a pediatric indication (Wharton et al., 2015). Challenges with dose selection and trial design have been reported as important contributing factors to trial failures in children (Momper et al., 2015; Benjamin et al., 2008).
The advances in the science of quantitative pharmacology and the use of model-based drug development have paralleled the advances in pediatric research (Vinks et al., 2015; Stockmann et al., 2015). The use of modeling and simulation (M&S) as an integral part and basis for improving efficiency, substantiating trial design, and optimizing dose selection in pediatric drug development have been communicated in recent guidance (2014 FDA Draft Guidance For Industry on General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products). Regulatory provisions also provide support for the role of M&S as a rational approach for describing dose-exposure and exposure-response relationships to support extrapolation of efficacy from adults to the pediatric population (21 CFR 314.55). In this case, the availability of rich prior data from adults as well as the ethical and practical constraints of conducting trials in children necessitates the use of M&S in pediatric drug development to integrate knowledge across trials and populations.

The experience with the use of model-based analyses to support regulatory decisions have been previously described (Bhattaram et al., 2007; Bhattaram et al., 2005; Jadhav et al., 2009; Leong et al., 2012; Wang et al., 2008). The objective of this manuscript is to provide detailed examples further highlighting the role of modeling and simulation in the development and approval of drugs and biological products in pediatric patients.
Material and Methods

The focus of this manuscript is to highlight the role of pharmacometrics in pediatric approval and labeling. We have presented four case studies which highlight the utilization of pharmacokinetic and exposure-response information for pediatric approval and labeling. In addition, regulatory experience with the use of physiologically based pharmacokinetic modeling (PBPK) in pediatric reviews is discussed followed by future vision on the role of PK/PD in pediatric drug development. For the purpose of this manuscript, unless otherwise specified, the term “sponsors” refers to the pharmaceutical companies.
Results [Case Studies]

Esomeprazole in pediatrics for the treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis: Intravenous (IV) dose selection

Background

On April 21, 2011, FDA approved IV esomeprazole in 1 month to 17 years of age for the treatment of GERD with Erosive Esophagitis (Package insert for Nexium IV (Esomeprazole)). IV esomeprazole is also approved for use in adults. The recommended dosing for adult patients is either 20 mg or 40 mg given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 to 30 minutes).

In the case of pediatric IV esomeprazole, the agency agreed to extrapolate evidence of efficacy from adults to pediatrics, 1 month – 17 years of age, based on the similar disease pathophysiology and the response to treatment between pediatrics and adults (FDA Gastrointestinal Drugs Advisory Committee Meeting 2010; Earp et al., 2011). For dose selection, a PK study was required and designed in pediatrics with the intent of matching exposures to adults and generate additional safety data.

Regulatory question

What doses in pediatrics result in comparable exposures to adults?
Role of Pharmacometric Review

Intra-gastric pH is a pharmacodynamic biomarker in this indication. The mean of the pharmacodynamics biomarker were plotted for each quartile of esomeprazole exposure. Based on the visual comparison, exposure-response relationships of intra-gastric pH measures were comparable between pediatrics and adults indicating that target effective concentrations exposures (AUC: Mean of 5.1 umol·hr/L, 90% CI of 3 – 9 umol·hr/L) in pediatrics and adults were similar (Earp et al., 2011).

Observed IV or oral esomeprazole PK data were available from 50 and 117 children, between birth and 17 years respectively, and from 65 adults, between 20 and 48 years. A population PK model developed by the sponsor using all the pediatric data was utilized to simulate steady-state esomeprazole exposures (AUC and Cmax) following IV administration for pediatric patients at different fixed-doses to match the observed exposures in adults. AUC and Cmax were compared for each dosing regimen to the exposures from the 20 and 40 mg IV doses in adults. A weight based dosing was proposed in pediatrics based on exposure matching. The dose for patients 1 month to 1 year of age was 0.5 mg/kg while in older children (1-17 years), the dose was 10 mg for patients < 55 kg and 20 mg for patients weighing > 55 kg. PK data indicated that a 3 minute injection in pediatrics exceeded the Cmax observed in adults with 20 and 40 mg dose while AUC between adults and pediatrics were comparable (Figure 1 a, b). PK simulations conducted using the population PK model indicated that increasing the duration of infusion to 10 -30 minutes resulted in Cmax values within those observed with effective doses in adults (20 and 40 mg) [Figure 1c]. A 3 minute injection option was not approved in pediatrics.


**Regulatory outcome**

Exposure-response analyses for intragastric pH supported exposure-matching analysis and approval of esomeprazole in pediatrics for the treatment of GERD with erosive esophagitis (Earp et al., 2011). Population PK simulations were useful in identifying a simple weight-based dosing regimen for children that resulted in comparable steady-state AUCs and C<sub>max</sub> to that observed after 20 mg in adults.

Similar approach for dose selection was taken for oral esomeprazole for use in infants one month to < 1 year of age with GERD associated with erosive esophagitis. This was reported in the FDA clinical pharmacology review document for oral esomeprazole review and is predicated based on similar exposure response relationship between infants and adults and also on the findings of the Nov. 5th 2010 FDA gastrointestinal drugs advisory committee meeting that concluded it is reasonable to extrapolate adult efficacy information to infants one month to < 1 year of age provided that supportive PK and PK/PD data are available (FDA Gastrointestinal Drugs Advisory Committee Meeting, 2010; Estes et al., 2009).

**Approval of Vigabatrin for refractory complex partial seizures in pediatrics**

**Background**

Vigabatrin was approved in 2009 as adjunctive therapy for adult patients with refractory complex partial seizures (rCPS) who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of vision loss (Package insert for Sabril (Vigabatrin)). A Pediatric Written Request (PWR) was issued in 2011 which included a
clinical trial required under the Pediatric Research Equity Act (PREA) to evaluate the safety and efficacy of vigabatrin as adjunctive therapy in pediatric patients 10 -17 years with rCPS. In addition, a 1 year safety study was also required. In two subsequent meetings with the Agency, the Sponsor provided an assessment that the available data from previously conducted controlled studies in the intended population, which terminated early, could be used to establish efficacy and provide pediatric dosing information. Specifically, the Sponsor proposed to combine data from three controlled pediatric trials with data from two adult trials and utilize a modeling approach to assess the similarity of the relationship between vigabatrin dose with seizure frequency in pediatric and adult populations.

**Regulatory Question**

Is the dose -response relationship similar between adult and pediatric patients with rCPS, thus providing for dosing in pediatric patients 10 years of age and above?

**Role of Pharmacometrics review**

The role of the pharmacometric review was to evaluate the data from previous studies that could be used to provide dosing recommendations in the pediatric population. Dose-response modeling of efficacy data from three controlled studies of vigabatrin as adjunctive therapy for pediatric patients with rCPS and two controlled studies of vigabatrin as adjunctive therapy for adult patients was performed by the Sponsor. All three pediatric studies were stopped for administrative reasons before their planned enrollments were attained. As part of the evaluation of the Sponsor’s data, the reviewer also performed an independent analysis using a different
approach compared to the sponsor. The reviewer’s dose-response analysis included change in standardized seizure frequency during the maintenance phase as the response variable and normalized dose as the dose variable. Equation below shows the dose normalization by total body weight.

\[ D_{\text{NORM}} = \text{DOSE} \cdot ( \frac{\text{WT}}{60} )^{-0.608} \]

Where, “\( D_{\text{NORM}} \)” is the normalized dose, “\( \text{DOSE} \)” is the fixed dose in mg administered to a pediatric patient and “\( \text{WT} \)” is body weight of pediatric patient in Kg. This relationship between \( D_{\text{NORM}}, \text{DOSE} \) and \( \text{WT} \) was developed using the data available from the pediatric clinical trials. The normalized dose, \( D_{\text{NORM}} \) should be considered as a surrogate for drug exposure such that a pediatric patient with higher weight will have a lower value of \( D_{\text{NORM}} \) and vice versa.

Age was not found to be a significant covariate on drug effect in the analysis. The reviewer also performed the analysis separately for adult and pediatric studies and found that the slope of the dose-response relationship was similar in adults and pediatric patients (Figure 2). The details of the sponsor’s and the FDA analysis are provided in the FDA clinical pharmacology review that demonstrated that dose-response relationship between children and adults is similar (Bhattaram et al., 2013). The final model was used by the Sponsor to propose a therapeutic dose range for children that would match vigabatrin concentrations in children to those in adults at the approved doses.
Regulatory outcome

The PWR was amended to remove the requirement to conduct a clinical trial and replace it with the above-mentioned dose-response analysis. Vigabatrin was approved for the treatment of rCPS in patients \( \geq 10 \) years of age thus alleviating the need for additional efficacy trial in this pediatric patient population.

Adalimumab for Crohn’s Disease in children: Dose selection

Background

On September 23, 2014, FDA approved adalimumab for reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn’s disease (CD) who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate (Package insert for Humira (adalimumab)).

Adalimumab is approved for CD in adults with initial dose of 160 mg followed by 80 mg two weeks later. Two weeks later, a maintenance dose of 40 mg EOW (every other week) is recommended. In the pivotal Phase 3 study in children 6 years and older, patients received a weight-based induction dosing regimen and then were randomized to high and low dose group stratified by weight cutoff of 40 kg, Week 4 response and prior infliximab use. The patients in the high dose group received either 40 mg for body weight \( \geq 40 \) kg or 20 mg for body weight \(< 40 \) kg and low dose group received 20 mg for body weight \( \geq 40 \) kg and 10 mg for body weight
<40 kg. Patients with inadequate response were allowed to escalate dose from EOW dosing to weekly dosing (EW) at Week 12. The primary efficacy endpoint was the proportion of subjects who were in clinical remission based on Pediatric Crohn’s Disease Activity Index (PCDAI) at Week 26.

A numerical trend of higher efficacy with high dose group was observed with PCDAI; however the dose response was not evident when PCDAI was converted to CDAI. This posed a question that whether or not high dose in pediatrics should be approved for both weight groups. Exposure-response analyses and PK comparison of exposures achieved with the proposed pediatric dose as compared to adults along with information for the secondary efficacy end points and safety was critical to determine the dose of adalimumab in pediatric patients with CD.

**Regulatory question**

Does the exposure-response relationship along with other efficacy and safety information supports the maintenance dose of 40 mg EOW for patients with body weight ≥40 kg and 20 mg EOW for patients with body weight <40 kg for the treatment of CD?

**Role of the Pharmacometric review**

A statistically significant exposure-response relationship (p-value for slope=0.006) between PCDAI clinical remission and trough concentration of adalimumab at Week 26 was observed which provided supportive evidence of effectiveness. In addition, this relationship also supported
approval of a higher dose, since efficacy increased with increasing exposures. This exposure-response relationship, although not steep, was also evident within each body weight group (Figure 3).

Adalimumab concentrations in both body weight groups of patients who received high dose were comparable with those in adults while adalimumab concentrations in both body weight groups of patients with low dose group were lower than those in adults (Table 1). Furthermore, patients in high dose group showed numerically higher clinical remission rates for both body weight groups (40.0% in <40 kg and 48.9% in ≥40 kg) than those with low dose group (26.3% in <40 kg and 42.6% in ≥40 kg), and they were comparable to the clinical remission rates observed in adults (Table 1). Although difference in clinical remission at week 26 in the ≥40 kg subgroup between 20 and 40 mg EOW was 6.3%, other secondary efficacy endpoints consistently showed higher efficacy of 40 mg EOW over 20 mg EOW in this subgroup (Table 2). For instance, the difference in clinical response at Week 26 between high dose group (48.3% in <40 kg and 64.1% in ≥40 kg) and low dose group (41.9% in <40 kg and 51.6% in ≥40 kg) was more remarkable. Longitudinal assessment of PCDAI also indicated that high dose had numerically better efficacy compared to low dose group throughout the treatment period. Moreover, smaller proportion of patients in the high dose group required dose escalation due to inadequate response (45.3% in patients ≥40 kg and 61.3% in patients <40 kg in the low dose group compared to 39.1% in patients ≥40 kg and 34.5% in patients <40 kg in the high dose group), thus supporting the approval of high dose in both weight subgroups. In addition, there were no major safety concerns associated with high dose group of adalimumab in the ≥40 kg subgroup (serious adverse events (SAE) 23.4% with 20 mg vs. 18.8% with 40 mg; Any AE 89.1% with 20 mg vs. 93.8% with 40 mg).
mg). Thus, an evidence base for a high dose as an adequate maintenance dose for both weight groups (40 mg EOW for patients with body weight $\geq$ 40 kg; 20 mg EOW for patients with body weight $<$ 40 kg) could be established (Lee et al., 2015).

**Regulatory outcome**

On the basis of the pharmacometric analyses and the observed efficacy and safety results from the clinical trial, maintenance doses of 40 mg EOW for pediatric patients with body weight $\geq$ 40 kg and 20 mg for those with body weight $<$ 40 kg were recommended in the label.

**Exposure-response and PK matching to bridge dosing for different patient populations in pediatrics for the treatment of HIV**

**Background**

Darunavir (DRV), a HIV protease inhibitor (PI), in combination with low-dose ritonavir (RTV) had been previously approved by the FDA in 2006 for the use in treatment-experienced adults and pediatric subjects aged 3 to $<$ 18 years old as a twice-daily (b.i.d.) regimen (Package insert for Prezista (Darunavir)). The once-daily (q.d.) regimen had also been approved in 2008 for use in treatment-naïve adults. To fulfill the PWR for DRV/RTV q.d. regimen in HIV-1 infected pediatric subjects aged 3 to $<$ 18 years who are treatment-naïve or treatment-experienced with no DRV resistance-associated mutations, a Phase II study in treatment-naïve pediatric subjects aged
12 to < 18 years and a 2-week q.d. substudy of the Phase II study in treatment-experienced pediatric subjects aged 3 to < 6 years was conducted.

**Regulatory question**

Data from these studies was utilized to determine the comparability of DRV/RTV q.d. exposure in pediatrics with that of adults while not exceeding DRV/RTV exposures observed with either the q.d. or b.i.d. regimen. Note, all comparisons below focus on DRV exposures as the role of RTV in the regimen is to inhibit CYP3A4 metabolism, thereby boosting exposure of DRV in what is referred to as a RTV-boosted PI-based regimen. In addition, no pediatric patients 6 to < 12 years of age were evaluated in the DRV/RTV q.d. studies, but in the interest of providing additional treatment options for this population, modeling and simulation were utilized to inform the appropriate DRV/RTV q.d. dosing regimen based on comparisons of exposures between adults and model predictions. Modeling and simulation was based on the previously developed model in adults and treatment-experienced pediatric subjects and incorporated new PK data from pediatric subjects with q.d. regimens. The updated model is consistent with the previous models (Vis et al., 2006).

**Role of Pharmacometrics review**

A quantitative clinical pharmacology analysis was first performed to confirm that the exposure-response relationship for efficacy in pediatric subjects is consistent with that in adults (Au et al.,
2013). The inhibitory quotient (IQ) is the ratio of steady-state trough concentration (C0h) and the baseline IC50 value for each subject. The IQ combines the drug concentration and the susceptibility of the virus to DRV. The pharmacometric analysis of DRV demonstrated that the probability of virologic response or success (measured as HIV-1 RNA <50 copies/mL or 1 log reduction in viral load by week 24) was strongly related to increasing IQ values. As shown in Figure 4, the relationship in pediatric subjects was consistent with the relationships previously observed in adults.

Based on the consistent exposure-response relationship for efficacy between pediatric subjects and adults, a dose selection approach for the q.d. regimen in pediatrics based on pharmacokinetic matching can be reasonably adopted. Also, because an adequate safety trial for the q.d. regimen had not been conducted in pediatric subjects 3 to < 12 years of age (< 40 kg), the safety decision has to rely on the safety data in pediatric subjects 3 to < 12 years of age with the b.i.d. dosing regimens. Therefore, the following considerations were taken into account for PK comparison:

- For efficacy, the expected C0h and AUC24h in pediatric patients with q.d. dosing should closely match C0h and AUC24h values observed in adults receiving the approved DRV/RTV 800mg/100mg q.d. regimen.

- For safety, the expected AUC24h, and Cmax in pediatric patients with q.d. dosing should not significantly exceed AUC24h, and Cmax observed in pediatric patients receiving the approved b.i.d. regimens.
**Regulatory Outcome**

Based on the model-based pharmacokinetic simulations and parameter estimations, and safety data from pediatric clinical studies with the b.i.d. regimen, different q.d. dosing regimens for treatment-naïve HIV-1 infected pediatric subjects 3 to < 12 years of age were evaluated. Comparisons between exposure from q.d. and b.i.d. dosing regimens based on PK simulation indicates that $C_{\text{max}}$ values in pediatric patients with the q.d. regimens proposed by the sponsor are 137%, 113% and 126% of those in pediatrics with the approved b.i.d. regimens weighing 10 to 15 kg, 15 to 30 kg, and 30 to 40 kg respectively. Because there is limited or no safety data at these higher $C_{\text{max}}$ values in the pediatric population, the agency therefore recommended the revised q.d. regimens (rows shaded light gray) in Table 3.
Discussion

At the FDA, Pharmacometrics which is also referred to as “quantitative clinical pharmacology” entails an understanding of pharmacokinetics, pharmacodynamics and exposure –response relationships to support approval and labeling-decisions (Bhattaram et al., 2007). In pediatric reviews, pharmacometrics is routinely used to make decisions about sample size, PK and PD sampling points, endpoint selection, providing supportive evidence of effectiveness, dose and dosing regimen selection amongst other things. The FDA engages with a sponsor early in drug development on topics related to trial design, specifically around dose selection in the registration trials. During the NDA or BLA review stage, the primary question is on appropriateness of doses in the intended pediatric population. Specifically, in this manuscript, we focus on the latter aspect to illustrate how pharmacometric principles were utilized to make regulatory decisions related to pediatric approval and labeling. Discussions around utilizing pharmacometric approaches to design informative clinical trials in pediatrics can be found elsewhere (Stockmann et al., 2015; Jadhav and Kern, 2010).

Understanding the effect of growth and development on PK and PD variability is critical to the pediatric dose selection. The developmental aspects of PK in children especially in neonates have now been well recognized (Offringa et al., 2015). In younger children (<2 years) additional considerations towards incorporating organ function and maturation processes are needed to accurately predict the pharmacokinetics in this age group. Within the neonate population, a range of weight and other factors related to receptor maturation contribute to the considerable inter- and intra-individual variability in PK and PD response. In contrast, the scaling of pharmacokinetics using allometry is largely applicable in children > 2 years of age (Holford,
2010). Given the potential limitations of studying this population, using fundamental principles of PK/PD and predicting key parameters (such as clearance, CL) and variability that incorporate prior data is important.

In case of esomeprazole, efficacy in pediatrics was extrapolated from adults. Furthermore, similarity of exposure-response meant that “PK matching” approach where a dose in pediatrics is selected such that the exposures are comparable with that of approved doses in adults is reasonable. In case of adalimumab for crohn’s disease, both exposure-response data and PK comparison data was utilized for dose selection. In case of vigabatrin, innovative and pragmatic approach followed by the sponsor and the FDA led to approval of vigabatrin in pediatric population without the need for additional efficacy trial.

There are several other examples where modeling and simulation has been utilized to make dosing decisions in pediatrics. For argatroban, dosing and titration scheme in pediatrics was based on PK-PD modeling and simulation (Package insert for Argatroban injection). Argatroban dose in pediatrics was selected based on the clinical trial simulations where the probability of achieving a target aPTT (activated partial thromboplastin time, a pharmacodynamic marker for coagulation) was utilized for dose selection (Madabushi et al., 2011). For oxcarbazapine and topiramate, exposure-response analysis was utilized to support the monotherapy indication approval by leveraging information from the adjunctive therapy approval in adults and pediatrics [Sekar et al., 2001; Marathe et al., 2011; Package insert for Trileptal (oxcarbazapine); Package insert for Topamax (topiramate)]. For guanfacine, exposure-response modeling and clinical trial simulations were utilized to design a pediatric trial (Knebel et al., 2015). For raxibacumab which was the first monoclonal antibody approved using animal rule, there were no studies of
raxibacumab in pediatric population (Package insert for raxibacumab). Dosing in pediatric patients was determined based on population PK simulations (FDA Anti-Infective Drugs Advisory Committee Meeting, 2012). In general, given the observation that limited amount of clinical data are available from pediatric dosing trials, the role of pharmacometrics is critical in supporting pediatric dosing determination.

While the examples and case studies described above represent “top-down” pharmacometric approaches, in some cases characterizing the sources of variability in pharmacokinetics in a more mechanism based fashion may be desirable. For such purpose, approaches like physiologically based pharmacokinetic modeling (PBPK), so called “bottom-up” approach have been utilized. Regulatory experience with PBPK in pediatric reviews is described below.

**Experience with PBPK in pediatric reviews**

PBPK models represent a quantitative system that combines human physiology and drug specific information, in which the impact of physiology changes, including those pertaining to age-dependent developmental changes on drug absorption, distribution, metabolism, and excretion (ADME) processes can be evaluated. The past decade observed an increased interest in applying PBPK in academic research and drug development (Sager et al., 2015; Rowland et al., 2011). The advent of specialized PBPK platforms further broadens the use of PBPK (Johnson et al., 2006; Edginton et al., 2006; Johnson et al., 2010; Edginton and Willmann, 2008; Rowland et al., 2011). Drug developers also increasingly use PBPK to predict the effect of intrinsic and
extrinsic factors on drug exposure to support dosing recommendations under specific clinical situations (Zhao et al., 2011; Huang et al., 2013).

Based on PBPK review knowledgebase of the Office of Clinical Pharmacology, there are 180 records between 2008 and 2015 addressing various clinical pharmacology issues. Sixty six percent of these records falls into the category of predicting drug drug interaction (DDI) potential, with the remaining 34% equally distributed between pediatric PK prediction and other applications (e.g., drug absorption, pharmacogenetics, and organ impairment) (Figure 5). Of the 31 pediatric review records, distribution of therapeutic areas is shown in Figure 5. Based on the regulatory experience, compared to DDI prediction, the confidence in prospectively using PBPK predictions to recommend pediatric dosing regimen is lower. The lower confidence in using PBPK to predict drug PK in pediatrics is mainly attributed to uncertainty and knowledge gaps in developmental changes governing ADME processes mediated by metabolizing enzymes, binding proteins, and transporters. Therefore, one anticipates the system model for pediatric population of a specific age group be updated when new information becomes available. Salem and colleagues recently utilized clinical PK data for CYP3A substrates to derive and update the ontogeny profile for the enzyme (Salem et al., 2014). At present time, the use of PBPK in regulatory submissions focuses on optimizing the study design of pediatric PK studies with the goal of maximizing the utility of knowledge gained from these studies upon completion. The regulatory review experiences and understanding of the state-of-science led to the conclusion that there is a lack of established predictive performance of PBPK in the area of pediatric PK prediction (Wagner et al, 2015).
Several groups reviewed the use of PBPK in pediatric drug development and research, with various versions of workflow being proposed to predict drug PK in pediatrics using PBPK [Leong et al., 2012; Barrett et al., 2012; Maharaj and Edginton, 2014; Jiang et al., 2013; Willmann et al., 2014]. All proposals articulate the importance of establishing/verifying adult PBPK model, followed by utilizing the most up-to-date pediatric physiology models to prospectively predict drug PK in subjects of different pediatric age groups.

**Future Direction**

Drug developers are encouraged by regulatory agencies to carry out studies in children and use models for pharmacokinetics (PK) and pharmacodynamics (PD) relevant to children. In general, the ability to extrapolate efficacy to children from adults is governed by three key questions –

- *Does the disease affect children?*
- *Is the disease / disease progression in children similar to that in adults?*
- *Is the outcome of therapy likely to be similar to that in the adult form of the disease?*

The ability to study each age group may not be practical and we are interested in the most scientific and practical drug development programs for each group. As an increased number of pediatric trials are being conducted, dose selection and trial design are being based on a
quantitative understanding of pharmacokinetics and pharmacodynamics prior to the conduct of efficacy and safety studies.

Figure 6 describes the fundamental principles in developing a pediatric clinical program. Modeling and simulation is a critical element important for dose selection and in designing informative and ultimately successful trials in children. A typical approach is to develop a PK model with data from adult subjects. To account for the growth effects, other covariates that influence PK such as body weight and maturation (e.g. for renal function) are incorporated to account for age specific effects on the PK. A second step is to assess the target concentration needed in pediatrics and conduct simulations to assess the percentage of patients which would be within the target range. When simulations include elements of trial design then additional aspects such as sample size, duration and sampling designs can be assessed. Finally, often a compromise may be needed such that the dose that is recommended in pediatrics may not be directly evaluated in the clinical trial. Specially, in neonates the use of dosing calculators is much needed.

A future direction is likely to be in two areas – (1) systematically assessing disease similarity between adults and pediatrics and (2) integrating aspects of innovative trial designs into approaches that may include one or more of the following:

- Adaptive designs and incorporation of prior information through Bayesian techniques.
- In measuring markers of efficacy and safety -use of sparse sampling techniques may involve improvements in analytical methodology.
- Use of modeling and simulation in “real time” setting to make dosing adjustments.
- Use of pragmatic trials which include patients in routine clinical practice settings and assessing data from electronic health records and other auditable sources of drug dose and response.
Acknowledgements

The authors would like to acknowledge the sponsors for the particular case studies and other examples presented in this manuscript, for generating data, developing and utilizing pharmacometric models to support pediatric dose selection. In addition, the authors would also like to acknowledge reviewers from Division of Clinical Pharmacology 1, Division of Clinical Pharmacology 3 and Division of Clinical Pharmacology 4 in Office of Clinical Pharmacology; Division of Neurology Products, Division of Antiviral Products and Division of Gastroenterology and Inborn Error Products in Office of New Drugs, who were associated in the review of the case studies described in this manuscript. Furthermore, authors would like to thank Dr. Shiew Mei Huang for providing insightful comments during the preparation of the manuscript.
Authorship Contributions

Performed data analysis: Mehrotra, Earp, Bhattaram, Eun Lee, Yeon Lee and Liu

Wrote or contributed to the writing of the manuscript: Mehrotra, Bhattaram, Earp, Florian, Krudys, Eun Lee, Liu, Mulugeta, Yu, Zhao and Sinha
References


Bhattaram VA, Lee JY, Yang X and Men Y (2013) FDA Clinical Pharmacology and Biopharmaceutics Review for Sabril (Vigabatrin)


Earp JC, Estes KE, Garnett CE, Lee SCH, and Bashaw ED (2011) FDA Clinical Pharmacology and Biopharmaceutics Review for Nexium IV (Esomeprazole)


Estes KE. Mehrotra N, Tornoe C, Bashaw D (2009) FDA Clinical Pharmacology and Biopharmaceutics Review for oral esomeprazole
FDA Anti-Infective Drugs Advisory Committee Meeting to discuss raxibacumab for the proposed indication of treatment of inhalational anthrax (Nov 2, 2012)

FDA Gastrointestinal Drugs Advisory Committee Meeting to discuss results from clinical trials of proton pump inhibitors in gastroesophageal reflux disease (GERD) in patients less than one year of age (Nov 05, 2010)

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products: Guidance for Industry (Draft, 2014),


Marathe A, Men Y and Wang Y (2011) FDA Clinical Pharmacology and Biopharmaceutics Review for Topamax (topiramate)


Package insert for Argatroban injection


Package insert for Humira (adalimumab):

Package insert for Nexium IV (Esomeprazole):


Package insert for Prezista (Darunavir)


Package insert for Raxibacumab


Package insert for Sabril (Vigabatrin):


Package insert for Topamax (topiramate)


Package insert for Trileptal (Oxcarbazapine)


Sekar V, Duan j, Uppoor R and Gobburu, JV (2001) FDA Clinical Pharmacology and Biopharmaceutics Review for Trileptal (Oxcarbazapine)


Footnotes

J.Y.L.: Author was the reviewer of one of the case studies presented in this manuscript. The review was conducted when author was in the Division of Pharmacometrics

Disclaimer: The opinions presented in this manuscript are of authors personally and do not necessarily reflect any position of the Government or the Food and Drug Administration
Legend for Figures

Figure 1: (a) The final FDA recommended dosing regimen of esomeprazole in pediatrics produces similar AUC values compared to those in adults, (b) Esomeprazole $C_{\text{max}}$ values following 3-min injections in pediatrics are higher than those after 20 mg in adults, (c) Increasing the IV esomeprazole infusion duration in children to 30-minutes results in comparable steady-state $C_{\text{max}}$ values to the 20 mg dose in adults. A 10-minute infusion duration in children produces steady-state $C_{\text{max}}$ values that are less than those observed after the 40 mg dose in adults (13.5 nM/mL).

Figure 2: Model-predicted relationship between normalized dose of vigabatrin and seizure rate during the maintenance phase. The red line is for adults and the black line is for pediatrics. The dotted lines represent the 95% prediction interval.

Figure 3: Exposure response and dose-response of adalimumab in pediatric patients with CD during the maintenance phase. Concentrations of adalimumab were divided into quartiles (lowest quartile Q1 and the highest Q4) for the exposure-response analysis.

Figure 4: Relationship between darunavir IQ and the Probability of Virologic Success (HIV-1 RNA < 50 copies/mL, Left) or the Probability of 1 Log Reduction in Viral Load (Right) at Week 24 in Adults and Pediatric Subjects. The solid line represents the logistic regression model fit for the data in adults. The dotted lines represent the 95% confidence interval.

Figure 5: Regulatory experience with PBPK submissions.

Figure 6: PK/PD Model informed development at the core of pediatric drug development.
Tables

Table 1. Adalimumab Concentrations and Clinical Remission (at Week 26 for pediatrics and at Week 24 for adults)

<table>
<thead>
<tr>
<th>Population</th>
<th>Subgroup</th>
<th>Dose</th>
<th>C_{\text{trough at Week 26}}**(\mu g/mL, mean ± SD)</th>
<th>Clinical Remission at Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>&lt; 40 kg</td>
<td>10 mg EOW</td>
<td>2.0 ±1.4</td>
<td>5/19 (26.3%)</td>
</tr>
<tr>
<td></td>
<td>(N=39)</td>
<td>(N=19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 40 kg</td>
<td>20 mg EOW</td>
<td>7.6 ± 3.6</td>
<td>8/20 (40.0%)</td>
</tr>
<tr>
<td></td>
<td>(N=94)</td>
<td>(N=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 40 kg</td>
<td>20 mg EOW</td>
<td>3.7 ± 2.71</td>
<td>20/47 (42.6%)</td>
</tr>
<tr>
<td></td>
<td>(N=94)</td>
<td>(N=47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 40 kg</td>
<td>40 mg EOW</td>
<td>10.7 ± 4.6</td>
<td>23/47 (48.9%)</td>
</tr>
<tr>
<td></td>
<td>(N=47)</td>
<td>(N=47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults*</td>
<td>N=94</td>
<td>40 mg EOW</td>
<td>6.8 ± 4.3</td>
<td>54/94 (57.4%)</td>
</tr>
<tr>
<td>Adults*</td>
<td>N=260</td>
<td>40 mg EOW</td>
<td>NA</td>
<td>87/260 (33.5%)</td>
</tr>
</tbody>
</table>

*Data in adults were taken from the submission for adult CD and the clinical remission was based CDAI (pediatrics clinical remission was based PCDAI)

**Data from 42 subjects are missing
### Table 2: Secondary Efficacy Endpoints by body Weight and Dose Group Following Adalimumab Administration in Pediatric Patients with CD

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dose</th>
<th>Clinical Response at Week 26</th>
<th>Clinical Remission at Week 52</th>
<th>Clinical Response at Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 kg (N=60)</td>
<td>10 mg (N=31)</td>
<td>13/31 (41.9%)</td>
<td>5/31 (16.1%)</td>
<td>8/31 (25.8%)</td>
</tr>
<tr>
<td></td>
<td>20 mg (N=29)</td>
<td>14/29 (48.3%)</td>
<td>8/29 (27.6%)</td>
<td>11/29 (37.9%)</td>
</tr>
<tr>
<td>≥ 40 kg (N=128)</td>
<td>20 mg (N=64)</td>
<td>33/64 (51.6%)</td>
<td>17/64 (26.6%)</td>
<td>19/64 (29.7%)</td>
</tr>
<tr>
<td></td>
<td>40 mg (N=64)</td>
<td>41/64 (64.1%)</td>
<td>23/64 (35.9%)</td>
<td>28/64 (43.8%)</td>
</tr>
</tbody>
</table>
**Table 3:** Comparison of the Expected Darunavir PK Exposures for Different Regimens per Weight Group. The bold text corresponds to sponsor’s proposed q.d. regimens. The rows shaded in dark grey correspond to the approved b.i.d regimens. The rows shaded in light gray correspond to FDA recommended q.d. regimens.

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>Dose</th>
<th>Median C0h (5th-95th percentile) ng/mL</th>
<th>Median AUC24h (5th-95th percentile) µg.h/mL</th>
<th>Median Cmax (5th-95th percentile) ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 15 kg</td>
<td>30 mg/kg q.d.</td>
<td>2202 (1337 – 4002)</td>
<td>77.2 (52.0 – 125)</td>
<td>5692 (4529 – 7885)</td>
</tr>
<tr>
<td></td>
<td>35 mg/kg q.d.</td>
<td>2570 (1560 – 4669)</td>
<td>90 (60.6 – 146)</td>
<td>6641 (5284 – 9199)</td>
</tr>
<tr>
<td></td>
<td><strong>40 mg/kg q.d.</strong></td>
<td><strong>2937 (1782 – 5336)</strong></td>
<td><strong>103 (69.3 – 167)</strong></td>
<td><strong>7590 (6039 – 10514)</strong></td>
</tr>
<tr>
<td></td>
<td>20 mg/kg b.i.d.</td>
<td>3270 (2035 – 5772)</td>
<td>103 (69.3 – 167)</td>
<td>5557 (4135 – 8234)</td>
</tr>
<tr>
<td>15 to 30 kg</td>
<td>475 mg q.d.</td>
<td>1947 (1049 – 4028)</td>
<td>73.9 (50.0 – 129)</td>
<td>5545 (4145 – 8224)</td>
</tr>
<tr>
<td></td>
<td>550 mg q.d.</td>
<td>2255 (1214 – 4664)</td>
<td>85.5 (55.6 – 149)</td>
<td>6420 (4800 – 9522)</td>
</tr>
<tr>
<td></td>
<td><strong>600 mg q.d.</strong></td>
<td><strong>2460 (1325 – 5088)</strong></td>
<td><strong>93.3 (60.6 – 163)</strong></td>
<td><strong>7004 (5236 – 10388)</strong></td>
</tr>
<tr>
<td></td>
<td>375 mg b.i.d.</td>
<td>3547 (2028 – 6944)</td>
<td>117 (75.7 – 203)</td>
<td>6222 (4335 – 10066)</td>
</tr>
<tr>
<td>30 to 40 kg</td>
<td>600 mg q.d.</td>
<td>1826 (1056 – 3556)</td>
<td>74.5 (51.2 – 120)</td>
<td>5642 (4455 – 7904)</td>
</tr>
<tr>
<td></td>
<td>675 mg q.d.</td>
<td>2084 (1190 – 4000)</td>
<td>83.8 (57.6 – 135)</td>
<td>6347 (5012 – 8892)</td>
</tr>
<tr>
<td></td>
<td>750 mg q.d.</td>
<td>2316 (1322 – 4445)</td>
<td>93.1 (64.0 – 150)</td>
<td>7052 (5569 – 9880)</td>
</tr>
<tr>
<td></td>
<td><strong>800 mg q.d.</strong></td>
<td><strong>2470 (1410 – 4741)</strong></td>
<td><strong>99.3 (68.3 – 160)</strong></td>
<td><strong>7522 (5940 – 10539)</strong></td>
</tr>
<tr>
<td></td>
<td>450 mg b.i.d.</td>
<td>3329 (2018 – 6021)</td>
<td>112 (76.8 – 180)</td>
<td>5963 (4397 – 8932)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td><strong>800 mg q.d.</strong></td>
<td><strong>1920 (1031 – 3948)</strong></td>
<td><strong>81.1 (53.8 – 137)</strong></td>
<td><strong>6066 (4615 – 8785)</strong></td>
</tr>
<tr>
<td></td>
<td>600 mg b.i.d.</td>
<td>3599 (2100 – 6831)</td>
<td>122 (80.7 – 205)</td>
<td>6426 (4559 – 10120)</td>
</tr>
<tr>
<td>Adult</td>
<td><strong>800 mg q.d.</strong></td>
<td><strong>2041 (911 – 4632)</strong></td>
<td><strong>87.9 (60.5 – 143)</strong></td>
<td><strong>6756 (1683)</strong></td>
</tr>
</tbody>
</table>

* Mean (SD) based on the non-compartmental analysis
C\textsubscript{max} values for the 3-minute injection are dose-normalized to 20 mg using the observed C\textsubscript{max} values for the 40 mg dose given as a 3-minute injection in adults.
Figure 2.

[Graph showing predicted seizure rate during maintenance phase versus dose (mg). The x-axis represents dose in mg ranging from 0 to 6000, and the y-axis represents predicted seizure rate ranging from 0 to 15. Several lines of different colors and styles depict the relationship between dose and seizure rate.]
Figure 3

**PCDAI Remission at Week 26 by Quartile**

- Quartile 1 (Q1): 0.94 μg/mL
- Quartile 2 (Q2): 4.07 μg/mL
- Quartile 3 (Q3): 7.4 μg/mL
- Quartile 4 (Q4): 13.4 μg/mL

**PCDAI Remission at Week 26 by Treatment**

- Mean trough:
  - 40 mg >40 kg: 19.7 μg/mL
  - 20 mg >40 kg: 3.7 μg/mL
  - 20 mg <40 kg: 7.5 μg/mL
  - 10 mg <40 kg: 1.98 μg/mL

**Patients’ Remission at Week 26 (%)**

- Q1 (N=23)
- Q2 (N=22)
- Q3 (N=23)
- Q4 (N=23)

**Concentration of Adalimumab at Week 26 (μg/mL)**

- 5 10 15 20
Figure 4

RNA < 50 Copies/ml

Log Reduction in Viral Load

Proportion of patients with virologic success

0.2 0.4 0.6 0.8

0 1 2 3 4 5

log10 IQ

Proportion of patients with virologic success

0.2 0.4 0.6 0.8 1.0

0 1 2 3 4 5

log10 IQ

Adult (N = 350)
Ped >6 y.o. (N = 64)
Ped 3-6 y.o. (N = 17)
Figure 5.

**Major clinical pharmacology issues**

- DDI: 66%
- Peds: 17%
- Others: 17%

**Therapeutic Areas**

- Anti-Viral/Anti-Infective: 37%
- GI: 10%
- Hematology-Oncology: 10%
- Medical-Imaging: 10%
- Metab-Endo: 10%
- Neurology: 3%
- Psychiatry: 3%
- Repro-Uro: 17%