

Special Section on Pediatric Drug Disposition and Pharmacokinetics

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, and Vikram Sinha

Division of Pharmacometrics, Office of Clinical Pharmacology (N.M., A.B., J.C.E., J.F., K.K., J.E.L., J.L., Y.M., J.Y., P.Z., V.S.), and Division of Biometrics VII, Office of Biostatistics (J.Y.L.), Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland

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ABSTRACT

Dose selection is one of the key decisions made during 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 examples in which pharmacometric analysis was used to support approval and labeling in pediatrics. In particular, the role of pharmacokinetic (PK) comparison of pediatric PK to adults and utilization of dose/exposure-response analysis for dose selection are highlighted. Dose selection for esomeprazole in pediatrics was based on PK matching to adults, whereas for adalimumab, exposure-response, PK, efficacy, and safety data together were 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 a twice-daily regimen, different once-daily dosing regimens for treatment-naïve human immunodeficiency virus 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 an 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 toward 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 of 2002 provides financial incentives (additional exclusivity) for pediatric studies conducted pursuant to a request by the Food and Drug Administration (FDA), and the Pediatric Research Equity Act (PREA) of 2003 requires clinical research to support pediatric applications for new drugs and biologic products. Together, these two legislations have generated information about the efficacy, safety, and dosing of

approximately 600 products in children. The permanent reauthorization in 2012 of both the Best Pharmaceutical Children's Act and PREA as part of the FDA Innovation and Safety Act 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 products are often 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 (Turner et al., 1999; Neubert et al., 2004). Drug development in children is further complicated by a relatively 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., 2014). Challenges with dose

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

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ABBREVIATIONS: AUC, area under the curve; AUC_{24h}, area under the curve over 24 hours; BID, twice daily; CD, Crohn's disease; DRV, darunavir; EOW, every other week; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; IQ, inhibitory quotient; M&S, modeling and simulation; PBPK, physiologically based pharmacokinetic modeling; PCDAL, Pediatric Crohn's Disease Activity Index; PD, pharmacodynamics; PK, pharmacokinetics; PREA, Pediatric Research Equity Act; PWR, pediatric written request; QD, once daily; rCPS, refractory complex partial seizures; RTV, ritonavir.

selection and trial design have been reported as important contributing factors to trial failures in children (Benjamin et al., 2008; Momper et al., 2015).

Advances in the science of quantitative pharmacology and the use of model-based drug development have paralleled the advances in pediatric research (Stockmann et al., 2015; Vinks et al., 2015). The use of modeling and simulation (M&S) as an integral part of and basis for improving efficiency, substantiating trial design, and optimizing dose selection in pediatric drug development has been communicated in recent guidance (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf>). 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 Code of Federal Regulation Section 314.55; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=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 has been previously described (Bhattaram et al., 2005, 2007; Wang et al., 2008; Jadhav et al., 2009; Leong et al., 2012). 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 biologic products in pediatric patients.

Materials and Methods

The focus of this manuscript is to highlight the role of pharmacometrics in pediatric approval and labeling. We present 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 of the role of pharmacokinetics (PK)/pharmacodynamics (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 with Erosive Esophagitis: Intravenous Dose Selection

Background. On April 21, 2011, the FDA approved i.v. esomeprazole in children 1 month to 17 years of age for the treatment of gastroesophageal reflux disease (GERD) with erosive esophagitis (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021689s0301bl.pdf). Intravenous esomeprazole is also approved for use in adults. The recommended dosing for adult patients is either 20 or 40 mg given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10–30 minutes).

In the case of pediatric i.v. esomeprazole, the FDA agreed to extrapolate evidence of efficacy from adults to pediatrics, 1 month to 17 years of age, based on the similar disease pathophysiology and response to treatment between pediatrics and adults (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM232026.pdf>; <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM258684.pdf>). For dose selection, a PK study was required and designed in pediatrics with the intent of matching exposures to adults and generating additional safety data.

Regulatory Question. What doses in pediatrics result in exposures comparable to those in adults?

Role of Pharmacometric Review. Intragastric pH is a pharmacodynamic biomarker in this indication. The mean of the pharmacodynamic biomarker was plotted for each quartile of esomeprazole exposure. Based on the visual comparison, exposure-response relationships of intragastric pH measures were comparable between pediatrics and adults, indicating that target effective concentration exposures [area under the curve (AUC): mean of 5.1 $\mu\text{mol}\cdot\text{h/l}$, 90% confidence interval of 3–9 $\mu\text{mol}\cdot\text{h/l}$] in pediatrics and adults were similar (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM258684.pdf>).

Observed i.v. or oral esomeprazole PK data were available from 50 and 117 children, respectively, between birth and 17 years of age, and from 65 adults between 20 and 48 years of age. A population PK model developed by the sponsor using all of the pediatric data was used to simulate steady-state esomeprazole exposures (AUC and C_{max}) following i.v. administration for pediatric patients at different fixed doses to match the observed exposures in adults. For each dosing regimen, AUC and C_{max} were compared to the exposures from the 20- and 40-mg i.v. 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, whereas 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 C_{max} observed in adults with 20- and 40-mg doses, whereas the AUC between adults and pediatrics was comparable (Fig. 1, A and B). PK simulations conducted using the population PK model indicated that increasing the duration of infusion to 10–30 minutes resulted in C_{max} values within those observed with effective doses in adults (20 and 40 mg) (Fig. 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 (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM258684.pdf>). Population PK simulations were useful in identifying a simple weight-based dosing regimen for children that resulted in steady-state AUCs and C_{max} comparable to that observed after 20 mg in adults.

A similar approach for dose selection was taken for oral esomeprazole for use in infants 1 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 relationships between infants and adults and on the findings of the November 5th, 2010 FDA Gastrointestinal Drugs Advisory Committee meeting, which concluded it is reasonable to extrapolate adult efficacy information to infants 1 month to <1 year of age provided that supportive PK and PK/PD data are available (Gastrointestinal Drugs Advisory Committee, 2010; <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM177428.pdf>).

Approval of Vigabatrin for Refractory Complex Partial Seizures in Pediatrics

Background. Vigabatrin was approved in 2009 as an 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 [http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020427s015,022006s0161bl.pdf]. A pediatric written request (PWR) was issued in 2011 which included a clinical trial required under the PREA to evaluate the safety and efficacy of vigabatrin as an adjunctive therapy in pediatric patients 10–17 years of age with

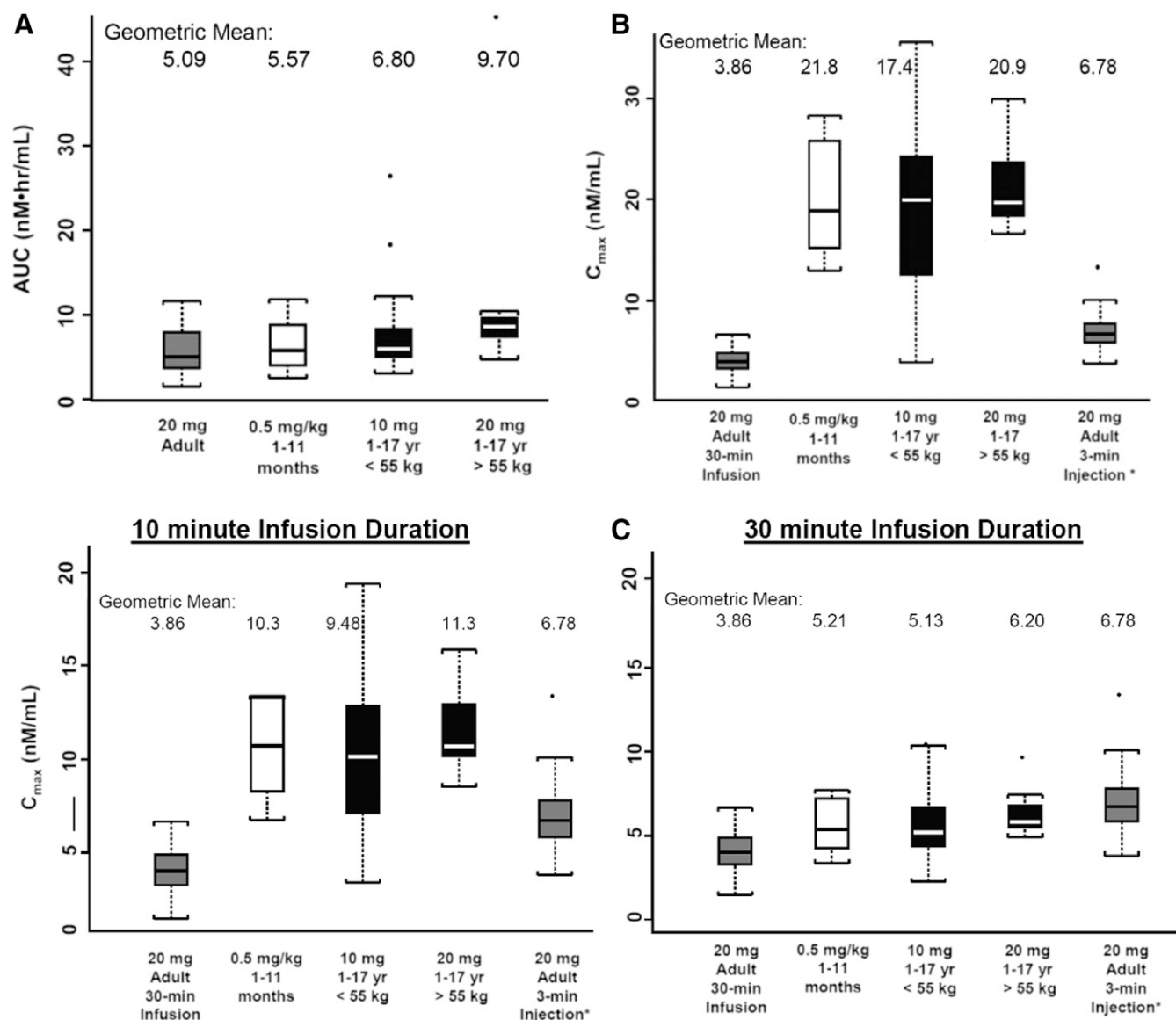


Fig. 1. (A) The final FDA-recommended dosing regimen of esomeprazole in pediatrics produces similar AUC values compared with those in adults. (B) Esomeprazole C_{max} values following 3-minute injections in pediatrics are higher than those after 20 mg in adults. (C) Increasing the i.v. esomeprazole infusion duration in children to 30 minutes results in steady-state C_{max} values comparable to the 20-mg dose in adults. A 10-minute infusion duration in children produces steady-state C_{max} values that are less than those observed after the 40-mg dose in adults (13.5 nM/ml).

rCPS. In addition, a 1-year safety study was also required. In two subsequent meetings with the FDA 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 use a modeling approach to assess the similarity of the relationship between vigabatrin dose and 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 an adjunctive therapy for pediatric patients with rCPS and

two controlled studies of vigabatrin as an 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 with 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. The following equation shows the dose normalization by total body weight:

$$D_{\text{NORM}} = \text{DOSE} \cdot (\text{WT}/60)^{-0.608}$$

where D_{NORM} is the normalized dose, DOSE is the fixed dose in milligrams administered to a pediatric patient, and WT is the body weight of the pediatric patient in kilograms. This relationship between D_{NORM} , DOSE, and WT was developed using the data available from the pediatric clinical trials. The normalized dose (D_{NORM}) should be

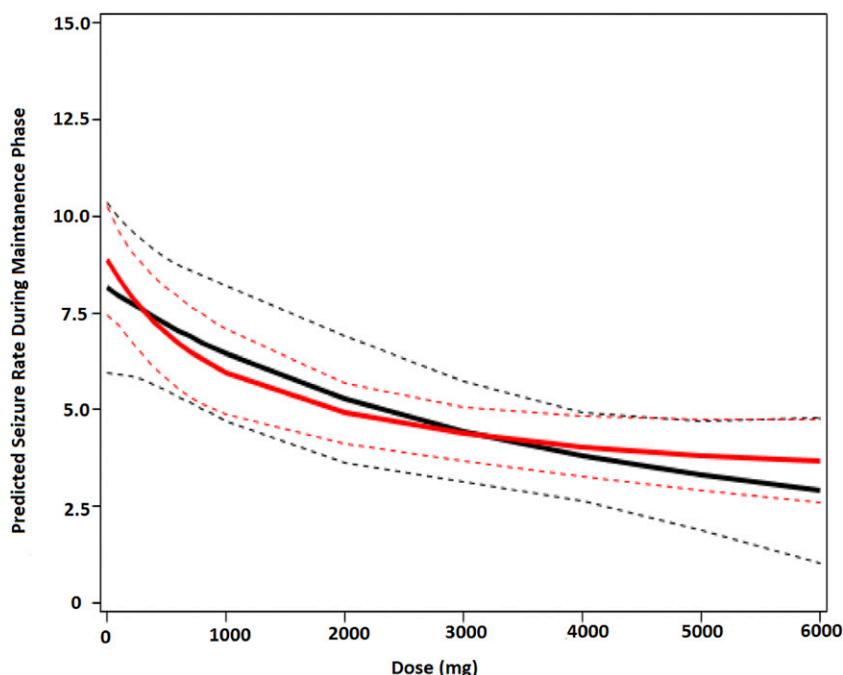


Fig. 2. Model-predicted relationship between normalized dose of vigabatrin and seizure rate during the maintenance phase. The red line is for adults, and the black line is for pediatrics. The dotted lines represent the 95% prediction interval.

considered as a surrogate for drug exposure, such that a pediatric patient with a higher weight will have a lower value of D_{NORM} , and vice versa.

Age was not found to be a significant covariate of 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 (Fig. 2). The details of the sponsor's and the FDA analysis are provided in the FDA clinical pharmacology review that demonstrated that the dose-response relationship between children and adults is similar (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM374644.pdf>). 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 aforementioned dose-response analysis. Vigabatrin was approved for the treatment of rCPS in patients ≥ 10 years of age, thus alleviating the need for an additional efficacy trial in this pediatric patient population.

Adalimumab for Crohn's Disease in Children: Dose Selection

Background. On September 23, 2014, the 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 (http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125057s3941bl.pdf).

Adalimumab is approved for CD in adults, with an initial dose of 160 mg followed by 80 mg 2 weeks later. Two weeks later, a maintenance dose of 40 mg every other week (EOW) is recommended. In the pivotal phase 3 study in children 6 years and older, patients received a weight-based induction dosing regimen, and were then randomized to high- and low-dose groups stratified by a 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 ≥ 40 kg or 20 mg for body weight < 40 kg,

and the low-dose group received 20 mg for body weight ≥ 40 kg and 10 mg for body weight < 40 kg. Patients with inadequate response were allowed to escalate the dose from EOW dosing to weekly dosing at week 12. The primary efficacy endpoint was the proportion of subjects who were in clinical remission based on the Pediatric Crohn's Disease Activity Index (PCDAI) at week 26.

A numerical trend of higher efficacy in the high-dose group was observed with the PCDAI; however, the dose response was not evident when the PCDAI was converted to the Crohn's Disease Activity Index. This presented a question of whether a high dose in pediatrics should be approved for both weight groups. Exposure-response analyses and comparison of exposures achieved with the proposed pediatric dose as compared with adults along with information on the secondary efficacy endpoints and safety were 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 support 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 (Fig. 3).

Adalimumab concentrations in both body weight groups of patients who received a high dose were comparable with those in adults, whereas adalimumab concentrations in both body weight groups of patients in the low-dose group were lower than those in adults (Table 1). Furthermore, patients in the high-dose group showed numerically higher clinical remission rates for both body weight groups (40.0% for < 40 kg and 48.9% for ≥ 40 kg) than those in the low-dose group (26.3% for < 40 kg and 42.6% for ≥ 40 kg), and these rates were comparable to the clinical remission rates observed in adults (Table 1). Although the difference in clinical remission at week 26 in the ≥ 40 -kg subgroup between 20 and

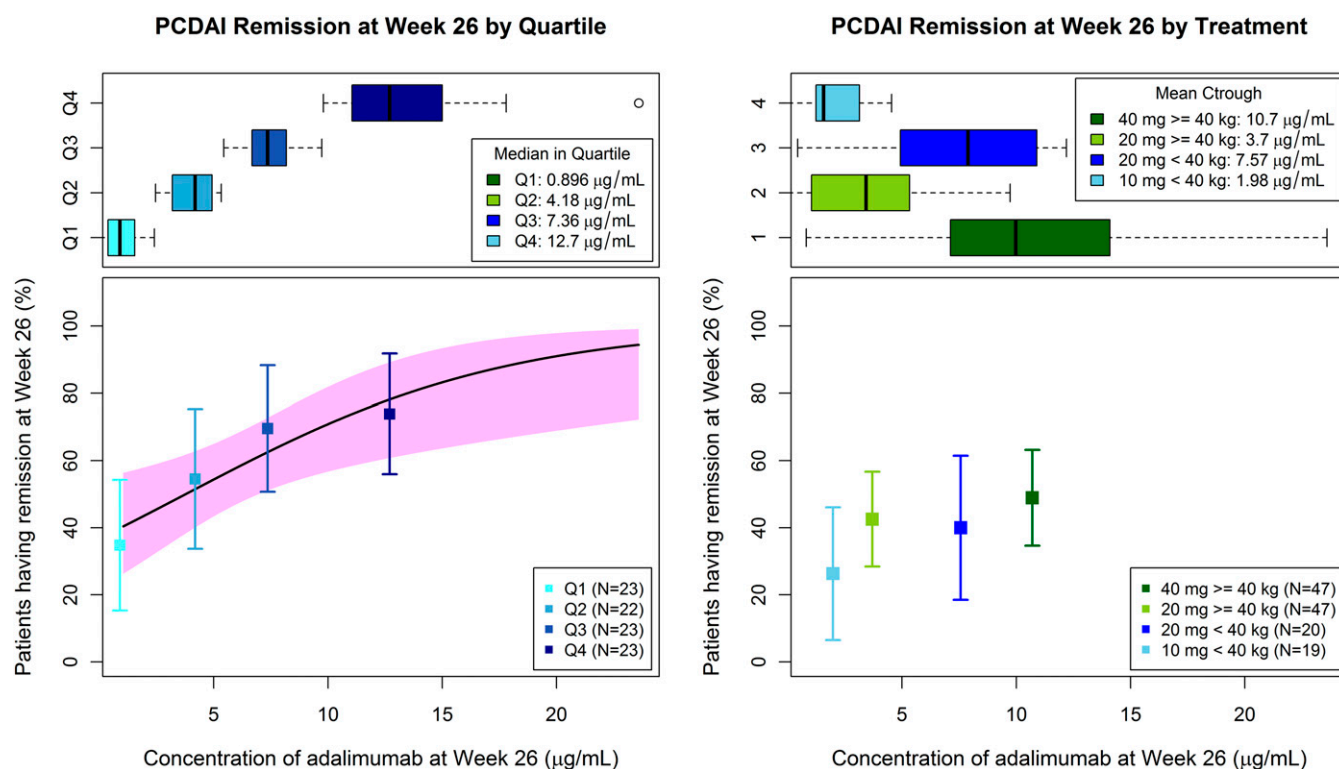


Fig. 3. Exposure-response and dose-response of adalimumab in pediatric patients with CD during the maintenance phase. Concentrations of adalimumab were divided into quartiles [lowest quartile (Q1) and highest quartile (Q4)] for the exposure-response analysis.

40 mg EOW was 6.3%, other secondary efficacy endpoints consistently showed a 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 the high-dose group (48.3% for <40 kg and 64.1% for \geq 40 kg) and the low-dose group (41.9% for <40 kg and 51.6% for \geq 40 kg) was more remarkable. Longitudinal assessment of PCDAI also indicated that high dose had numerically better efficacy compared with the low-dose group throughout the treatment period. Moreover, a smaller proportion of patients in the high-dose group required dose escalation due to inadequate response (45.3% in patients \geq 40 kg and 61.3% in patients <40 kg in the low-dose group compared with 39.1% in patients \geq 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 the high-dose group of adalimumab in the \geq 40-kg subgroup (serious adverse events: 23.4% with 20 mg vs. 18.8% with 40 mg; any adverse event: 89.1% with 20 mg vs. 93.8% with 40 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.

TABLE 1
Adalimumab concentrations and clinical remission (at week 26 for pediatrics and week 24 for adults)

Population	C _{trough} at Week 26 ^a (Mean \pm S.D.)	Clinical Remission at Week 26
	$\mu\text{g/mL}$	
Pediatrics		
<40 kg (N = 39)		
10 mg EOW (N = 19)	2.0 \pm 1.4	5/19 (26.3%)
20 mg EOW (N = 20)	7.6 \pm 3.6	8/20 (40.0%)
\geq 40 kg (N = 94)		
20 mg EOW (N = 47)	3.7 \pm 2.71	20/47 (42.6%)
40 mg EOW (N = 47)	10.7 \pm 4.6	23/47 (48.9%)
Adults ^b		
N = 94		
40 mg EOW	6.8 \pm 4.3	54/94 (57.4%)
N = 260		
40 mg EOW	NA	87/260 (33.5%)

^aData from 42 subjects are missing.

^bData in adults were taken from the submission for adult CD, and the clinical remission was based on the Crohn's Disease Activity Index (pediatrics clinical remission was based the PCDAI).

TABLE 2

Secondary efficacy endpoints by body weight and dose group following adalimumab administration in pediatric patients with CD

Body Weight/Dose	Clinical Response at Week 26	Clinical Remission at Week 52	Clinical Response at Week 52
<40 kg (N = 60)			
10 mg (N = 31)	13/31 (41.9%)	5/31 (16.1%)	8/31 (25.8%)
20 mg (N = 29)	14/29 (48.3%)	8/29 (27.6%)	11/29 (37.9%)
≥40 kg (N = 128)			
20 mg (N = 64)	33/64 (51.6%)	17/64 (26.6%)	19/64 (29.7%)
40 mg (N = 64)	41/64 (64.1%)	23/64 (35.9%)	28/64 (43.8%)

Exposure-Response and PK Matching to Bridge Dosing for Different Patient Populations in Pediatrics for the Treatment of Human Immunodeficiency Virus

Background. Darunavir (DRV), a HIV protease inhibitor, in combination with low-dose ritonavir (RTV) was previously approved by the FDA in 2006 for use in treatment-experienced adults and pediatric subjects aged 3 to <18 years as a twice-daily (BID) regimen (http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021976s036%2c202895s0131bl.pdf). The once-daily (QD) regimen had also been approved in 2008 for use in treatment-naïve adults. To fulfill the PWR for the DRV/RTV QD 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 QD substudy of the phase II study in treatment-experienced pediatric subjects aged 3 to <6 years were conducted.

Regulatory Question. Data from these studies were used to determine the comparability of DRV/RTV QD exposure in pediatrics with that of adults while not exceeding DRV/RTV exposures observed with either the QD or BID regimen. All subsequent comparisons 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 an RTV-boosted protease inhibitor-based regimen. In addition, no pediatric patients 6 to <12 years of age were evaluated in

the DRV/RTV QD studies, but in the interest of providing additional treatment options for this population, modeling and simulation were used to inform the appropriate DRV/RTV QD dosing regimen based on comparisons of exposures between adults and model predictions. Modeling and simulation were based on the previously developed model in adults and treatment-experienced pediatric subjects and incorporated new PK data from pediatric subjects with QD regimens. The updated model is consistent with the previous models (<http://www.page-meeting.org/?abstract=964>).

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 (<http://www.fda.gov/downloads/Drugs/Development-ApprovalProcess/DevelopmentResources/UCM346671.pdf>). The inhibitory quotient (IQ) is the ratio of steady-state trough concentration (C_{0h}) and the baseline IC_{50} 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 Fig. 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 QD regimen in pediatrics based on pharmacokinetic matching can be

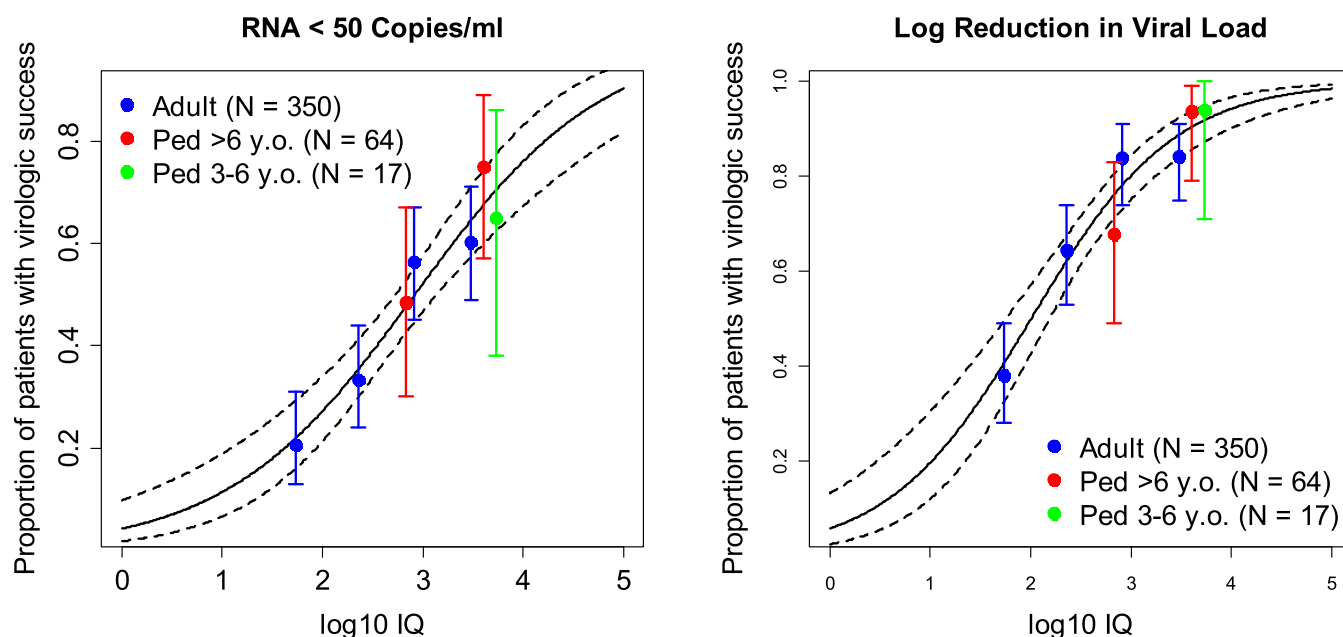


Fig. 4. Relationship between darunavir IQ and the probability of virologic success (HIV-1 RNA <50 copies/ml, left) or the probability of 1 log reduction in viral load (right) at week 24 in adults and pediatric subjects. The solid line represents the logistic regression model fit for the data in adults. The dotted lines represent the 95% confidence interval.

reasonably adopted. Also, because an adequate safety trial for the QD 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 BID dosing regimens. Therefore, the following considerations were taken into account for PK comparison:

- For efficacy, the expected C_{0h} and (AUC over 24 hours) AUC_{24h} in pediatric patients with QD dosing should closely match C_{0h} and AUC_{24h} values observed in adults receiving the approved DRV/RTV 800-/100-mg QD regimen.
- For safety, the expected AUC_{24h} and C_{max} in pediatric patients with QD dosing should not significantly exceed AUC_{24h} and C_{max} observed in pediatric patients receiving the approved BID regimens.

Regulatory Outcome. Based on the model-based pharmacokinetic simulations and parameter estimations, and safety data from pediatric clinical studies with the BID regimen, different QD dosing regimens for treatment-naïve HIV-1-infected pediatric subjects 3 to <12 years of age were evaluated. Comparisons between exposure from QD and BID dosing regimens based on PK simulation indicate that C_{max} values in pediatric patients with the QD regimens proposed by the sponsor are 137, 113, and 126% of those in pediatric patients with the approved BID regimens who weigh 10–15, 15–30, and 30–40 kg, respectively. Because there are limited or no safety data at these higher C_{max} values in the pediatric population, the FDA recommended the revised QD regimens 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, and endpoint

selection, and to provide supportive evidence of effectiveness, dose, and dosing regimen selection, among 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 New Drug Application or Biologics License Application 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 used 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 (Jadhav and Kern, 2010; Stockmann et al., 2015).

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, are now well recognized (Offringa et al., 2015). In younger children (<2 years), additional considerations toward 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 intraindividual 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) and variability that incorporate prior data are important.

In the case of esomeprazole, efficacy in pediatrics was extrapolated from adults. Furthermore, similarity of exposure-response meant that the “PK matching” approach, in which a dose in pediatrics is selected such that the exposures are comparable with that of approved doses in adults, is reasonable. In the case of adalimumab for Crohn’s disease, both exposure-response data and PK comparison data were used for dose selection. In the case of vigabatrin, an innovative and pragmatic approach followed by the sponsor and the FDA led to approval of

TABLE 3
Comparison of the Expected Darunavir PK Exposures for Different Regimens per Weight Group.

Weight Category/Dose	Median C_{0h} (5th-95th percentile)	Median AUC_{24h} (5th-95th percentile)	Median C_{max} (5th-95th percentile)
	ng/mL	μg.h/mL	ng/mL
10 to 15 kg			
30 mg/kg q.d.	2202 (1337 – 4002)	77.2 (52.0 – 125)	5692 (4529 – 7885)
35 mg/kg q.d. ^a	2570 (1560 – 4669)	90 (60.6 – 146)	6641 (5284 – 9199)
40 mg/kg q.d. ^b	2937 (1782 – 5336)	103 (69.3 – 167)	7590 (6039 – 10514)
20 mg/kg b.i.d. ^c	3270 (2035 – 5772)	103 (69.3 – 167)	5557 (4135 – 8234)
15 to 30 kg			
475 mg q.d.	1947 (1049 – 4028)	73.9 (50.0 – 129)	5545 (4145 – 8224)
550 mg q.d.	2255 (1214 – 4664)	85.5 (55.6 – 149)	6420 (4800 – 9522)
600 mg q.d. ^b	2460 (1325 – 5088)	93.3 (60.6 – 163)	7004 (5236 – 10388)
375 mg b.i.d. ^c	3547 (2028 – 6944)	117 (75.7 – 203)	6222 (4335 – 10066)
30 to 40 kg			
600 mg q.d.	1826 (1056 – 3556)	74.5 (51.2 – 120)	5642 (4455 – 7904)
675 mg q.d. ^a	2084 (1190 – 4000)	83.8 (57.6 – 135)	6347 (5012 – 8892)
750 mg q.d.	2316 (1322 – 4445)	93.1 (64.0 – 150)	7052 (5569 – 9880)
800 mg q.d. ^b	2470 (1410 – 4741)	99.3 (68.3 – 160)	7522 (5940 – 10539)
450 mg b.i.d. ^c	3329 (2018 – 6021)	112 (76.8 – 180)	5963 (4397 – 8932)
≥40 kg			
800 mg q.d. ^b	1920 (1031 – 3948)	81.1 (53.8 – 137)	6066 (4615 – 8785)
600 mg b.i.d. ^c	3599 (2100 – 6831)	122 (80.7 – 205)	6426 (4559 – 10120)
Adult			
800 mg q.d. ^c	2041 (911 – 4632)	87.9 (60.5 – 143)	6756 (1683) ^d

^aFDA recommended q.d. regimens.

^bSponsor’s proposed q.d. regimens.

^cApproved regimens.

^dMean (SD) based on the NCA.

vigabatrin in the pediatric population without the need for additional efficacy trials.

There are several other examples where modeling and simulation were used to make dosing decisions in pediatrics. For argatroban, the dosing and titration scheme in pediatrics was based on PK/PD modeling and simulation (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020883s016lbl.pdf). The argatroban dose in pediatrics was selected based on the clinical trial simulations where the probability of achieving a target activated partial thromboplastin time (a pharmacodynamic marker for coagulation) was used for dose selection (Madabushi et al., 2011). For oxcarbazepine and topiramate, exposure-response analysis was used to support the monotherapy indication approval by leveraging information from the adjunctive therapy approval in adults and pediatrics (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021014_S003_TRILEPTAL%20TABLETS_BIOPHARMR.pdf; <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM272684.pdf>; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020505s055,020844s046lbl.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021014s033,021285s027lbl.pdf). For, guanfacine, exposure-response modeling and clinical trial simulations were used to design a pediatric trial (Knebel et al., 2015). There were no studies of raxibacumab, which was the first monoclonal antibody approved using animal rule, in the pediatric population (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125349s000lbl.pdf). Dosing in pediatric patients was determined based on population PK simulations (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM326184.pdf>). In general, given the observation that limited amount of clinical data are

available from pediatric dosing trials, the role of pharmacometrics is critical in determining the pediatric dose.

Whereas the previously described examples and case studies 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 a purpose, approaches such as PBPK, the so-called “bottom-up” approach, have been used. Regulatory experience with PBPK in pediatric reviews is described in the following section.

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 physiological changes (including those pertaining to age-dependent development) on drug absorption, distribution, metabolism, and excretion processes can be evaluated. The past decade observed an increased interest in applying PBPK in academic research and drug development (Rowland et al., 2011; Sager et al., 2015). The advent of specialized PBPK platforms further broadens the use of PBPK (Edginton et al., 2006; Johnson et al., 2006, 2010; Edginton and Willmann, 2008; Rowland et al., 2011). Drug developers are also increasingly using 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 the 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 fall into the category of predicting drug-drug interaction potential, with the remaining 34% equally distributed between pediatric PK prediction and other applications (e.g., drug absorption, pharmacogenetics, and organ

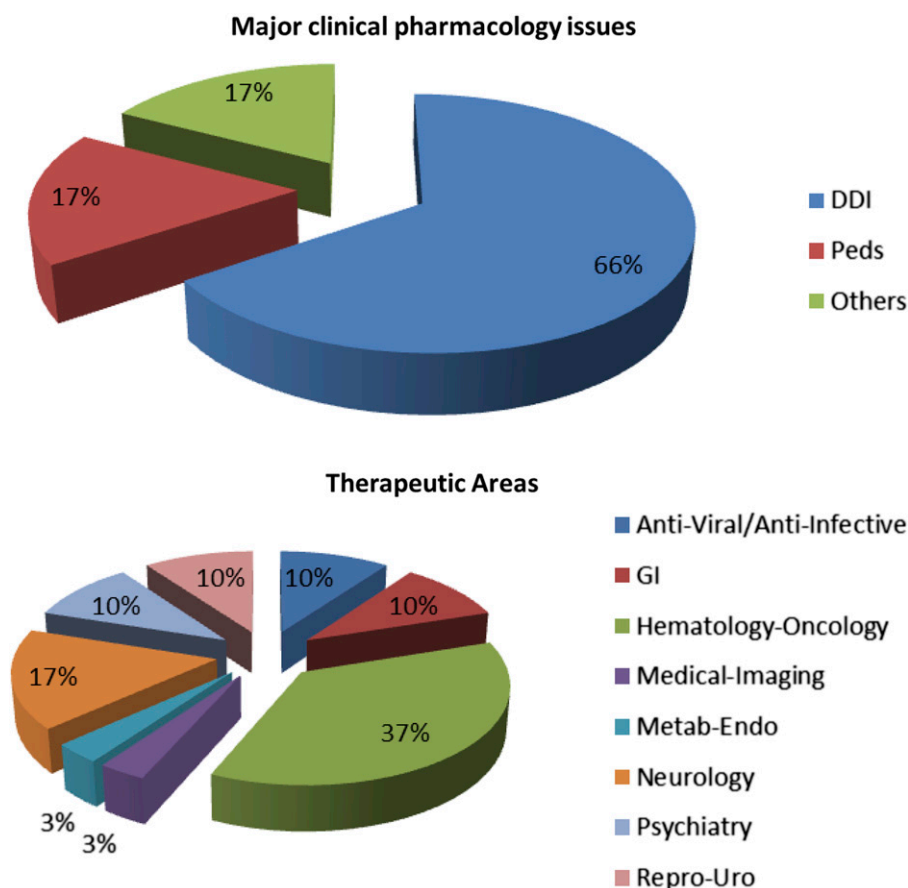


Fig. 5. Regulatory experience with PBPK submissions. DDI, drug-drug interaction; GI, gastrointestinal; Metab-Endo, Metabolism & Endocrinology; Repro-Uro, Reproductive-Urology.

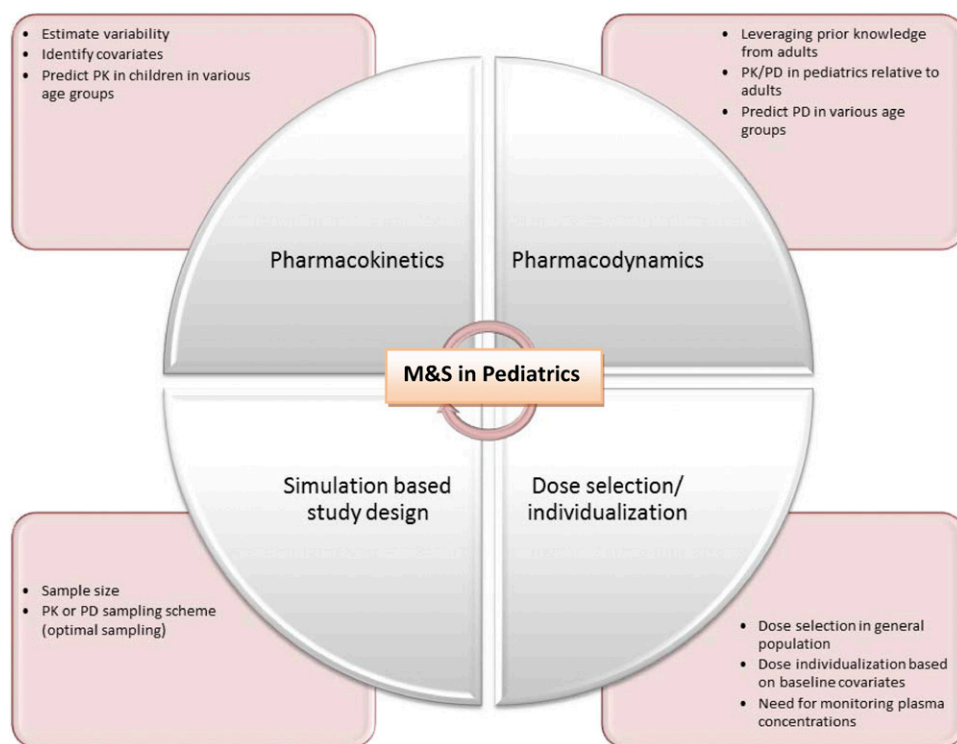


Fig. 6. PK/PD model-informed development at the core of pediatric drug development.

impairment) (Fig. 5). Of the 31 pediatric review records, distribution of therapeutic areas is shown in Fig. 5. Based on the regulatory experience, compared with drug-drug interaction 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 absorption, distribution, metabolism, and excretion processes mediated by metabolizing enzymes, binding proteins, and transporters. Therefore, one anticipates the system model for the pediatric population of a specific age group to be updated when new information becomes available. Salem and colleagues (2014) recently used clinical PK data for CYP3A substrates to derive and update the ontogeny profile for the enzyme. At the 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 (Barrett et al., 2012; Leong et al., 2012; Jiang et al., 2013; Maharaj and Edginton, 2014; Willmann et al., 2014). All proposals articulate the importance of establishing/verifying an 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 PK and 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 are critical elements 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 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. In particular, 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, which may involve improvements in analytical methodology.

- Use of modeling and simulation in a “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.

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Authorship Contributions

Performed data analysis: Mehrotra, Earp, Bhattaram, J. E. Lee, J. Y. Lee, Liu.

Wrote or contributed to the writing of the manuscript: Mehrotra, Bhattaram, Earp, Florian, Krudys, J. E. Lee, Liu, Mulugeta, Yu, Zhao, Sinha.

References

- Barrett JS, Della Casa Alberighi O, L  r S, and Meibohm B (2012) Physiologically based pharmacokinetic (PBPK) modeling in children. *Clin Pharmacol Ther* **92**:40–49.
- Benjamin DK, Jr, Smith PB, Jadhav P, Gobburu JV, Murphy MD, Hasselblad V, Baker-Smith C, Califf RM, and Li JS (2008) Pediatric antihypertensive trial failures: analysis of end points and dose range. *Hypertension* **51**:834–840.
- Bhattaram VA, Bonapace C, Chilukuri DM, Duan JZ, Garnett C, Gobburu JV, Jang SH, Kenna L, Lesko LJ, and Madabushi R, et al. (2007) Impact of pharmacometric reviews on new drug approval and labeling decisions—a survey of 31 new drug applications submitted between 2005 and 2006. *Clin Pharmacol Ther* **81**:213–221.
- Bhattaram VA, Booth BP, Ramchandani RP, Beasley BN, Wang Y, Tandon V, Duan JZ, Baweja RK, Marroum PJ, and Uppoor RS, et al. (2005) Impact of pharmacometrics on drug approval and labeling decisions: a survey of 42 new drug applications. *AAPS J* **7**:E503–E512.
- Edginton AN, Schmitt W, and Willmann S (2006) Development and evaluation of a generic physiologically based pharmacokinetic model for children. *Clin Pharmacokinet* **45**:1013–1034.
- Edginton AN and Willmann S (2008) Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. *Clin Pharmacokinet* **47**:743–752.
- Holford N (2010) Dosing in children. *Clin Pharmacol Ther* **87**:367–370.
- Huang SM, Abernethy DR, Wang Y, Zhao P, and Zineh I (2013) The utility of modeling and simulation in drug development and regulatory review. *J Pharm Sci* **102**:2912–2923.
- Jadhav PR and Kern SE (2010) The need for modeling and simulation to design clinical investigations in children. *J Clin Pharmacol* **50**(9, Suppl):121S–129S.
- Jadhav PR, Zhang J, and Gobburu JV (2009) Leveraging prior quantitative knowledge in guiding pediatric drug development: a case study. *Pharm Stat* **8**:216–224.
- Jiang XL, Zhao P, Barrett JS, Lesko LJ, and Schmidt S (2013) Application of physiologically based pharmacokinetic modeling to predict acetaminophen metabolism and pharmacokinetics in children. *CPT Pharmacometrics Syst Pharmacol* **2**:e80.
- Johnson TN, Boussey K, Rowland-Yeo K, Tucker GT, and Rostami-Hodjegan A (2010) A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. *Clin Pharmacokinet* **49**:189–206.
- Johnson TN, Rostami-Hodjegan A, and Tucker GT (2006) Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin Pharmacokinet* **45**:931–956.
- Knebel W, Rogers J, Polhamus D, Ermer J, and Gastonguay MR (2015) Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD. *J Pharmacokinet Pharmacodyn* **42**:45–65.
- Lee JE, Wang J, Wang YW, Dannis M, Rajpal A, Mulberg M, and Mehrotra N (2015) Clinical pharmacology perspectives on recommended dose of adalimumab in pediatric crohn's disease. *Gastroenterology* **148**:S639–S640.
- Leong R, Vieira ML, Zhao P, Mulugeta Y, Lee CS, Huang SM, and Burckart GJ (2012) Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. *Clin Pharmacol Ther* **91**:926–931.
- Madabushi R, Cox DS, Hossain M, Boyle DA, Patel BR, Young G, Choi YM, and Gobburu JV (2011) Pharmacokinetic and pharmacodynamic basis for effective argatroban dosing in pediatric patients. *J Clin Pharmacol* **51**:19–28.
- Maharaj AR and Edginton AN (2014) Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacometrics Syst Pharmacol* **3**:e150.
- Momper JD, Mulugeta Y, and Burckart GJ (2015) Failed Pediatric Drug Development Trials. *Clin Pharmacol Ther* **98**:245–251.
- Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, Brune K, and Hinz B (2004) The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf* **27**:1059–1067.
- Offringa M, Davis JM, Turner MA, Ward R, Bax R, Maldonado S, Sinha V, McCune SK, Zajicek A, and Benjamin DK, et al. (2015) Applying Regulatory Science to Develop Safe and Effective Medicines for Neonates: Report of the US Food and Drug Administration First Annual Neonatal Scientific Workshop, October 28–29, 2014. *Ther Innov Regul Sci* **49**:623–631.
- Rowland M, Peck C, and Tucker G (2011) Physiologically-based pharmacokinetics in drug development and regulatory science. *Annu Rev Pharmacol Toxicol* **51**:45–73.
- Sager JE, Yu J, Ragueneau-Majlessi I, and Isoherranen N (2015) Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A Systematic Review of Published Models, Applications, and Model Verification. *Drug Metab Dispos* **43**:1823–1837.
- Salem F, Johnson TN, Abduljalil K, Tucker GT, and Rostami-Hodjegan A (2014) A re-evaluation and validation of ontogeny functions for cytochrome P450 1A2 and 3A4 based on in vivo data. *Clin Pharmacokinet* **53**:625–636.
- Stockmann C, Barrett JS, Roberts JK, and Sherwin C (2015) Use of Modeling and Simulation in the Design and Conduct of Pediatric Clinical Trials and the Optimization of Individualized Dosing Regimens. *CPT Pharmacometrics Syst Pharmacol* **4**:630–640.
- Turner S, Nunn AJ, Fielding K, and Choonara I (1999) Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr* **88**:965–968.
- Vinks AA, Emoto C, and Fukuda T (2015) Modeling and simulation in pediatric drug therapy: Application of pharmacometrics to define the right dose for children. *Clin Pharmacol Ther* **98**:298–308.
- Wagner C, Zhao P, Pan Y, Hsu V, Grillo J, Huang SM, and Sinha V (2015) Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK. *CPT Pharmacometrics Syst Pharmacol* **4**:226–230.
- Wang Y, Bhattaram AV, Jadhav PR, Lesko LJ, Madabushi R, Powell JR, Qiu W, Sun H, Yim DS, and Zheng JJ, et al. (2008) Leveraging prior quantitative knowledge to guide drug development decisions and regulatory science recommendations: impact of FDA pharmacometrics during 2004–2006. *J Clin Pharmacol* **48**:146–156.
- Wharton GT, Murphy MD, Avant D, Goldsmith JV, Chai G, Rodriguez WJ, and Eisenstein EL (2014) Impact of pediatric exclusivity on drug labeling and demonstrations of efficacy. *Pediatrics* **134**:e512–e518.
- Willmann S, Becker C, Burghaus R, Cobocken K, Edginton A, Lippert J, Siegmund HU, Thelen K, and M  ck W (2014) Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. *Clin Pharmacokinet* **53**:89–102.
- Zhao P, Zhang L, Grillo JA, Liu Q, Bullock JM, Moon YJ, Song P, Brar SS, Madabushi R, and Wu TC, et al. (2011) Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther* **89**:259–267.

Address correspondence to: Dr. Nitin Mehrotra, Division of Pharmacometrics, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. 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