# Exposure Matching for Extrapolation of Efficacy in Pediatric Drug Development

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#### Abstract

During drug development, matching adult systemic exposures of drugs is a common approach for dose selection in pediatric patients when efficacy is partially or fully extrapolated. This is a systematic review of approaches used for matching adult systemic exposures as the basis for dose selection in pediatric trials submitted to the US Food and Drug Administration (FDA) between 1998 and 2012. The trial design of pediatric pharmacokinetic (PK) studies and the pediatric and adult systemic exposure data were obtained from FDA publicly available databases containing reviews of pediatric trials. Exposure-matching approaches that were used as the basis for pediatric dose selection were reviewed. The PK data from the adult and pediatric populations were used to quantify exposure agreement between the 2 patient populations. The main measures were the pediatric PK studies' trial design elements and drug systemic exposures (adult and pediatric). There were 31 products (86 trials) with full or partial extrapolation of efficacy with an available PK assessment. Pediatric exposures had a range of mean  $C_{max}$  and AUC ratios (pediatric/adult) of 0.63 to 4.19 and 0.36 to 3.60, respectively. Seven of the 86 trials (8.1%) had a predefined acceptance boundary used to match adult exposures. The key PK parameter was consistently predefined for antiviral and anti-infective products. Approaches to match exposure in children and adults varied across products. A consistent approach for systemic exposure matching and evaluating pediatric PK studies is needed to guide future pediatric trials.

#### Keywords

pediatrics, drug development, dosing, exposure matching, extrapolation

Extrapolation of efficacy findings from adults to the pediatric population is an approach that was first proposed by the US. Food and Drug Administration (FDA) in the 1994 Pediatric Labeling Rule to maximize the use of adult and other data when designing pediatric drug development programs. The Rule was supplanted by the Best Pharmaceuticals Children's Act (BPCA) in 2002 and the Pediatric Research Equity Act (PREA) in 2003. These requirements and incentives were made permanent as of 2012 with the passing of the FDA Safety and Innovation Act (FDASIA). The extrapolation concept was reflected in Regulations under 21 CFR 314.55 and has been further described in a pediatric study-planning algorithm published by the FDA.<sup>1</sup>

Extrapolation of efficacy from adults to pediatric patients relies on the assumptions that the course of the disease and the response to the investigational drug are sufficiently similar between the adult and intended pediatric population. Based on the sufficiency of the data in support of these assumptions, extrapolation of efficacy from adequate, well-controlled studies with adults to the pediatric population can be categorized as either full extrapolation or partial extrapolation. In <sup>1</sup>Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

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Gilbert J. Burckart, PharmD, US Food and Drug Administration, White Oak Building 51, Silver Spring, MD 20903 Email: gilbert.burckart@fda.hhs.gov either circumstance, a pharmacokinetic (PK) study in the relevant age group may be conducted to determine dosing in the pediatric population. In 2011 the experience of the FDA in interpreting the use of extrapolation of efficacy in pediatric drug development programs was reviewed.<sup>2</sup> Extrapolation of efficacy from adult data occurred for 82.5% of the drug products (137 of 166). Extrapolation was defined as full for 14.5% of the products (24 of 166) and partial for 68% (113 of 166). When extrapolation was used, a larger percentage (61%) of the drug products (84 of 137) obtained a new pediatric indication or extension into a new age group, but this number decreased to 34% (10 of 29) when there was no extrapolation.

A key component for both partial and full extrapolation is selecting dosing regimens that achieve pediatric exposures "similar" to those in adults.<sup>1</sup> A dosing regimen must be identified that results in an exposure range or distribution comparable to what has been observed in the reference population, most often adults. However, currently guidance is lacking about the best methods for matching adult systemic exposures in pediatric studies. The objective of this study was to examine prior approaches to exposure matching and exposure agreement for adult and pediatric patients as the basis for pediatric dose selection for trials submitted to the FDA under BPCA from 1998 to 2012 and PREA from 2007 to 2012.

## Methods

#### **Clinical Trials Selection**

Pediatric trials that used full extrapolation of efficacy or partial extrapolation of efficacy with confirmation of response were included in our reviews. Pediatric trials submitted to the Agency in response to written requests (WR) issued by the FDA under the Pediatric Exclusivity Provision between February 1998 and August 31, 2012 and in response to PREA between September 27, 2007 and August 31, 2012 were included. Locally acting products (eg, nasal sprays, ophthalmic drops) were excluded from our review because PK for locally acting drugs is more often related to safety and less correlated with efficacy. Clinical pharmacology reviews were retrieved for each product from the FDA public database either containing medical, statistical, and clinical pharmacology reviews of pediatric trials submitted to FDA (http://www.fda. gov/scienceresearch/specialtopics/pediatrictherapeutics research/default.htm) or containing reviews for FDAapproved drug products (http://www.accessdata.fda. gov/Scripts/cder/drugsatfda/index.cfm). Products for which mean values of PK parameters and a measure of variability in the relevant pediatric age group and the reference adult population were reported in the clinical pharmacology review were included. Products lacking these data were excluded from this review.

For the purpose of this study the pediatric population was defined as the collective pediatric age group from birth to 16 years of age [21 CFR201.57 (f) (9)]. Subgroups of pediatric patients based on age may be identified in pediatric study planning based on expected differences in PK or drug response.

#### Data Extraction

Available data on the design and conduct of the PK study including criteria for exposure matching, key exposure metric(s), justification for the target systemic exposure, and/or post-hoc acceptance criteria for a no clinically meaningful effect boundary were obtained from the FDA clinical pharmacology review for each product. Reported systemic exposure data (eg, Cmax, AUC) of the parent drug when applicable in the relevant pediatric and adult populations were extracted. Other data pertinent to the therapeutic class of the product, indication, age group and doses studied, and discussion of the PK results were captured. Development of dosing recommendations, including the FDA reviewer's assessment of exposure-response data and whether dosage adjustment is warranted in pediatric patients, was included when available.

#### Analysis

Mean and variance exposure measures from each study were extracted for both the pediatric and referenced adult populations to derive the relative mean exposure ratios and associated 90% confidence intervals (CIs). The 90%CIs for exposure ratios were constructed using the Fieller method (PROC TTEST in SAS 9.3, SAS Institute, Cary, North Carolina). Studies with variability reported as standard deviation (SD) or percentage coefficient of variation (%CV) were included in the analysis. For a larger proportion of studies included in this analysis, the arithmetic means rather than the geometric means were reported. Because patient-level data were not available, and the summary statistics provided were mixed (most were arithmetic means), it was not possible to perform a detailed analysis, and this has restricted our choice of methods. Consequently the statistical analysis results, specifically the 90%CIs presented in this article, are exploratory in nature and should be interpreted as such. The Spearman rank correlation coefficient was used to quantify the linear association between observed C<sub>max</sub> ratios and AUC ratios. The Bland-Altman plot was also used to graphically view the agreement between the 2 measures.

In order to evaluate concurrence between the FDA clinical pharmacology reviews and the study reports, electronically available study reports for products



Figure 1. Distribution of products reviewed (1998-2012).

reviewed by the Agency between 2008 and 2012 were reviewed. Available data on the design and conduct of the PK study were retrieved and compared to data available in the clinical pharmacology reviews.

#### Results

Data from 31 products (86 trials) with full or partial extrapolation of efficacy with an available PK assessment were included in the analysis (see Figure 1). Of 31 products, 12 (38.7%) relied completely on extrapolation of efficacy for labeling in 1 or more pediatric age groups, and 19 (61.3%) relied on partial extrapolation of efficacy with confirmation of response and assessment of safety. In both forms of extrapolation, the pediatric dose was selected to match the adult systemic exposures. In the partial extrapolation studies, efficacy in pediatric patients was used as evidence to support the efficacy observed in adults. In all cases safety was assessed in the target pediatric population.

The majority of the products were antivirals (54.8%), antihistamines (12.5%), histamine H2-receptor blockers (6.25%), and anti-infectives (6.25%). The rest of the products were analgesics, sedatives, proton pump inhibitors, and drugs in other drug classes. Of the 31 products, 25 (78.1%) were studied in more than 1 pediatric age group. Thus, 6 products had clinical pharmacology reviews that included studies in only 1 age group for emtricitabine, famotidine, fentanyl transdermal system, midazolam, peg-interferon alfa-2b (alone), and ranitidine. A list of the products and the age groups studied is provided in Supplemental Table S1.

Of the 86 trials, 69 (80.3%) used an intensive sampling strategy and performed a noncompartmental analysis (NCA), 8 (9.3%) used a sparse sampling design and conducted population PK analysis (Pop PK), and 9 (10.4%) used both NCA and Pop PK analyses. Assessment of similarity between pediatric and adult systemic exposures in the clinical pharmacology review was



Figure 2. Ratios (pediatric/adult) for products approved at the studied dose. The solid line corresponds to a ratio of 1. The 90% confidence intervals are based on the Fieller method.

based on a cross-study comparison. Adult data were obtained from separate studies using either healthy volunteers or subjects with the condition/disease. Seven of the 86 trials (8.1%) had a predefined acceptance boundary used to match adult exposures. The boundary either included specific target values or an acceptable percentage of the adult exposure (ie, 80% to 125% of the comparator value). For the remaining trials, the clinical pharmacology review did not explicitly outline the acceptable boundaries for exposure similarity. The key exposure metric was consistently predefined for antiviral and anti-infective products.

Of the 86 trials, 20 (23.3%) did not result in an indication in all or part of the population included in the trial. Of these, 13 had insufficient evaluation of efficacy, or qualitative efficacy was not demonstrated in the pediatric study. For the remaining 7 trials, an indication was not granted because dosing could not be established in part or all of the population included in the study or an insufficient number of subjects were included in the studied pediatric population, the dose studied was the dose approved for 48 (72%) of the trials. The majority of the dose modifications resulted from the FDA clinical pharmacology reviewer's assessment that the pediatric exposures did not match the adult

reference exposures. In a few cases the modifications were to provide a fixed dose recommendation for the specific weight bands that would match the dose studied in the trial. Regardless of the rationale for dose modification, modeling and simulation were used post hoc to derive a potentially unstudied pediatric dosing strategy that met exposure-matching criteria using available adult and pediatric data. A list of approved doses for the indications studied is provided in Supplemental Table S1.

Pediatric exposures for approved doses were generally higher than those for adults in most studies in this data set (Figures 2–4). The range of the mean  $C_{max}$ ratios (pediatric/adult) were 0.63 to 4.19, and the range of the mean AUC ratios (pediatric/adult) were 0.36 to 3.60. In several cases the review included statements that the observed difference in systemic exposure was unlikely to result in a clinically significant difference in outcome. Typically, language stating that the proposed dose was found to be appropriate was used in the absence of actual examined exposure criteria.

In the 86 trials there were a total of 90 age groups for which complete information for both  $C_{max}$  and AUC was available. The Bland and Altman plot revealed an agreement between  $C_{max}$  ratios and AUC ratios for these 90 groups. Figure 5 displays a scatter diagram



Figure 3. Forest plot of  $C_{max}$  and AUC ratios (pediatric/adult) for products without a pediatric indication. The solid line corresponds to a ratio of I. The 90% confidence intervals are based on the Fieller method.



Figure 4. Forest plot of  $C_{max}$  and AUC ratios (pediatric/adult) for products approved with a different dose. The solid line corresponds to a ratio of I. The 90% confidence intervals are based on the Fieller method.

of the differences between the AUC and  $C_{max}$  ratios against the averages of the 2 measurements. The 2 red horizontal lines are the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. Because the majority of the observations are within these limits and clustered around zero, there appears to be good agreement between the 2 measures. The Spearman rank correlation coefficient between  $C_{max}$  ratios and AUC ratios was 0.85 (P < .001), implying a strong linear association between the 2 ratios.

In order to evaluate concurrence between the FDA clinical pharmacology review and the study report, electronically available study reports were compared to clinical pharmacology reviews. Of the 10 products included in the analysis with a study report submission date after 2008, 8 had protocols available electronically for review. Of these, 6 (75%) had complete concordance between the clinical pharmacology review and the protocol. For 2 out of 8 (25%) of the products,

the prespecified criteria were discussed in the study protocol but not in the FDA clinical pharmacology reviews.

The case of tipranavir illustrates the many considerations other than simple exposure matching that influence review and approval of pediatric doses. Furthermore, it provides an example where doses that were not directly studied were included in labeling. Pediatric approval of tipranavir was based on the results of an open-label clinical trial of 2 doses of tipranavir  $(290 \text{ mg/m}^2 \text{ and } 375 \text{ mg/m}^2)$  with low-dose ritonavir in HIV-infected children 2 to 18 years of age. Although the low dose (290 mg/m<sup>2</sup>) reasonably matched adult exposure at the approved adult dose of 500 mg, the higher dose  $(375 \text{ mg/m}^2)$  was ultimately approved for pediatric use. This decision was supported by the exposureresponse relationships for efficacy and safety and the desire to maximize benefit in a treatment-experienced population with resistance to more than 1 protease inhibitor. A body weight-based dosing regimen was



**Figure 5.** Bland-Altman plot of  $C_{max}$  pediatric/adult ratios and AUC pediatric/adult ratios. Bland-Altman plot of the data obtained from 90 age groups with  $C_{max}$  pediatric/adult ratios and AUC pediatric/adult ratios. Correlation R = 0.85 (P < .001). The blue line corresponds to the mean difference of the 2 ratios; the lower and upper red lines correspond to the lower and the upper 95% confidence limits for the mean difference.

also included in labeling because it was thought that dosing based on weight would be more convenient than body surface area (BSA) in some healthcare settings. Simulations were used to predict the distribution of minimum concentrations under various body-weight dosing regimens. These predictions were compared to a therapeutic window based on exposure-response relationships. This exercise resulted in the approval of a 14 mg/kg dose that was predicted to provide similar exposures to the 375 mg/m<sup>2</sup> dose. The experience with tipranavir demonstrates the importance of collecting quality PK data to enable exposure-response modeling and dosing simulations and highlights the regulatory flexibility that enables the consideration of factors beyond exposure matching.

Another example that illustrates the challenges with matching adult systemic exposures in infants and neonates is the case of nelfinavir. Four studies were conducted to evaluate twice-daily (BID) and threetimes-daily (TID) dosing of nelfinavir in pediatric patients, including infants less than 2 years of age. Results from all pediatric studies were characterized by high interindividual PK variability as was observed in the adult population. However, variability was highest in infants and neonates. In addition, none of the doses studied in this younger age group reliably achieved the target nelfinavir exposure associated with efficacy in adult studies (arithmetic mean AUC of 44 and 53  $\mu$ g · h/mL in 2 studies). An additional PK study in patients less than 2 years of age was not requested by the Agency because it would be unlikely that the additional data would allow selection of a dose for this age group. This assessment resulted in the lack of approval and dosing recommendation for nelfinavir use in pediatric patients less than 2 years of age.

#### Discussion

The use of extrapolation allows for a reduced number and complexity of studies to provide data sufficient for pediatric labeling.<sup>1,2</sup> As a result, extrapolation has been used increasingly in pediatric drug development over the last decade.<sup>3–8</sup> Moreover, the use of extrapolation has resulted in a higher proportion of products obtaining new FDA labeling for pediatric use compared to products for which extrapolation was not used.<sup>2</sup> This study reviewed the FDA's experience with adult exposure matching as the basis for pediatric dose selection in pediatric clinical trials submitted to the Agency under BPCA and PREA.

In a prior review of the FDA's experience with pediatric extrapolation,<sup>2</sup> the level of evidence in support of extrapolation and the type of studies used for pediatric labeling in 370 pediatric studies (166 products) conducted under the Pediatric Exclusivity Provision was assessed. Some form of extrapolation of efficacy from adult data was cited for the majority of the drug products (82.5%), with partial extrapolation used for 68% of the products, and full extrapolation used for 14.5% of the products. For full extrapolation where there are sufficient data about the similarity of disease and response to the intervention, the evidence required to label the product for use in the pediatric population was PK and safety data or safety data in the relevant age group. For partial extrapolation, where there is some uncertainty about the similarity of disease and/or response to intervention, the evidence required for labeling was a "confirmation of efficacy" in addition to PK and safety data. For partial extrapolation, this confirmation of efficacy was either through a single, controlled or uncontrolled efficacy and safety trial, or

| FDA Guidance  | Proposed Approach I   | Proposed Approach 2   |
|---|---|---|
| Pharmacokinetics in patients with impaired renal function (Draft, 2010) <sup>18</sup>   | Mathematical modeling of the relationship<br>between measures of renal function and<br>PK parameters  | Provide analysis of study data to show relevant PK measurements are similar   |
| Bioavailability and bioequivalence studies<br>submitted in NDAs or INDs—General<br>Considerations (Draft, 2014) <sup>9</sup>    | Standard 90%Cl of 80% to 125% for AUC<br>and C <sub>max</sub>   |   |
| Drug Interactions Guidance (Draft, 2012) <sup>17</sup>  | Specific no-effect boundaries or clinical<br>equivalence intervals; no-effect<br>boundaries represent the interval within<br>which a change in systemic exposure is<br>considered not clinically meaningful | A no-effect boundary of 90%Cl of 80% to 125% for AUC and $C_{max}$  |
| Pharmacokinetics in patients with impaired hepatic function (Draft, 2003) <sup>19</sup>   | Delineation of a no-effect boundary based<br>on dose- and/or concentration-response<br>studies  | Employment of a standard 90%CI of 80% to 125% for AUC and C <sub>max</sub>  |
| Clinical pharmacology data to support a<br>demonstration of biosimilarity to a<br>reference product (Draft, 2014) <sup>20</sup> | Starting point for an acceptable limit for<br>the confidence interval of the ratio,<br>which may be 80% to 125%   | Selection of the confidence interval and acceptance<br>limits may vary among products; alternatively, a<br>similarity study with low, intermediate, and highest<br>approved dose where a clear dose-response is<br>observed; EC50, $E_{max}$ , and slope of the<br>concentration-effect relationship should be<br>evaluated for similarity. |

 Table I. FDA Guidance Discussing Approaches for Matching Systemic Exposures

a single exposure-response trial, in addition to PK and safety data.

PK differences between adults and some pediatric age groups are expected to occur because postnatal growth and development can affect drug disposition and action.<sup>9–12</sup> Examples include developmental changes in metabolism including the maturation rate of phase I and II enzyme activities, body composition such as water and lipid partitioning, receptor expression and function, growth rate, and organ functional capacity.<sup>13–16</sup> PK studies are therefore essential to permit an assessment of the degree of impact of age-related differences.

The comparison of PK parameters between 2 populations or 2 products is discussed in several FDA Guidances for Industry: Drug Interactions (2012),<sup>17</sup> Pharmacokinetics in Patients with Impaired Renal Function (2010),<sup>18</sup> Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (2003),<sup>9</sup> Pharmacokinetics in Patients with Impaired Hepatic Function (2003),<sup>19</sup> and Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.<sup>20</sup> An evaluation of confidence intervals for the mean difference in key exposure metrics such AUC and C<sub>max</sub> is a proposed approach in 4 out of the 5 guidance documents, with all 4 proposing a 90%CI of 80% to 125% for  $C_{max}$  and AUC (Table 1) as an acceptable approach. This boundary of 80% to 125%<sup>9</sup> may not be meaningful for many drugs, and an acceptable boundary that better reflects the context of the therapeutic range of the drug and the riskbenefit of the product for a given pediatric indication would be more desirable. A delineation of a no-effect boundary based on dose or concentration-response studies is proposed as an alternative method in the drug interaction and hepatic impairment guidances. Finally, the renal impairment guidance recommends mathematical modeling of the relationship between measures of renal function and the PK parameters of interest to provide a rational quantitative basis for dosage adjustment.

Exposure matching was an important part of pediatric extrapolation for both full and partial extrapolation. For these studies, information regarding study design and methods for assessing similarity of systemic exposures was highly variable. Given this heterogeneity, mean exposure measures from each study were extracted for both the pediatric and referenced adult population to derive the relative exposure ratios and associated 90%CIs. Variability was not consistently reported or derivable from the available data.

The magnitude of systemic exposure similarity/ dissimilarity varied within the same drug class and between different age groups for the same product. No specific trend was noted by therapeutic area or indication for systemic exposures on the extreme ends of the pediatric/adult exposure ratio spectrum. Adult data were obtained from separate studies, either in healthy volunteers or in patients with the condition/disease. Insufficient information was available to evaluate whether the adult and pediatric study conditions (eg, sampling scheme, inclusion/exclusion criteria, assays) were similar. Weight-based dosing was used in 44.8% of the reviewed trials, and BSA-based and fixed dosing strategies were used in 24.1% and 31.1% of the trials, respectively.

As stated earlier, the 90%CIs for the exposure ratios were constructed using the Fieller method. This method relies on the assumption of normality. However, because of the small sample sizes, the normality assumptions may not be valid. Additionally, for the majority of cases, the arithmetic mean ratios were used. Therefore, the 90%CIs should be interpreted with caution.

The current study has some limitations. Our review was limited to information reported in FDA clinical pharmacology review documents, which are publicly available. Information that may influence the conclusion of this review may have been available at the study protocol or study report level. However, based on our review of a subset of the trials, there was complete concordance between the clinical pharmacology review and the protocol for the majority (75%) of the trials. Another possible limitation is that our review focused on 31 products, and thus, the results of this study may not reflect approaches used in all therapeutic areas.

Antiviral agents and anti-infective agents comprised over 60% of the products in this evaluation. These classes of agents had consistently predefined the exposure-matching criteria. Even so, a separate evaluation of exposure matching by Zimmerman et al (manuscript in preparation) also found that precise matching of exposures in pediatric patients was generally not achieved in drug development studies.

Considering the frequency of use of exposure matching in pediatric studies, (1) an assessment of when the use of exposure matching is appropriate and (2) establishment of a consistent approach to assess similarity between the reference population (usually adult) and the pediatric population are warranted.<sup>2,16</sup> Consideration should be given to the design and conduct of the pediatric study as well as the data analysis, presentation, and evaluation of results of exposure-matching studies.

No official criteria have been established for selecting the appropriate metric and acceptance boundary for exposure matching, and additional work will likely need to be done to clarify this approach. As stated above, a single acceptance boundary across drug products and drug classes will not provide a meaningful approach in this setting. Instead, when possible, the target exposure metric, range, and acceptance criteria should be specified a priori and should be defined in the context of the disease, treatment duration, route of administration, and formulation in addition to other considerations. The assessment of exposure similarity can be an empirical comparison, similar to a bioequivalence type of approach discussed above, where similarity is assessed based on comparison of observed adult and pediatric exposure data alone from a prospectively designed pharmacokinetic trial. An acceptance criterion is used to assess similarity based on the preset criteria. The limitations of this approach include the lack of ability to adjust for interstudy variability or to derive a new dosing regimen if the initial criterion is not met. To overcome some of these challenges, a model-based approach can be used to integrate existing adult and pediatric PK data.

An alternative approach is a model-based approach in which, using simulation, the model can explore a variety of pediatric dosing strategies to achieve a target exposure range, including those not directly studied in a PK trial. This approach provides flexibility and accounts for interstudy variability. Comparing means alone without consideration of population variability provides limited value in establishing exposure similarity. Instead, a simulation of the percentage of subjects at different age/weight bins that lie within a predefined exposure range may provide a more meaningful assessment when appropriate. However, there are assumptions that are carried forward with model-based approaches, and this approach requires confirmatory pediatric clinical studies unless there are sufficient clinical data to support the modeled dose(s).

Regardless of the approach, simulations can be used in the setting of exposure matching for extrapolation of efficacy to guide the design of pediatric trials including the sample size and sample scheme. Simulations should take into consideration that matching all exposure metrics may not often be feasible. Finally, regulatory flexibility has allowed the use of modeling and simulation post hoc to derive a potentially unstudied pediatric dosing strategy that meets exposure-matching criteria using available PK and safety data.

Our retrospective analysis of historical trials in which pediatric drug exposures have been compared to adult reference populations suggests that past performance was variable. The practice of an NCA-based BE analysis using an adult reference population to anchor comparisons should probably evolve to accommodate more model-based approaches that reflect developmental influences on PK/PD. The target concentration(s) needed in pediatrics can be assessed a priori, and simulations can be conducted to assess the percentage of patients who would be within the target range. Data from a prospective pediatric clinical study can then be used to confirm simulation predictions. Adaptive study designs may provide utility in establishing dosing in pediatric patients, especially in infants and neonates, where PK predictions may be less reliable and large interpatient variability is expected.

In summary, a review of 86 trials from 31 pediatric drug development programs completed and reviewed by the Agency between 1998 and 2012 demonstrated that various approaches to matching adult and pediatric exposures were used. For some drug classes (antivirals and anti-infectives), the key exposure metric for exposure matching was consistently predefined. Pediatric exposure ranges were 0.63 to 4.19 and 0.36 to 3.60 for  $C_{max}$  ratios and AUC ratios, respectively.

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#### Disclaimer

The opinions expressed are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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## **Conflict of Interest Disclosures**

The authors have no conflicts of interest to disclose.

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