

Role of Model-Informed Drug Development in Pediatric Drug Development, Regulatory Evaluation, and Labeling

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Abstract

The unique challenges in pediatric drug development require efficient and innovative tools. Model-informed drug development (MIDD) offers many powerful tools that have been frequently applied in pediatric drug development. MIDD refers to the application of quantitative models to integrate and leverage existing knowledge to bridge knowledge gaps and facilitate development and decision-making processes. This article discusses the current practices and visions of applying MIDD in pediatric drug development, regulatory evaluation, and labeling, with detailed examples. The application of MIDD in pediatric drug development can be broadly classified into 3 categories: leveraging knowledge for bridging the gap, dose selection and optimization, and informing clinical trial design. In particular, MIDD can provide evidence for the assumption of exposure-response similarity in bridging existing knowledge from reference to target population, support the dose selection and optimization based on the “exposure-matching” principle in the pediatric population, and increase the efficiency and success rate of pediatric trials. In addition, the role of physiologically based pharmacokinetics in drug-drug interaction in children and adolescents and in utilizing ontogeny data to predict pharmacokinetics in neonates and infants has also been illustrated. Moving forward, MIDD should be incorporated into all pediatric drug development programs at every stage to inform clinical trial design and dose selection, with both its strengths and limitations clearly laid out. The accumulated experience and knowledge of MIDD has and will continue to drive regulatory policy development and refinement, which will ultimately improve the consistency and efficiency of pediatric drug development.

Keywords

dose selection and optimization, informing clinical trial design, leveraging knowledge, model-informed drug development, pediatric drug development, pediatric ontogeny

Despite tremendous efforts and numerous regulatory initiatives in advancing pediatric drug development, such as the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act,^{1,2} off-label medicine use is still at an unsatisfactory level of 40% in pediatric populations and up to 90% in neonates.³ On average, it takes 9 years from the time of a product’s approval for use in adults until the incorporation of pediatric information in the label.⁴ There are unique challenges in pediatric trials: enrollment difficulties, small number of patients, variability in physiological characteristics, uncertainties in dose selection, and ethical complexities.⁵ These unique challenges require innovative and efficient tools to bridge knowledge gaps and facilitate the development process. MIDD is one such tool that can help avoid unnecessary pediatric studies and enroll the smallest number of pediatric patients possible to generate appropriate data.⁶

Model-informed drug development (MIDD) refers to the application of quantitative models in facilitating drug development and informing decision making.⁷

The experience with the use of MIDD in facilitating drug discovery, development, and regulatory evaluation has been well documented.^{7–13} MIDD has been applied across drug discovery and development to increase confidence in candidate selection and mechanistic understanding, optimize trial design and dose selection, inform internal “go/no-go decisions” and regulatory policy, and provide supportive evidence for efficacy and benefit-risk assessment.^{7,11} One of the significant performance goals and procedures listed in the Prescription Drug User Fee Act reauthorization fiscal years 2018 through 2022 is to advance MIDD.¹⁴ This article discusses the current practices and visions of

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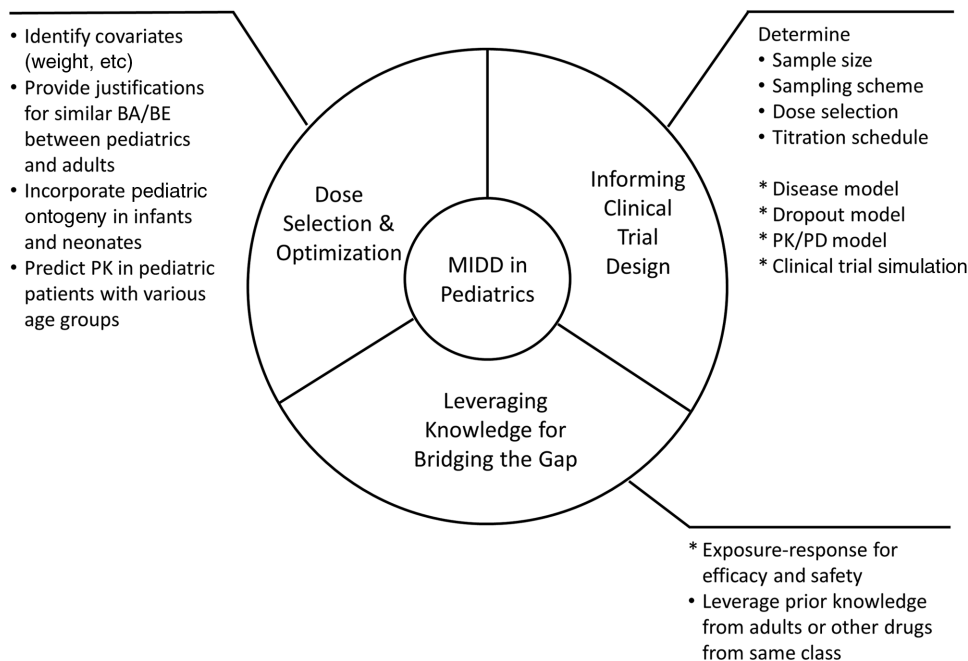


Figure 1. Application of model-informed drug development in pediatric drug development. This figure illustrates the 3 main areas of MIDD application in pediatric drug development. The bullets discuss the typical types (*) or common uses (•) of MIDD in each area. BA, bioavailability; BE, bioequivalence; MIDD, model-informed drug development; PD, pharmacodynamic; PK, pharmacokinetic.

applying MIDD in pediatric drug development, regulatory evaluation, and labeling.

Applications

The MIDD applications in pediatric drug development can be broadly classified into 3 categories: leveraging knowledge for bridging the gap, dose selection and optimization, and informing clinical trial design (Figure 1).

Leveraging Knowledge for Bridging the Gap

According to US Food and Drug Administration (FDA) and International Conference on Harmonization guidance,^{6,15} effectiveness in pediatric patients may be extrapolated from adequate and well-controlled studies in adults where the course of disease and the effects of the drug are sufficiently similar in pediatric and adult populations. MIDD approaches can be helpful in justifying the assumption of similar response to treatment.⁶ Safety information for pediatric drug development and approval may also be leveraged using MIDD approaches based on existing knowledge from reference (adult and other pediatric) populations.^{6,16}

One example of using MIDD to leverage existing knowledge is related to pediatric efficacy extrapolation for antiepilepsy drug approvals. Collaborative efforts among the FDA, academia, and industry have led the FDA to conclude that the efficacy of drugs approved

for the treatment of partial-onset seizures can be extrapolated from adults to pediatric patients aged 4 years and older.¹⁷ This policy was based on the evidence of similar pathophysiology of partial-onset seizures and similar response to several drugs from registration trials in adults and pediatric patients aged 4 years and older. To support the assumption of exposure-response (ER) similarity between adult and pediatric patients, the FDA in collaboration with University of Maryland conducted quantitative ER analyses for standardized seizure frequency data in 7 antiepileptic drugs approved in both adult and pediatric patients. Graphical display of observed concentration response data showed a similar ER relationship between adult and pediatric patients for a given drug. Model-based analyses also showed that the difference in the slope of ER was not statistically significant between adult and pediatric patients.^{18,19} The systematic and quantitative assessment of ER relationships for 7 approved antiepileptic drugs provided evidence for the assumption of ER similarity, which supported the development of a “full extrapolation” policy in pediatric patients aged 4 years and older. Following establishment of the policy for a drug with an approved indication for the treatment of partial-onset seizures in adults, the only required data to apply for an indication for treatment of partial-onset seizures in pediatric patients aged 4 years and older is the pharmacokinetic (PK) data of the active drug/metabolite and the long-term safety data in pediatric patients aged 4 years and older.¹⁷

In the case of adalimumab to treat adolescent patients aged 12 years and older with hidradenitis suppurativa (HS), no efficacy or safety data of adalimumab were available in adolescent HS patients, as a clinical trial in adolescent patients is not feasible for a rare disease like HS. The efficacy of adalimumab in adolescent HS patients is supported by evidence from adequate and well-controlled studies of adalimumab in adult HS patients. Modeling and simulation predicting the recommended dosage in adolescent HS patients can provide generally similar exposure and benefit/risk profiles to adult HS patients. No trial safety data are available for adalimumab use in adolescent HS patients. However, adalimumab has a well-established, long-term safety profile in various diseases in pediatric populations such as pediatric plaque psoriasis, Crohn disease, and juvenile idiopathic arthritis. No apparent relationship was identified between adalimumab exposure and adverse events in these pediatric patients. The consistent, well-characterized exposure-safety relationship across several pediatric indications provided supportive evidence that no additional safety concern should be expected in adolescent HS patients.

Dose Selection and Optimization

Model-based analyses, such as population PK (popPK) models and physiologically based pharmacokinetic (PBPK) models, are commonly used to derive pediatric dosing regimens that can match the safe and effective exposure achieved in the adult patients. The assumption with such an “exposure-matching” strategy is that ER relationships for both efficacy and safety are similar between pediatric and adult patients. There are various cases in which model-based analyses, along with ER relationships for efficacy and safety were the pivotal evidence to support the approval of untested doses in the pediatric population.

In the above-mentioned case of adalimumab in treating adolescent HS, an unstudied weight-tiered dosing regimen with a cutoff weight of 60 kg was approved in adolescent HS patients. The exposure of adalimumab in adolescent HS patients achieved by different dosing regimens was predicted based on the simulation results from a robust popPK model. The model prediction was considered reliable even without PK data for adalimumab in adolescent HS patients because extensive PK data are available for adult HS patients and pediatric patients with other diseases. Simulation results suggested that the recommended weight-tiered dosing regimens would achieve similar exposure in adolescent HS patients to adult HS patients across all weight ranges. It also suggested the predicted adalimumab exposure in adolescent HS patients is within the range of observed adalimumab concentrations in pediatric

Crohn disease patients. These simulation results, along with a positive exposure-efficacy relationship in adult HS patients, provided pivotal evidence to support the approval of an untested weight-tiered dosing regimen in adolescent HS patients without the need for collecting additional efficacy and safety data. Other notable examples include approval of an untested dosing regimen of esomeprazole in pediatrics for the treatment of gastroesophageal reflux disease with erosive esophagitis,²⁰ and approval of canakinumab in children younger than 2 years of age with the 3 conditions of periodic fever syndromes.²¹

MIDD also plays a critical role in deriving pediatric dosing regimens for products developed under the Animal Rule, as it is often not feasible nor ethical to conduct a clinical trial in pediatric subjects. The approval of tecovirimat for treatment of human smallpox disease in pediatric patients weighing at least 13 kg is one such example.²² The recommended dosing regimen, 600 mg twice daily under fed conditions, was considered acceptable, as it provides higher exposure in humans compared to those associated with the fully effective dose in nonhuman primates. Due to ethical concerns, a PK study cannot be conducted in healthy children; thus, a weight-tiered pediatric dosing regimen has been proposed solely based on the popPK simulation results after weighing the balance between the risk and benefit. Another example of deriving pediatric doses for products developed under the Animal Rule includes approval of raxibacumab for treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.²³

In infants and neonates, mechanism-based models incorporating pediatric ontogeny can potentially accurately predict the drug PK compared to allometry when there is a sufficient understanding of the ADME (absorption, distribution, metabolism, and excretion) process of the drug and ontogeny is well characterized for those processes. The dose selection of gadolinium-based contrast agents in infants and neonates is a good example to illustrate how a mechanism-based model was applied in predicting PK in neonates and aiding drug development. For products like gadolinium-based contrast agents, which are cleared almost completely (>95%) by renal elimination, clearance in infants and neonates can be described by the maturation of renal function established previously by Anderson and Holford.²⁴ Two products, Dotarem (Guerbet, Villepinte, France) and MultiHance (Bracco, Princeton, New Jersey), added pediatric patients aged 0 to 2 years to their labeled indication in 2017. The efficacy data for both products and safety data for MultiHance provided favorable benefit/risk profiles in pediatric patients aged 0 to 2 years. The mechanism-based model incorporating renal maturation supported the approval

of a 0.1 mmol/kg dose in pediatric patients aged 0 to 2 years for both products. For Dotarem, use of this mechanism-based model led to a better fit of PK data in infants than the empirical statistical model including the covariate effect of creatinine clearance.²⁵ For MultiHance, the mechanism-based model provided supportive evidence to select the dose in infants and neonates with PK data only for patients aged 2 years and older.²⁶

MIDD also contributed to the general dose selection in adolescent oncology patients. In March 2019, a draft FDA guidance was issued to call for including adolescents in disease or target-appropriate adult oncology clinical trials at all stages of development.¹⁶ In the draft guidance, it is recommended if the cancer is shown to be similar in histology and biologic behavior between adolescent and adult patients, adolescent patients should receive the same body size–adjusted dose as adults. For drugs administered as a fixed dose, where body size is shown to have no clinically meaningful effect on drug exposure and response, adolescent patients who weigh at least 40 kg can receive the same fixed dose administered in adults. A greater understanding of the effect of body size on drug exposure and the accumulated experience with dosing recommendation for oncology products in adolescent and adult patients have enabled the general dose recommendation for adolescent patients in oncology. MIDD contributed to the development this policy: PopPK modeling allows for the estimation of effect of weight on drug clearance when sparse samples are collected in the clinical trials; ER modeling can be applied to evaluate the effect of weight on efficacy and safety. These quantitative models contributed to the general dose selection in adolescent patients as well as the criteria to select the cutoff value on a case-by-case basis.

Informing Clinical Trial Design

Another area of applying MIDD in driving efficient medical product development is informing clinical trial design in pediatric patients. The drug developer is encouraged to apply clinical trial simulation and quantitative modeling of all prior knowledge (eg, disease, drug, placebo effect, PK/pharmacodynamic relationship) to make more informed drug development decisions on trial designs.²⁷

In one case, a placebo-controlled adaptive design (seamless phase 2/3 design) evaluating multiple doses was recommended by the FDA to test the intravenous (IV) formulation of drug A (masked to protect proprietary information) in pediatric patients. Exposure matching based on modeling and simulation supported the 3-dose-arm design and provided the rationale for dose selection, which consists of a low dose, a dose

matching exposure of the therapeutic adult dose and a high dose. Although this drug is approved as an oral formulation in adults and the trial is evaluating only IV dosing, the data may be sufficient to label the untested oral formulation in pediatric patients if sufficient ER data are available for adult and pediatric patients to bridge the oral and IV formulation. In this example, the adaptive trial design supported by the MIDD can potentially be more efficient for both the oral and IV development in pediatrics and may offer better dose selection.

In another case, ER, placebo, and dropout models were incorporated in a clinical trial simulation to inform the study design of guanfacine extended release in adolescent patients (13–17 years old) with attention deficit hyperactivity disorder.¹⁹ Quantitative analyses suggest a strong effect of body weight on drug exposure and a larger placebo effect for adolescent patients than pediatric patients younger than 12 years old. The flexible titration schedule to allow dose optimization and body weight–based dosing regimen were implemented in the trial, as simulation suggested these components would increase the success rate. Consistent with the model prediction, adolescent patients receiving a body weight–adjusted dose of guanfacine in this trial showed statistically significantly greater improvement on the ADHD Rating Scale-IV total score compared with patients receiving placebo.²⁸

Another use of MIDD in pediatric trial design is optimization of the sampling strategy to minimize blood sampling in pediatric patients. A common regulatory recommendation is that the pediatric PK study must be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution in each subgroup with at least 80% power.²⁹ When popPK is planned as the analysis method, both sample size and sampling schedule need to be considered to calculate the sample size. Clinical trial simulation can help design the optimal sampling schedule to minimize the blood samples while ensuring robust estimates of the PK parameters.

Mechanistic Models

Mechanistic models have the potential to support drug target authorization, explore potential mechanisms, and make predictions beyond the observed exposure range. PBPK, one of the most common mechanistic models, has been increasingly applied in pediatric drug development.

Approximately 60% of the intended uses of PBPK in regulatory decision making are related to drug–drug interaction. The PBPK predictions for the drug–drug interaction in children and adolescents, such as

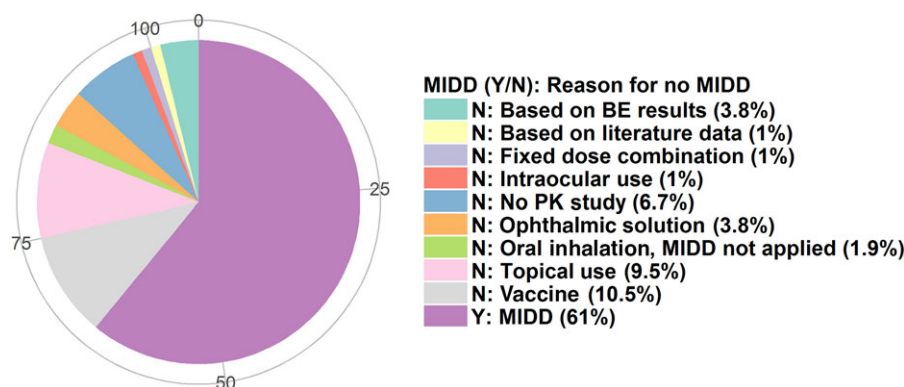


Figure 2. Application of MIDD in approval of 105 pediatric indications by US Food and Drug Administration between January 2017 and June 2019. BE, bioequivalence; MIDD, model-informed drug development; PK, pharmacokinetic.

the interaction with concomitant administration of CYP3A modulators, have been accepted as supportive evidence for the proposed dosing recommendations on the deflazacort label.³⁰

Pediatric PBPK modeling is the second-highest area (15%) of PBPK application in the regulatory submission.³¹ It is mainly used to propose initial dosing recommendations for clinical trials in the investigational new drug stage. Pediatric PBPK modeling is a powerful tool in utilizing ontogeny data to predict drug PK in neonates and infants where ontogeny is an important determinant of a drug's ADME process. One recent publication illustrates that for drugs that are excreted mainly through the renal pathway, such as tazobactam and oseltamivir, a pediatric PBPK model incorporating transporter ontogeny can better predict the exposure over allometry in pediatric patients younger than 2 years old.³²

PBPK can also be applied to investigate the potential mechanism that may cause different absorption behavior in pediatric subjects compared to adult subjects. The relative bioavailability between 2 formulations has been shown to be different in pediatric and adult subjects in a few cases: In the case of lamivudine, the relative bioavailability of lamivudine oral solution is approximately 40% lower than the tablet formulation in pediatric subjects, despite no difference between the 2 formulations in adults³³; in the case of dasatinib, the relative bioavailability of powder for oral suspension (PFOS) compared to tablets is lower in pediatric subjects (64.4%) than in adults (81.8%).³⁴ A PBPK model was developed to investigate the mechanism of the reduced bioavailability for PFOS relative to tablets.³⁵ Results suggested that dasatinib oral absorption and PK can be sensitive to changes in gastric pH and gastric transit time differences. The reduced bioavailability in PFOS compared with tablets may be inherent to the in vivo gastric behavior of the 2 different dosage forms such as shorter gastric transit for suspensions. The

even lower bioavailability of PFOS relative to tablets in pediatric subjects compared to adult subjects could be due to the shorter gastric transit time in children. The use of a PBPK model in this case generates and supports the hypothesis of the mechanism of different bioavailability results between pediatric and adult subjects.

Discussion

The unique challenges in pediatric drug development and high percentage of off-label use in pediatric patients call for innovative and efficient tools to streamline and optimize pediatric drug development. MIDD is a powerful tool to integrate and leverage existing knowledge to facilitate the decision-making process, and it has already been applied frequently in pediatric drug development. Among 105 new pediatric indications approved by the FDA between January 2017 and June 2019, MIDD contributed in 64 instances (61%). Among these 64 new pediatric indications, popPK modeling was applied in all of them, and ER modeling was performed in 37 (57.8%) instances. The main reason for lack of MIDD in the remaining 41 pediatric indications is either no available PK data or local administration (33 of 41). Another 5 applications lacking an MIDD component are 505(b) applications based on bioequivalence results or literature data (Figure 2).

This article illustrates the 3 main areas of MIDD applications in pediatric drug development: leveraging knowledge for bridging the gap, dose selection and optimization, and informing clinical trial design (Figure 1). A suggested “Integrate-Simulate-Optimize” workflow of applying MIDD in these 3 main areas is presented in Figure 3. The understanding of the pathophysiology or the expression of the disease is the main driver for leveraging existing knowledge, as well as extrapolation of information from other populations (adults or other pediatric populations). MIDD approaches have proven

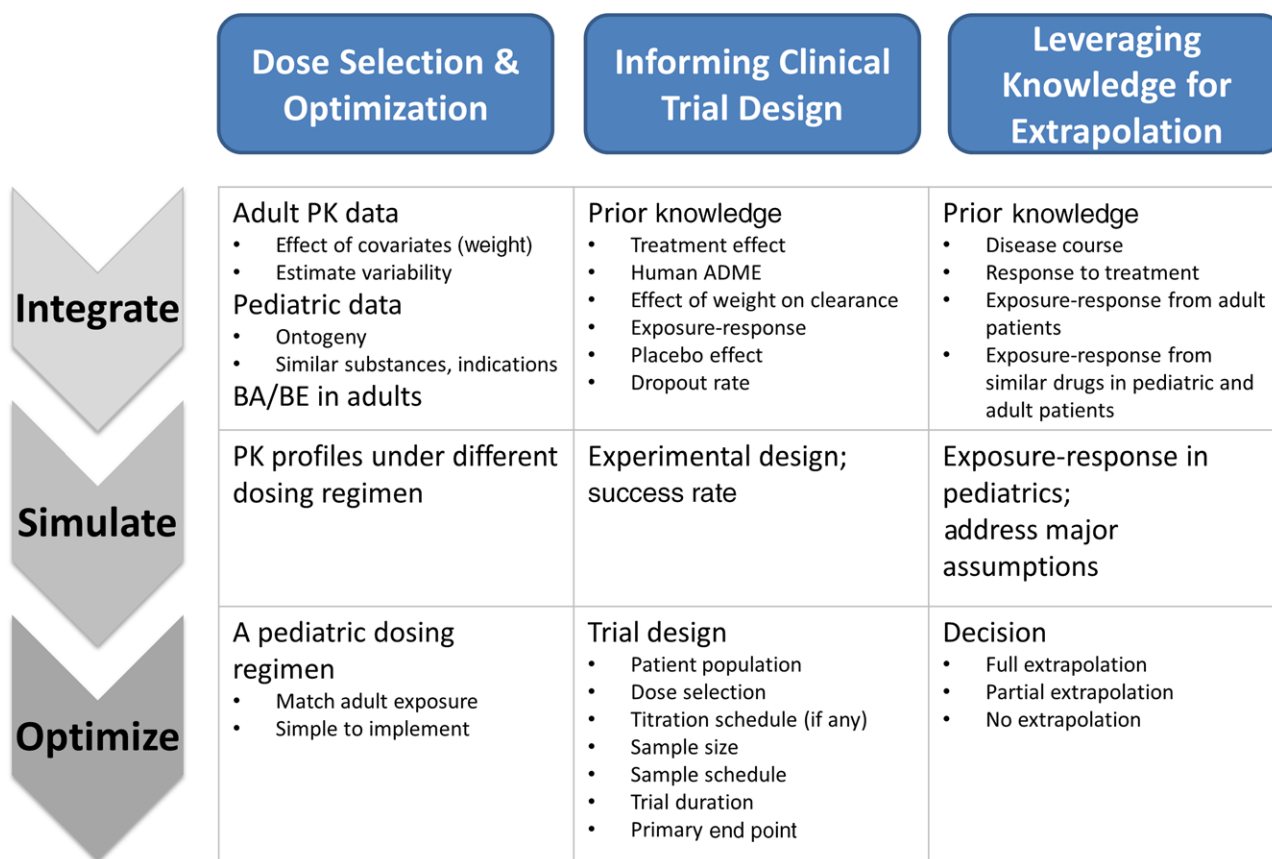


Figure 3. Suggested workflow of applying MIDD in pediatric drug development. The figure illustrates the suggested workflow for drug developers to consider when applying MIDD methods in pediatric drug development. The bullets cover some common considerations at each “Integrate-Simulate-Optimize” procedure. BA, bioavailability; BE, bioequivalence; PK, pharmacokinetic.

useful in quantifying available information regarding the compound, the patients, and the trials, defining the degree of the similarity in ER relationship between adult and pediatric patients, which can provide supportive evidence for extrapolation.

Understanding the effect of growth and organ development on PK/pharmacodynamic variability is critical to the pediatric dose selection. Allometric scaling is the most commonly used method to relate drug clearance and exposure to body weight.³⁶ Generally appropriate doses can be derived in adolescent patients based on modeling and simulation alone. A high correlation (R^2 , 0.97) was found between allometry-predicted and observed adolescent clearance for IV and oral products in an FDA review.³⁷ This argument is also supported by the fact that 87 of 92 (94.5%) products with the same indication for the adolescent and adult population had identical adolescent and adult dosing. Some observed PK data are usually needed to confirm the model prediction in pediatric patients younger than 12 years old because of the uncertainty and knowledge gaps regarding the effects of developmental changes on drug behavior. For pediatric patients younger than

2 years old, a model-based approach, such as PBPK, after accounting for ontogeny and receptor maturation is considered favorable over an unadjusted allometric scaling approach in deriving dosing regimen.³¹

Due to the enrollment difficulties and ethical complexities, MIDD should be conducted routinely in all stages of pediatric drug development to enroll the smallest number of pediatric patients possible to generate appropriate information and to maximize the success rate of any pediatric study. Every pediatric clinical trial should include a model-based justification for selected doses based on desired exposure, sampling schedule, and sample size. An innovative MIDD pilot meeting program was introduced in the Prescription Drug User Fee Act reauthorization fiscal years 2018 through 2022 to provide drug developers and regulatory scientists with enough resources and time to discuss specific issues thoroughly.³⁸ In this regard, more successful examples of applying MIDD in driving successful and efficient pediatric clinical trials should be expected.

Accumulated experience with the application of MIDD in drug development and regulatory evaluation

can lead to policy development and refinement. In the pediatric setting, 2 notable examples are related to pediatric efficacy extrapolation for antiepilepsy drugs and inclusion of adolescent patients in the adult oncology trials, as discussed above. This type of policy development is based on consistent findings from multiple compounds through extensive model-based analyses. It can greatly improve consistency and efficiency in pediatric drug development. For example, the issuance of FDA guidance is expected to promote the enrollment of adolescent patients in relevant adult oncology trials before regulatory approval, which can facilitate earlier access to potentially effective therapies for adolescent patients with cancer. And since the issuance of the draft guidance for extrapolation of partial-onset seizures in pediatric patients aged 4 years and older, the FDA has already approved 4 drugs—eslicarbazepine and lacosamide in 2017 and pregabalin and brivaracetam in 2018—to treat partial-onset seizures in pediatric patients aged 4 years and older based on extrapolation of efficacy from successful adult trials.³⁹

MIDD offers very efficient and powerful tools for pediatric drug development in integrating knowledge/information from different sources and leveraging them for decision making. To ensure the appropriate use of these powerful tools given its complexity and its criteria, which include the intended use of the model, the quality and the extent of the existing knowledge, and the assumptions should be carefully assessed. Risk assessment should also be a critical part of MIDD. The validity of the modeling assumptions and the clinical context of model prediction should be clearly communicated and thoroughly assessed. Ideally, a series of *learn and confirm*⁸ cycles should be used for model building and simulation, and the model prediction should be confirmed as soon as the new information is available.

Conclusion

The unique challenges in pediatric drug development require efficient and innovative tools. MIDD has proven useful in its ability to integrate and leverage existing knowledge to optimize pediatric drug development programs without reducing evidentiary standards. The 3 major areas of MIDD applications in pediatric drug development include leveraging knowledge for bridging the gap, dose selection and optimization, and informing clinical trial design. Moving forward, MIDD should be incorporated into all pediatric drug development at every stage to inform clinical trial design and dose selection, with both its strengths and limitations clearly laid out. Accumulated experience and knowledge of MIDD has and will continue to drive regulatory policy development and refinement, which

will ultimately improve the consistency and efficiency of pediatric drug development.

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Conflicts of Interest

The authors declare no conflicting interests.

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Disclaimer

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