

Development of Drug Therapies for Newborns and Children



The Scientific and Regulatory Imperatives

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KEYWORDS

• Pediatric • Neonatal • Research • Extrapolation • Dosing • Regulations

KEY POINTS

- Pediatric drug development laws have improved labeling of products, including off-patent products, for use in pediatric patients.
- Extrapolation of efficacy data from adults relies on the understanding of the disease and response to therapy in adults and application to pediatric patients.
- Dose selection in pediatric patients, including neonates, should be based on understanding the influence of growth and development on pharmacokinetics and pharmacodynamics.
- Data on age- and disease-appropriate biomarkers in pediatric patients are critically lacking.
- Tremendous strides are being made in establishing consortia and clinical research infrastructure to facilitate drug development in pediatric patients, including neonates.

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INTRODUCTION

Pediatric advocacy and legislative initiatives have propelled pediatric drug development forward. There still remain significant challenges, including lack of basic science knowledge of disease mechanism for some conditions affecting neonates and children, application of extrapolation and dose-ranging studies to pediatric populations, and incorporation of Good Clinical Practice guidance into clinical trials. This paper will discuss these and other topics from a regulatory, industry, and academic/NIH point of view.

PEDIATRIC LEGISLATION AND IMPACT

For new medications to be marketed in the United States, they must be approved under the Food, Drug, and Cosmetic (FD&C) Act. Under the FD&C Act, drug manufacturers must demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies to obtain marketing approval. During the review of the marketing application, the US Food and Drug Administration (FDA) must assess whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks. Pediatric disasters such as the sulfanilamide tragedy (where sulfanilamide was dissolved in an elixir flavored with diethylene glycol and resulted in 100 fatalities) prompted many of the FDA's current regulations that require drugs to be safe and effective, as well as pure. Despite this, in 1968 Dr Harry Shirkey published an editorial in the *Journal of Pediatrics* in which he stated, "By an odd and unfortunate twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans."¹ His editorial noted that most drugs approved by FDA, including drugs that were commonly used in infants and children, were not approved for children and product labeling contained no information about the efficacy or safety of the drug when used in children.

Indeed, many pharmaceutical manufacturers were reluctant to study drugs in children owing to ethical and financial constraints or trial design challenges. Medications were often administered to children empirically, assuming that they were "little adults." This simplistic and often erroneous assumption resulted in pediatric dosing recommendations derived solely as fractions of adult dosing rather than on intrinsic factors based on known differences in growth and development (eg, volume of distribution and maturation of the metabolic and excretory pathways). Safety and efficacy were also simply assumed to be the same in the pediatric and the adult populations, and did not take into account both known and potential safety and efficacy differences that may be present in a growing and developing pediatric patient.²

Efforts to increase the availability of clinical data to support evidence of efficacy and safety of drugs used in infants and children were made over the next 20 years, but it was not until congress passed the first incentives for conducting pediatric studies in the Food and Drug Modernization Act of 1997 that drug development began to include children more consistently. This provision allowed the FDA to issue a Written Request outlining the studies needed on a specific drug for 1 or more conditions or indications, including indications not approved in adults. The FDA can grant 6 months of marketing exclusivity to sponsors who complete the voluntary pediatric studies included in a Written Request. The incentives first authorized under the Food and Drug Modernization Act of 1997 were reauthorized in 2002 in the Best Pharmaceuticals for Children Act (BPCA). BPCA was permanently reauthorized for FDA in 2012 under the FDA Safety and Innovation Act. Additionally, the ability to obtain pediatric exclusivity was extended to biologic products under the Patient Protection and Affordable Care Act of 2010. The BPCA also established a partnership between the FDA and the National Institutes of Health (NIH) to conduct studies on older drugs (eg, off-patent products) used in children for which pediatric information is lacking.

In addition to incentives to conduct pediatric studies under the BPCA, congress also passed legislation to require pediatric studies for certain drugs and biologics approved in adults. The Pediatric Research Equity Act (PREA), first enacted in 2003, requires pediatric assessments of new drugs for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration. The pediatric assessment must include data adequate to assess the dosing, safety, and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations. PREA works in conjunction with the BPCA but, unlike the BPCA, PREA applies only to those drugs developed for diseases and/or conditions that occur in both the adult and pediatric populations. PREA, like the BPCA, was also permanently reauthorized in 2012 under FDA Safety and Innovation Act.

EVIDENCE TO SUPPORT APPROVAL AND PEDIATRIC EXTRAPOLATION

For new medications to be marketed in the United States, they must be approved under the FD&C Act. Under the FD&C Act, drug manufacturers must demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies to obtain marketing approval. In certain cases, the effectiveness of an approved drug product may be demonstrated adequately without additional adequate and well-controlled studies. Pediatric extrapolation is an approach that allows for effectiveness to be established in pediatric populations without controlled clinical trials and relies on a series of evidence-based assumptions. Two fundamental assumptions are that there are similar disease progressions and similar responses to intervention in the adult and pediatric populations.

Pediatric extrapolation has evolved as an approach to maximize the use of available data and to minimize the exposure of children to unnecessary clinical trials.^{3,4} When pediatric extrapolation is considered, the appropriate design of pediatric studies is determined based on the level of uncertainty in the prior data and therefore the level of extrapolation (**Table 1**). The degree of uncertainty in the prior data relies on the understanding of the similarity in the natural history, pathophysiology, clinical characteristics, and outcome measures between the target pediatric population and adults. In addition, knowledge of developmental changes related to the drug target as well as on the similarity in outcomes in adults and for other drugs or biological products evaluated for the same indication provides support for leveraging prior data.

The use of pediatric extrapolation in pediatric drug development has been previously reviewed by the FDA.⁵ Among 366 studies submitted to the FDA between 1998 and 2008, 1 or more adequate and well-controlled studies were required in almost 60% of the cases reviewed, suggesting that there were limitations in the available data to support extrapolation of efficacy from adult data. The FDA review also revealed that a rigorous and consistent approach to defining and establishing disease and response similarity (or lack thereof) is still missing. As the approach to pediatric extrapolation evolves, there is increasing interest in the application of Bayesian statistical methods to provide more scientific rigor and consistency when pediatric extrapolation is used. Similar to pediatric extrapolation, the ability to “borrow” adult data using Bayesian statistics relies on the understanding of degree of disease and response similarity between the 2 populations.⁶ To date, there has been limited application of formal Bayesian strategies in pediatric product development. However, increased use of Bayesian strategies may improve the interpretability of data generated from pediatric studies when extrapolation of efficacy from adults is justified.

Table 1 Examples of extrapolation approaches and study designs		
Level of Uncertainty (Similarity of Disease, Response Similarity and/or Exposure-Response Between Adults and Pediatric Patients)	Design of Pediatric Studies	Examples with Pediatric Labeling Updates (2015–2017)
Low uncertainty	PK and safety study	Partial onset seizures (perampanel), asthma in adolescents (omalizumab, reslizumab), GERD (dexlansoprazole, omeprazole), cIAls (moxifloxacin), ABSSI and CAPB (ceftaroline)
Some uncertainty around one of the assumptions	PK/PD studies	Regional anesthesia (tetracaine/oxymetazoline), control of serum phosphorus in chronic kidney disease (sevelamer), HIV (emtricitabine/tenofovir alafenamide), treatment of anemia (darbepoetin)
	Dose-controlled efficacy/safety study Uncontrolled efficacy/safety study	Ulcerative colitis (mesalamine), Medical imaging (gadobutrol, sulfur hexafluoride/Lumason,
High uncertainty	Adequate and well-controlled efficacy/safety study	Type 2 diabetes, multiple sclerosis, migraine (topiramate, zolmitriptan, sumatriptan/naproxen), pain in infants (intravenous acetaminophen, oxycodone), fibromyalgia (pregabalin), chemotherapy induced nausea/vomiting (aprepitant), attention deficit hyperactivity disorder (methylphenidate-Aptensio XR), schizophrenia (asenapine), Lennox Gastaut (rufinamide), plaque psoriasis (etanercept)

Abbreviations: ABSSI, acute bacterial skin and skin structure infections; CAPB, community-acquired bacterial pneumonia; cIAls, complicated intraabdominal infections; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; PD, pharmacodynamics; PK, pharmacokinetics.

PEDIATRIC DOSE SELECTION

Drug development in children is 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.⁷ Challenges with dose selection have been reported as important contributing factors to trial failures in children.^{8,9} Therefore, understanding the effect of growth and maturation on pharmacokinetic (PK) and pharmacodynamic (PD) variability is critical for the design of pediatric trials.^{10,11}

Ultimately, the goal of research and development of new medicines is to identify and confirm safe and effective dosing tailored to the target pediatric population for the intended indication. Historically, dosing in children has been viewed as a scaling exercise with a simple normalization of bodyweight or body surface area applied to the adult dose:

$$\text{Dose}_P = \text{dose}_A \times \frac{\text{BW}_P}{\text{BW}_A}$$

Where P is pediatric, A is adult, and BW is bodyweight.

With this equation, the developing child is ignored and the approach relies on linear scaling of body weight to adjust dose. This approach underpredicts dose requirements across the pediatric continuum though it is not equally flawed in all age and weight ranges. Substituting body surface area for bodyweight in a similar manner is used extensively in pediatric oncology settings. Again, there is sufficient experience to know that this linear scaling method underpredicts infant and neonate dosing requirements.¹²

Although the knowledge supporting dosing for older children down to infants has improved,¹³ neonates and the complexities of their age, weight, and maturity continue to create a mostly empiric practice. The issue of size has been rigorously examined,¹⁰ although the mathematical explanations defining the nonlinear relationships that govern how dosing should (or could) be optimized often confuse the caregiver and more simplistic approaches prevail.

Two primary factors drive dosing considerations for the neonate—namely, size and maturation (development stage). The issue of size is complicated by the confounding of 2 measured physiologic variables, body weight and age. In older children (>2 years of age), weight-adjusted dosing via allometric relationship or staggered by age groups (linear scaled within a common age group and then adjusted across age groups) is sufficient to address size. This is not the case for neonates. Body composition in the neonate is a dynamic variable, changing with time. Depending on the attributes of the drug itself (molecular weight, lipophilicity, permeability, etc), the impact of these shifts on drug disposition may be projected, but this effect must be balanced against what would happen owing to absorption (depending on route of administration) and elimination (based on the specific clearance mechanisms).

Allometric or power models are used in various biological settings to adjust for size dependencies of growing and developing systems. The value of the exponent varies with the type of biologic variable and there is certainly no consensus on the numeric validity of these generalized constants.

$$Y = a \times \text{BW}^b \begin{cases} b = 0.25, \text{ time - related variables} \\ b = 0.75, \text{ metabolic variables} \\ b = 1, \text{ anatomic variables} \end{cases}$$

Where Y is the body part being measured in relationship to size, a is the initial growth index, b is the scaling exponent, and BW is bodyweight.

Systemic clearance (CL) as a key population parameter from which both maturation (MF) and organ function (OF) require consideration when adjusting for pediatric populations:

$$CL_P = CL_A \times \left(\frac{BW}{70}\right)^{0.75} \times MF \times OF$$

Maturation is generally considered a continuous function that achieves an asymptote at the adult value ($MF = 1$) at some finite point in development. Usually the MF is derived from a time index related to birth. Expressions for MF based on postconceptual age, postmenstrual age, postnatal age, and gestational age have been considered.¹⁰

Inconsistent use of terminology has limited the accurate interpretation of data on health outcomes for newborn infants, especially for those born preterm or conceived using assisted reproductive technology.¹⁴ See Figure 1 in the article “Age Terminology During the Perinatal Period” (<http://pediatrics.aappublications.org/content/114/5/1362.long>) where Engle illustrates the relationship between the various age indices. These relationships are critical for the refinement of dosing considerations in the neonate and infants. Likewise, the construction of these relationships depends on the design of pediatric clinical trials, particularly the collection of within patient data in the developing neonate and infant.

DESIGNS OF PEDIATRIC PHARMACOKINETIC AND PHARMACOKINETIC/PHARMACODYNAMIC STUDIES

The design of PK and PK/PD studies in pediatric patients should be based on the understanding of the impact of developmental changes on PK and PD. In patients 2 years of age and older, given that most metabolic and excretory pathways are mature, PK data may be collected in a small cohort of patients as a lead-in phase to an efficacy/safety study or in some cases (adolescents) using sparse sampling during the phase III trials rather than conducting a separate PK study. In addition, age cohorts can be enrolled simultaneously rather than sequentially by age unless there are specific PK and/or safety data needed from older cohorts. A sequential design is often justified in infants and neonates where PK and/or safety data from older infants may be used for dose selection in subsequent cohorts. “Caution” alone does not justify a sequential approach, because it leads to significant delay in the completion of PK studies in pediatric patients.

The rich prior data in pediatric drug development coupled with the small population to study make the use of adaptive designs a necessity. Seamless phase II/III design is a form of adaptive design that has high relevance to pediatric development. Similar to other adaptive designs, this design provides an opportunity to adapt (eg, drop or add dose arm[s]) based on data from the early phase of study (typically PK/PD) and reduces overall sample size. As such, a seamless phase II/III design achieves within a single trial objectives that are normally achieved through 2 trials: a separate PK/PD and subsequent efficacy trial, avoiding delays from having to complete one trial before starting another. The suitability of this approach ultimately depends on many factors, including PK/PD in adults, the disease state, the safety of the product, and the age group under consideration. Furthermore, modeling and simulation can be used to predict PK and select the initial dose(s).

ROLE OF BIOMARKERS

The need for efficient and feasible pediatric drug development programs has stimulated interest in the development of biomarkers that may substitute for clinical endpoints or optimize clinical trials. A biomarker is “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.” Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives. Categories of biomarkers include susceptibility/risk, diagnostic, monitoring, prognostic, predictive, PD/response, and safety. Owing to the frequent confusion about identification and qualification among researchers, the FDA–NIH Joint Leadership Council developed a resource called the BEST Resource (Biomarkers, EndpointS, and other Tools).¹⁵

To date, there are a limited number of validated biomarkers for use in the pediatric population.¹⁶ In the absence of pediatric data, adult biomarkers are often applied directly to children. This approach may not take into consideration the pathophysiology of the pediatric disease and developmental impacts on the biomarker. Age-related changes in biologic surrogates are illustrated by the use of systolic blood pressure in antihypertensive drug trials. Blood pressure in adults is not only a biomarker, but also a surrogate marker of risk for myocardial infarction and stroke in adults. After the passage of the BPCA, the FDA issued several Written Requests to industry sponsors to perform pediatric studies for antihypertensive drugs. Contrary to findings in adults, most pediatric studies failed to show a significant reduction in systolic blood pressure. A secondary analysis of these data was performed by the FDA,⁹ showing that the reason for the primary outcome failing was multifactorial (lack of dose ranging and pediatric formulations, etc) and revealed that use of diastolic blood pressure rather than systolic blood pressure reduction would have been an age-appropriate PD/response biomarker.

Biomarker development is even more challenging in neonates given that most diseases are unique to the neonatal age group and may not have a close correlate in older pediatric patients or adults. Pediatric trials should therefore be designed to collect and analyze biomarker data and assess PK–biomarker or biomarker–clinical endpoint relationships when applicable. Where there is an adult correlate, these data may inform the ability to extrapolate adult efficacy data to children using a biomarker endpoint in future trials.

ROLE OF MODELING AND SIMULATION

In addition to innovative trial designs and development of biomarkers, modeling and simulation is increasingly used to optimize pediatric drug development. Modeling and simulation is a useful tool to systemically evaluate existing data and integrate knowledge across trials and populations. The experience with the use of model-based analysis to support regulatory decisions in pediatric drug development has been previously described and includes optimization of dose selection; substantiation of trial design; and description of dose–exposure and exposure–response relationships to support extrapolation of efficacy from adult data.^{17–19}

As science and technology continue to advance, *in silico* and other alternative modeling study methods may be developed that can provide preliminary data to inform the design and conduct of PK/PD studies for investigational drugs in pediatric populations including term and preterm infants. For example, the development of a physiologically based PK *in silico* model that integrates drug-dependent parameters (eg, renal clearance, metabolic pathways) and system-dependent parameters (eg,

non-drug parameters such as blood flow rate, protein binding, and enzyme and transporter activities) is a possible approach. Physiologically based PK has been used in pediatric drug development programs for (a) planning for a first-in-pediatric PK study, (b) optimizing the study design, (c) verifying the model in specific age groups, (d) recommending starting doses, (e) informing enzyme ontogeny using a benchmark drug, and (f) facilitating covariate analysis for the effects of organ dysfunction or drug interactions in pediatric patients.¹⁹ The model selected should incorporate in vivo PK/PD data obtained in other groups of pediatric and adult patients as well as healthy human volunteer studies, as appropriate.

Clinical trial simulations can be performed to integrate PK, PD, disease progression, and study design considerations to help guide a pediatric drug development program. In term and preterm infants, owing to constraints related to enrollment and blood sampling, clinical trial simulations can be particularly helpful to assess sample size considerations and design a trial that is both feasible and can adequately evaluate drug exposure, effectiveness, and safety in this population.

NEED FOR DATA SHARING AND COLLABORATION

Data sharing and cross-collaboration among investigators have been mandated by the NIH for several years,²⁰ but true access to raw data has been difficult to achieve. This is due to many factors, including lack of uniformity in data collection methods and data fields across investigators. Several NIH initiatives have sought to fix this, with the use of common data bases such as i2b2, and common data elements. The Eunice Kennedy Shriver National Institute of Child Health and Human Development has developed the Data and Specimen Hub,²¹ which stores raw data from clinical trials in an accessible format for data manipulation.

The challenges with conducting clinical trials in the pediatric population require innovative approaches leveraged from the rare disease experience. It is imperative that the pediatric community work collaboratively to develop and label drugs for pediatric diseases including neonatal diseases. In 2014, the FDA worked with the Critical Path Institute to determine if there was sufficient interest in developing a neonatal consortium. Based on the identification of a significant number of stakeholders, the International Neonatal Consortium (INC) was launched in May 2015.²² INC is composed of stakeholders from academia, industry, regulatory agencies, other government agencies, neonatal/parent advocacy groups, and neonatal nurses. INC has created a forum for the global neonatal community to share data, knowledge, and expertise to advance medical innovation and regulatory science for neonates to maximize opportunities to label drugs for use in neonates. Initial priorities for INC include a master protocol for the treatment of neonatal seizures, as well as white papers on neonatal clinical pharmacology white paper,²³ long-term outcome measures, classification of adverse events, and endpoints for therapeutic trials in bronchopulmonary dysplasia. New working groups have been established to discuss hemodynamic adaptation, retinopathy of prematurity, necrotizing enterocolitis, and communications.

Adequately developed clinical research infrastructure is essential to address operational challenges in pediatric drug development. In 2011, the European Network of Pediatric Research at the European Medicines Agency was established as a network of research networks to enable collaboration between academia and the pharmaceutical industry, both within and outside the European Union.²⁴ In 2017, Institute for Advanced Clinical Trials for Children (available: <https://www.iactc.org/>) was launched as a new nonprofit using public-private collaboration to “optimize pediatric study designs, protocols, best practices, training and engagement of patients and parents to

advance clinical trials to improve children's health.²⁵ These collaborative trial networks will provide the foundation to support the increase in pediatric trials that will be needed in the future.

EXPERIENCE WITH DRUG DEVELOPMENT FOR OFF-PATENT DRUGS

Under the BPCA, funding can be granted through the NIH to studies to obtain pediatric-specific labeling information in off-patent drugs. Under this program, the Eunice Kennedy Shriver National Institute of Child Health and Human Development has been tasked to develop a program for pediatric drug development, prioritize drugs and therapeutic areas in need of study, sponsor clinical trials, and submit the data to FDA for review and potential labeling changes. The National Institute of Child Health and Human Development has sponsored more than 2 dozen pediatric clinical trials under the BPCA program resulting in more than 7 drug or device labeling changes. The experience since 2002 indicates that (a) there is a paucity of investigators with the capabilities to design and perform pediatric clinical trials, (b) there is likewise a lack of pharmacometricians with pediatric expertise, (c) incorporation of data from other sources, such as electronic health record, can provide needed real-world data that can augment prospective clinical trials, and (d) investigators must become familiar and adhere to cGCP guidance to attain FDA labeling, the highest bar for data quality.

OPPORTUNITIES AND CHALLENGES

The implementation of the BPCA and PREA has led to the addition of specific pediatric information in more than 650 drugs and biological products (1997–2016, [Fig. 1](#)). Pediatric-specific product development plans are now more commonly incorporated into overall product development. However, despite the successes over the last 20 years, many challenges and opportunities remain. More than 50% of drugs commonly used in pediatrics are not labeled for pediatric use.²⁶ In addition, the

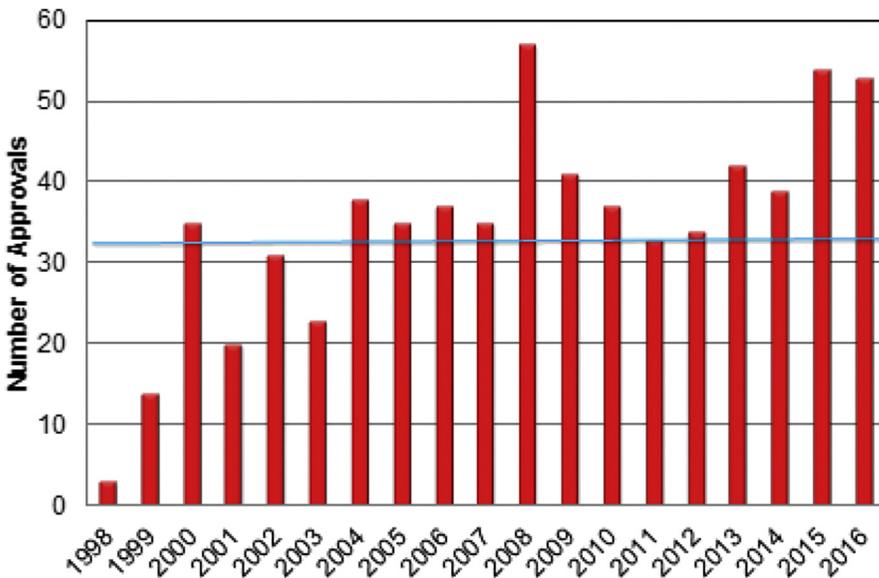


Fig. 1. Pediatric labeling changes from 1998 to 2016.

development of therapies for pediatric-specific diseases (eg, neonatal diseases, pediatric cancer) has lagged behind development of other pediatric diseases, in part because the requirements for conducting pediatric studies under PREA generally pertain to drugs and indications that are developed for adults. The FDA can issue Written Requests under the BPCA to encourage drug manufacturers to conduct studies for pediatric-specific diseases; however, this process is voluntary.

Despite an increasing understanding of PK, PD, and clinical conditions, clinical trials in children continue to pose practical and ethical challenges. Phenotypic variability, poorly understood natural history, maturational changes related to PK and PD, and the lack of biomarkers, outcome measures, and endpoints underscore the need to optimize the collection, analysis, and interpretation of data on PK, PD, safety, and efficacy in children.

In addition, there are clinical and operational challenges that can affect the efficiency of pediatric product development. For example, some pediatric product development programs face feasibility issues, including a small number of eligible children for clinical research. Current standards of care can influence physician and patient treatment choices that may impact pediatric clinical trial design. Alternative approaches may provide opportunities to address these issues when structured and integrated into the development program. Innovative clinical trial designs that can increase feasibility while obtaining necessary information to support the efficacy and the safety of the product for use in all relevant pediatric populations should be considered. Successful pediatric product development programs rely on the ability to recruit and retain pediatric patients. Strategies that foster input from children, their caregivers, and the advocacy communities can facilitate participation, recruitment, and acceptability of a clinical study. Finally, many pediatric product development programs are multiregional and must adhere to regional regulatory requirements. Therefore, the development of a scientific approach that is aligned across regulatory authorities can improve the efficiency and success of pediatric clinical trials.

Despite the overall advances in therapeutics development for children, there remains, on average, an 8-year lag between the time of a drug's initial approval in adults and the addition of pediatric-specific labeling information.¹⁷ During this time, prescribers are forced to use products off-label in their pediatric patients. Many studies have shown that off-label drug use in pediatrics is associated with significantly increased risk for developing adverse drug reactions.^{27,28}

Finally, pediatric-specific safety data, including long-term safety, are often not available at the time of approval. Therefore, the development of strategies to systematically capture and evaluate long-term effects in a disease or condition, and increase data interpretability should be considered. Such strategies have included patient registries that prospectively collect safety data and can include both untreated patients and patients treated with different products (eg, multiproduct and disease-based registries). The use of larger data sources, such as electronic health records systems may also be useful, if appropriate data collection methods can be standardized and consistently applied.

Meeting these challenges and opportunities will hopefully guide the future direction of pediatric therapeutics development.

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