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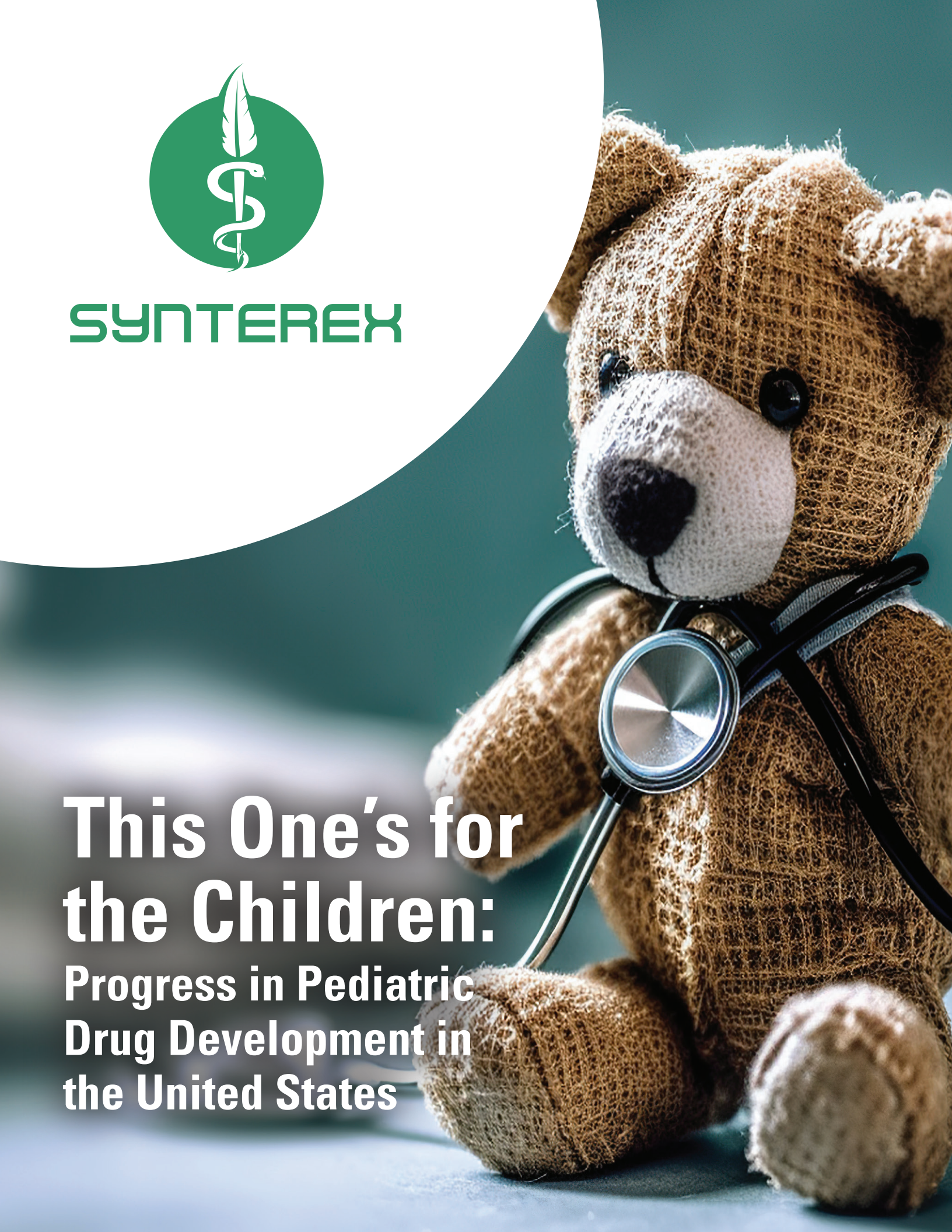


This One's for the Children:

Progress in Pediatric Drug Development in the United States

THIS ONE'S FOR THE CHILDREN: PROGRESS IN PEDIATRIC DRUG DEVELOPMENT IN THE UNITED STATES

Introduction

The pediatric population includes patients from birth to 17 years of age, and subpopulations include: (1) neonates (birth to 27 days old [gestationally corrected age]); (2) infants (28 days to 23 months); (3) children (2 to 11 years old); and (4) adolescents (12 to <17 years old).1 Patients within these groups are considered vulnerable populations, and though they can get many of the same diseases as their adult counterparts, safety and efficacy data collected during drug development are lacking.2 Appropriate drug dosing is of particular concern because factors such as body weight and age potentially play an important role in the effectiveness of a drug. Physiology and rate of growth or maturity of biological systems are markedly different at each phase of pediatric development and can result in numerous ethical, clinical, and logistical challenges when planning and conducting clinical trials. Careful and specific considerations should be made for customized dosages, formulations, and administration routes to maximize the drug's bioavailability and ensure its safety; these considerations should also be clearly spelled out in informed consent and assent forms.

The concept of drug safety came to the forefront of drug development beginning in the late 1930s when the development of a liquid formulation of sulfanilamide, a potent antibiotic, led to a grave discovery. The diluent used to make the liquid formulation, diethylene glycol, a byproduct of many commercial antifreeze additives, was discovered to be a sweet but lethal poison.3 Following the release of liquid sulfanilamide to the market, 105 deaths were reported,4 and many of them were children being treated for a sore throat. To prevent future tragedies, the 1938 Federal Food, Drug, and Cosmetic (FD&C) Act was formed.

Prior to the FD&C Act, pharmaceutical companies were not required to provide proof of drug safety or a disclosure of all active ingredients. Since then, all new drugs undergo an intensive review process by the Food and Drug Administration (FDA), and ever-evolving guidance and regulations ensure that both new drugs and those with updated characteristics, such as dosing, delivery, and expanded indications, are safe and effective for the intended populations. A gap remains, however, for drug investigations including and targeted for children of varying ages.

Regulation of Pediatric Drug Development

After the FD&C Act, there was not much legislation or guidance focused on drug development for the pediatric population until the Labeling for Prescription Drugs Rule of 1979 was approved. Since then, the biggest surge of pediatric-focused legislation occurred between 1994 and 2003 as summarized in Table 1.

Table 1: Important Legislation Regulating US Pediatric Drug Development [5-11]

Years	Regulatory Body	Legislation or Guidance	Impact
1975-79	FDA	Content and Format for Labeling for Human Prescription Drugs 40 FR 15,392[a] 44 FR 37,434[a]	Companies are required to include information about the use of drugs in children directly on the label with a disclaimer stating that safety and efficacy in children was not studied.
1992-94	FDA	Content and Format for Labeling for Human Prescription Drugs (revisions) 57 FR 47,423[a] 59 FR 64,240[a]	A product's label must include information about safety, effectiveness, or dosing for children. • Supplemental application is required for pediatric indication. • Pediatric indication can be approved based on adult data.
1997	US Congress	FDAMA PL 105-115 §111 Pediatric Studies of Drugs	An additional 6 months of market exclusivity (economic incentive) is given when a company submits reports of pediatric studies that fairly respond to a written request from FDA and are conducted in accordance with generally applicable scientific principles and protocols.
1998	FDA	Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients 63 FR 66,632[a]	The conduct of studies assessing the safety and efficacy of new drugs and biological products is mandated to provide adequate labeling for use in pediatric patients.
2002	US Congress	BPCA PL 107-109 §409I Program for Pediatric Studies of Drugs	Pediatric studies are defined to mean at least 1 clinical investigation in "pediatric" age groups (including neonates in appropriate cases) in which a drug is anticipated to be used. • FDA is authorized to request studies of pediatric indications (approved and/or unapproved).
2003	US Congress	PREA PL 108-155 §2 Research into Pediatric Uses for Drugs and Biological Products	Any application for a new active ingredient, indication, dosage form, dosing regimen, or route of administration must include pediatric assessments in all relevant pediatric subpopulations.
2011-12	US Congress	Creating Hope Act 21 USC 360aa FDASIA PL 112-144 §908 Rare Pediatric Disease Priority Review Voucher Program	BPCA and PREA are permanently authorized. This allowed for the transferable "priority review" voucher program to be applicable to rare pediatric diseases. • A voucher can be transferred or sold an unlimited number of times.

Abbreviations: BPCA = Best Pharmaceuticals for Children Act; FDA = Food and Drug Administration; FDAMA = Food and Drug Administration Modernization Act; FDASIA = Food and Drug Administration Safety and Innovation Act; FR = Federal Register; PL = Public Law; PREA = Pediatric Research Equity Act; US = United States.

[a] Full text can be obtained via the Federal Register database.

General Pediatric Drug Development Guidance Under the Pediatric Research Equity Act and Best Pharmaceuticals for Children Act

The current FDA guidance "Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations"[2] and "Pediatric Drug Development: Regulatory Considerations – Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act,"[1] both drafted in May 2023, specifically highlight pediatric drug development under the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). These guidelines replace the 2005 draft guidance "How to Comply with the Pediatric Research Equity Act."[12] The PREA and BPCA were designed to function in tandem to promote the generation and analysis of safety and efficacy data for pediatric populations during drug development. The PREA applies to applications and application supplements for a new active ingredient, indication, dosage form, dosing regimen, or route of administration submitted under section 505 of the FD&C Act or section 351 of the Public Health Service (PHS) Act. The PREA also applies to original applications submitted under the same sections on or after August 18, 2020, for a new active ingredient relevant to pediatric cancer but originally designated to treat cancer in adults.

Pediatric studies are defined under the BPCA as at least 1 clinical investigation in "pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used and, at the discretion of the Secretary, may include preclinical studies."[1] PREA, however, requires safety and efficacy studies to be performed in all pediatric age groups relevant to the indication if there are no waived or deferred assessments.[13,14] For a drug that was previously approved, if the company is seeking approval for a new dosage form, route of administration, or active ingredient through submission of an Abbreviated New Drug Application (ANDA), then the FDA must have waived the pediatric assessment requirements under PREA.[15,16] If the FDA has not waived the pediatric assessment requirements, the application is no longer eligible as an ANDA submission.

Written Requests (WRs) under the BPCA can be placed by companies through submission of a proposed pediatric study request (PPSR) or are administered by the FDA at their discretion. The WR functions to request that the company complete studies that may expand indications that have the potential to offer health benefits for pediatric populations but may be currently approved or pending approval in adults.[1,17] Sources consulted in this decision-making process include adult safety and efficacy data, postmarketing safety reports, unapproved uses, and the current body of literature. The WR details voluntary study elements that must be fulfilled for the company to qualify for 6 months of pediatric exclusivity (marketing exclusivity), which functions to extend an existing patent or period of exclusivity that has already been granted.[1] A second 6-month period of pediatric exclusivity may be granted to companies submitting an application supplement for which a second WR has been issued by the FDA only if the company meets the additional pediatric study

requirements and the supplemental application for a new use is approved.[18] For the second 6-month exclusivity period to be granted, the supplemental application must also qualify for 3-year exclusivity defined under sections 505(c)(3)(E)(iv)19 and 505(j)(5)(F)(iv)19 of the FD&C Act.

A PPSR may be voluntarily submitted by the company at any time during product development to request a WR from the FDA under BPCA. The company should allow for an appropriate amount of time prior to submitting a PPSR to account for FDA review of the submission, completion of pediatric studies, 180 days for the FDA to make a determination on the exclusivity request, and a minimum of 9 months remaining on a current patent or exclusivity period.[20-22]

An initial pediatric study plan (iPSP) functions to establish considerations for a pediatric clinical development program in the early stages of the overall clinical development plan. The iPSP is required for studies performed under PREA and must be submitted prior to any: (1) pediatric assessments or (2) reports on investigations for molecularly targeted pediatric cancers.[23] The iPSP should be submitted as early as possible but no later than 60 days following the end-of-Phase 2 meeting or another date approved by the FDA.[24,25] A company should not submit a marketing application (or supplement) until there is an agreed iPSP.

For both a PREA or WR response under BPCA, product labeling must include a description of pediatric study results regardless of whether they are favorable, unfavorable, or inconclusive.[26] Labeling must also include information where drugs are evidenced to be unsafe or ineffective in the pediatric population, leading to a grant of a full or partial waiver.[27-29] In the event label changes are not agreed upon between the company and FDA, the matter is referred to the Pediatric Advisory Committee (PAC).[30,31] The PAC must submit a recommendation to the FDA within 90 days.[32,33] The FDA then has 30 days to send updated labeling requests to the company,[34,35] and a drug will be considered misbranded if the company does not apply the updated labeling changes within 30 days of receiving the FDA's request.[36,37] Labeling changes that are initiated as a result of studies conducted under section 505A of the FD&C Act will receive priority review following submission of the application (or supplement).[38]

When submitting study reports requested in a WR, the company must submit all postmarketing reports of adverse events concurrently with responses to the WR under the BPCA. The format of this report should align with the periodic safety update report presented in the International Council for Harmonisation for Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance "E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)" published in July 2016.[39] In the event a label change is submitted resulting from studies conducted under PREA or BPCA, a description of all adverse events reported in the 18 months post-label change must be submitted to the Office of Pediatric Therapeutics (OPT). The OPT will, in turn, present an analysis to the PAC, who will then issue recommendations on an adverse event monitoring extension based on this analysis.

A comparison of PREA and BPCA legislation is summarized in Figure 1.

Figure 1: Similarities and Differences Between PREA and BPCA[1,2,40,41]

PREA

- Mandatory pediatric assessments:
  - For drug products under section 505B(a)(1) of the FD&C Act with new active ingredient, indication, dosage form, dosing regimen, or route of administration (can also request waiver or deferral)
  - Molecular targets for pediatric cancer for original NDAs or BLAs submitted on or after August 18, 2020, if the drug has a new active ingredient or is intended to treat adult cancer and the molecular target is relevant to pediatric cancer progression
- Studies conducted ONLY for the indication(s) under review
- Although pediatric assessments are not required on drugs with approved orphan designation, this orphan exemption does NOT apply to molecularly targeted pediatric cancers
- Medical, statistical, and clinical pharmacology reviews must be published by the FDA within 330 days after submission
- iPSP required

Applies to drugs, biologics, and molecularly targeted cancers
Pediatric Review Committee (PeRC) consults on: iPSPs and amendments, PPSRs, WRs and amendments, deferrals, deferral extensions, and waivers
Pediatric study results must be described in labeling

BPCA

- Voluntary pediatric assessments:
  - Written Requests (WRs):
    - Companies can decline to commence studies
    - Companies may qualify for an additional 6 months of marketing exclusivity for completing studies required under PREA if FDA determines a new drug may produce health benefits in the pediatric population
- Studies can expand indications:
  - Broader scope: FDA may request via WR the study of indications for pediatric application not currently approved in adults
- FDA may request studies for orphan designations
- Medical, statistical, and clinical pharmacology reviews must be published by the FDA within 210 days after submission
- PPSR required for company to voluntarily seek a WR

Abbreviations: BLA = biologics license application; BPCA = Best Pharmaceuticals for Children Act; FDA = Food and Drug Administration; FD&C = Federal Food, Drug, and Cosmetic; iPSP = initial pediatric study plan; NDA = new drug application; PeRC = Pediatric Review Committee; PPSR = proposed pediatric study request; PREA = Pediatric Research Equity Act; WR = written request.

Key Regulatory Considerations That Drive a Company's Pediatric Drug Development Plan[2]:

Drugs for Life-Threatening or Severely Debilitating Conditions and Unmet Medical Needs

- FDA encourages drug development companies to discuss preparation of the pediatric plan at Pre-Investigational New Drug Application (pre-IND) and end-of-Phase 1 meetings.
- Early initiation of trials for life-threatening or severely debilitating conditions without adequate therapies may be justified if the prospective benefits outweigh the risks, even when there is a lack of safety and efficacy data available in humans.

Drugs for Diseases or Conditions That Occur Primarily in Pediatric Populations

- Study plans should be discussed with the FDA as early in the drug development process as possible, such as at the pre-IND meeting.
- The company's iPSP should be submitted earlier than PREA requirements since initial clinical studies will likely include pediatric participants.

Neonates

- PREA: The iPSP should include a rationale and supporting data if the drug is not appropriate for neonatal application and the company does not plan to pursue investigation in this population.
- BPCA: The company should include in the PPSR a rationale and supporting data if the drug is not appropriate for neonatal application and no investigational studies will be pursued in this population.

Orphan Products

- If an orphan designation has been granted to a drug or biological product, PREA requirements generally do not apply; however, molecularly targeted pediatric cancer investigations that are subject to PREA requirements are excluded from this orphan exemption.
- Under PREA, pediatric assessments must be submitted for all indications that do not have an orphan designation if the company is seeking drug marketing approval for multiple indications; however, if an indication has an orphan designation but involves the pediatric population, the company is encouraged to conduct studies within this population.

Drug Development in Foreign Countries

- Companies with clinical programs outside the United States should engage the FDA early in the drug development process to allow sufficient time to provide any required pediatric information with applications.
- Agreed upon iPSPs should be included in any New Drug Application (NDA), Biologics License Application (BLA), or supplement required by PREA.

Drugs for Diseases or Conditions That Only Occur in Adults

- An iPSP must be submitted for development of drugs used to treat diseases and conditions that occur only in adults if the application is applicable to PREA.
- A waiver may be issued for drug applications intended to treat diseases or conditions that rarely or never occur in the pediatric population if study execution is not feasible.

Study Design and Data-Related Considerations for Pediatric Drug Development

When a pediatric development program under PREA or the BPCA is planned, the following considerations may be relevant to the overall drug development strategy.

Scheduling and Initiation of Studies

Pediatric clinical studies generally may be started if data from animal disease models and/or the adult population support scenarios in which the risk of intervention or procedure is low or if the direct benefit of the intervention or procedure outweighs any perceived risk.[42] Critical analysis should be made on a case-by-case basis to identify any potential risks of pediatric participation in clinical studies and their impact on when studies should be initiated in the drug development timeline. In some instances, it may be necessary to defer pediatric study initiation until safety and efficacy data are analyzed from the adult population. When clinical studies are required for neonatal patients, timing of these studies is especially important. Dosing parameters, safety, and effectiveness established in other pediatric groups or adults may not always be appropriately applied to a neonatal patient. The FDA recommends that unless safety and efficacy are required to be established in other patient groups first or data have already been generated that indicate safety or efficacy concerns for the neonatal group, neonatal studies should occur concurrently with those in older pediatric populations.[2] A collective balance should be struck between safe and early initiation of the pediatric studies, and companies are encouraged to engage in open dialogue with the FDA for planning purposes.

Formulation Development

As a requirement of PREA, drugs must be appropriately formulated according to each age group they will be used for, which applies to both pediatric assessments and molecularly targeted pediatric cancer investigations.[43,44] Alternative considerations for pediatric population formulation development that may differ from adult populations include dosage form and strength. Particularly for oral administration, children may require a reduced dosage in varying forms to enhance palatability, such as an oral liquid that can be mixed in soft foods or a chewable tablet. Assessments should be made for drug product stability when delivered in aqueous solutions. Potential interactions with any additives such as dyes, alcohols, flavoring agents, or preservatives (excipients) should also be considered. Additionally, if a specialized device, such as a dropper, syringe, measuring cup, or inhaler, is required to assist with drug administration, the company should factor in requirements of device calibration and packaging. Studies should be conducted to ensure no toxic components leach from the delivery device and that the drug substance is compatible and stable in the presence of excipients during storage and while in use. Last, pediatric formulation development may require studies assessing dissolution characteristics in conditions that mimic the in vivo delivery environment, such as gastric fluids. A partial waiver may be administered if an age-appropriate formulation is unable to be developed after reasonable attempts have been made by the company.[45]

Nonclinical Data

For pediatric drug development to progress to the clinical stage, nonclinical studies designed specifically with the pediatric population in mind may be needed to investigate potential drug effects at different stages of development and any unique pharmacokinetic (PK) and pharmacodynamic (PD) characteristics at those stages. The use of juvenile animal models that are representative of the targeted pediatric population may be appropriate for these hazard assessment studies, particularly if there is not sufficient supporting data from previous human and animal studies.[2] Nonclinical toxicology studies using juvenile animal models may inform potential developmental adverse effects associated with the intended pediatric age group(s). Considerations should be made for the use of specific animal disease models for which any congenital disorders reflect the intended condition or disease to be treated in the pediatric population.[2] Companies considering a nonanimal model for drug evaluation are encouraged to consult with the FDA to determine if these alternative testing methods could be assessed for equivalency to an animal model.[46,47] Companies should also consult with the FDA to assess if nonclinical data are sufficient to begin clinical studies in all relevant pediatric age groups.[2]

Clinical Pharmacology

Best efforts to maximize efficiency of early-phase dosing studies should be made during pediatric drug development to streamline future efficacy studies. In younger pediatric groups, it may be necessary to utilize PK and/or PD studies if dose selection cannot reliably be extrapolated from data in adolescents and adults.[2] Recommendations and considerations for PK and PD study design include the following:

Pharmacokinetic Studies

- Some drugs may not require individual PK studies for all pediatric age groups if sufficient justification can be drawn from adult studies.[48] However, if they are required, a justification of sample size with assessment of PK parameter variability is needed for the relevant age group(s).
- Matching exposure to adult populations is most relevant when pediatric extrapolation is being used.
- Efficient study design can reduce the burden and quantity of blood sampling using sparse PK sampling techniques and population PK.
- Determine any potential development-related pharmacogenetic differences in neonates and infants compared with older pediatric populations and adults that may impact a drug's PK, efficacy, or safety.[49]
- Companies should consider combining PK studies with safety or efficacy studies to demonstrate direct clinical benefit to the relevant pediatric group(s) if administration of the drug will result in more than a minor increase over minimal risk.[2,42,50]

Pharmacodynamic Studies

- It is of particular importance to consider PD characteristics that may be unique to and vary within age groups of the pediatric population, such as differential receptor expression and organ system maturation, and their potential effects on drug dosing and study endpoints.
- Companies should consider implementation of bridging studies and appropriate application of PD modeling.[2]

Safety Information and Neonatal Patients

Studies in pediatric populations are almost always required to glean the most accurate information on adverse effects during pediatric drug development. Nevertheless, review of data from adult populations treated with the same drug or closely related drugs may still yield helpful safety information for the pediatric population. Long-term follow-up studies may also be needed to fully understand effects and risks of the investigative drug throughout development, particularly for younger pediatric age groups. FDA draft guidance on this topic was published in February 2023 titled, "Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development."[51] Strategies for risk evaluation, mitigation, and safety monitoring should be applied to pediatric populations where appropriate.

The neonatal period inherently poses challenges due to its short window available for study enrollment, and parents may have a general aversion to exposing their newborn child to investigational therapies and/or procedures. Children at this stage also have physical limitations requiring restrictions on blood sample collection, which may affect the frequency and type of assays that can be conducted. Furthermore, physiological development may be vastly different in preterm neonates compared with full-term neonates, thereby having potentially substantial effects on drug dosing and formulation.[52,53]

A general lack of high-quality data is a persistent challenge in this neonatal group, which BPCA and PREA are designed to address. For example, when PREA requires pediatric assessments, the application must detail safety and efficacy assessments for the neonatal group if relevant to the indication.[43] Additionally, if a WR is issued under the BPCA and the FDA does not explicitly request studies in neonates, the FDA must provide a rationale for this decision.[54]

Pediatric Extrapolation

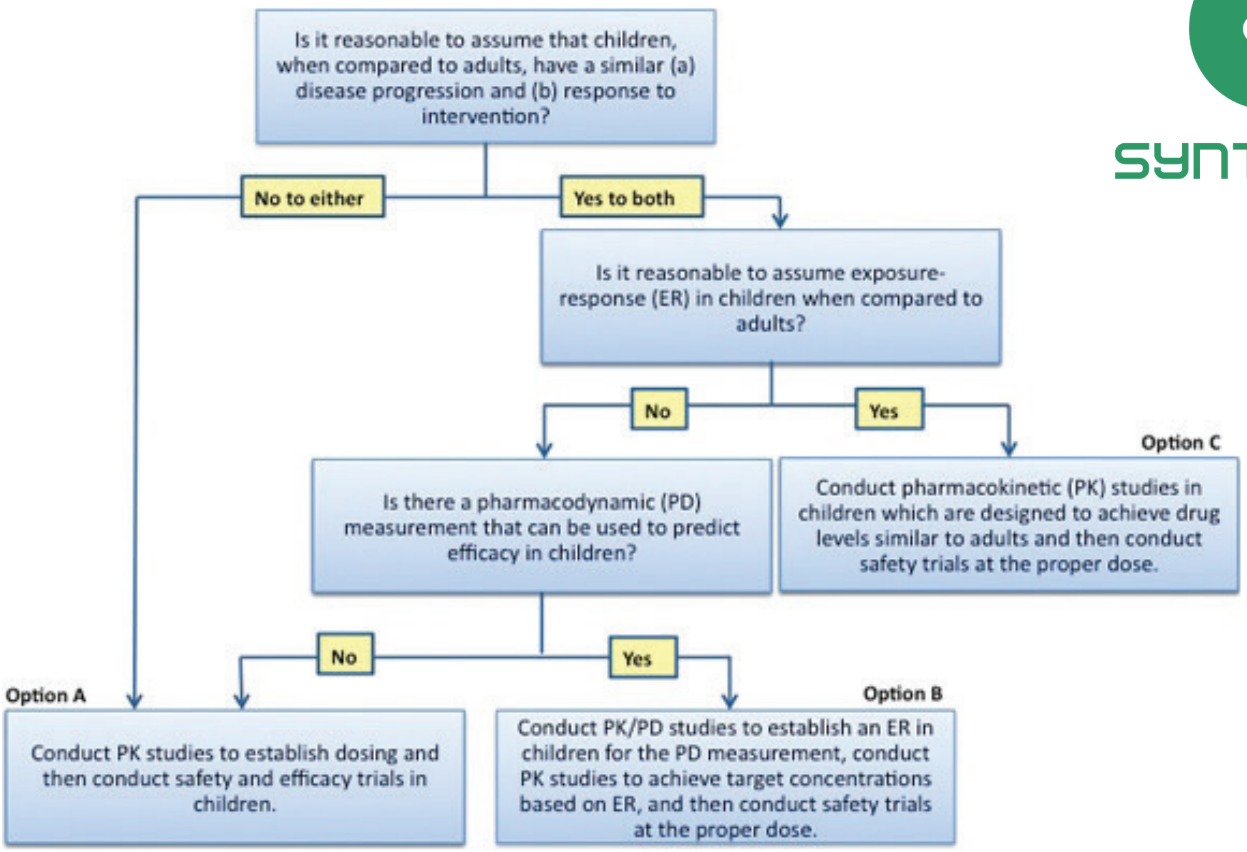
Developing protocols for pediatric clinical studies is uniquely challenging when compared with those designed for adult populations. Because of the pediatric population's inherent status as a vulnerable group, ethical concerns exist when enrolling pediatric patients to participate in clinical studies.[55] A limited number of patients may be available for participation, particularly for rare indications, and development of age-appropriate endpoints can be challenging. Implementation of surrogate endpoints may be necessary as an alternative to measuring clinical outcomes in cases where the clinical outcome may take an unreasonable amount of time to study or is unethical or

where there is a well-established clinical benefit to improving the surrogate endpoint.[56] For example, measuring blood pressure does not directly quantify the clinical benefit of how a patient feels, functions, or survives as a result of taking antihypertensive medication, but surrogate endpoints of risk reduction for cardiovascular events and death can be measured and are associated with correcting high blood pressure.[57] Specifically for pediatric populations, quality-of-life assessments should be adapted to serve as a developmentally appropriate tool that enables participant comprehension and accurate data reporting.[58] Classical parallel study design, in which participants are randomly assigned to a study treatment arm, can lead to a statistically underpowered study in pediatric populations if there is low enrollment. Furthermore, assigning children to a less superior treatment or placebo control group raises further ethical concerns.[59] Alternative study designs can take many forms; for example, a sequential design involves an unfixed sample size in which the trial can be concluded as soon as the participant observes a clinical benefit from the treatment. This design requires a sufficient patient recruitment rate and reasonably short duration of treatment but has potential to reduce the burden of participation and require fewer overall participants.[59] Taking into consideration these challenges, the feasibility of conducting clinical studies in some or all pediatric age groups may be a severe limitation. Furthermore, companies should work to reduce and limit unnecessary exposure of pediatric populations to the risk and potential burden of clinical study participation while advancing crucial therapeutics to market in a timely manner.

Collectively, these circumstances may lead the company to instead extrapolate safety and efficacy data from reference adult populations that have completed clinical studies for the same drug indication. Quantitative tools including statistical methods, modeling, and simulation can be used to extrapolate data. These approaches are ideal for when the disease profile is similar in both adult and pediatric populations, or if key differences have been identified. Extrapolation is limited for when a disease is rare or manifests differently in pediatric populations. The ICH endorsed a draft guidance on this topic in August 2022 titled "E11A Pediatric Extrapolation"[60] that further discusses the strategies, conditions, and appropriateness of pediatric extrapolation.

As seen in Figure 2, the FDA Pediatric Study Decision Tree provides the framework for necessary studies based on the similarity of the disease progression and response to intervention between adults and children.

Figure 2: United States Food and Drug Administration Pediatric Study Decision Tree[6]



Abbreviations: ER = exposure-response; PD = pharmacodynamic; PK = pharmacokinetic.

Evaluation of Updated FDA Pediatric Drug Development Guidance

The 2023 updated FDA guidances on pediatric clinical studies have provided a centralized outline of the FDA's current thinking on how to facilitate development of safe and effective drugs, biological products, and vaccines for children in a timely manner.[1,2] The fundamental processes of drug development require at their core a priceless commodity: time. There is a collective goal among regulatory bodies and companies to reduce the amount of time between when a product is approved in adults and when it is approved in pediatric populations by streamlining the approval process while also ensuring compliance with applicable regulations. Data collected from July 1, 2017, to June 30, 2020, showed an average of approximately 6 years from the time of application approval under section 505(b)(1) of the FD&C Act or section 351(a) of the PHS Act to the inclusion of any pediatric use information in the approved product's labeling.[61] This substantial delay is a pain point the FDA has aimed to alleviate by requiring iPSP submissions to fall within 60 days following the end-of-Phase 2 meeting or another FDA-approved timeline. Success of this implemented timeframe will likely be analyzed in the next report to Congress in 2025.

There is a demand and unmet need for pediatric interventions for rare diseases. As a direct result of their rare nature, enrollment for these studies can be low, and recruitment can be slow or delayed. Special considerations should be made for these unique challenges and whether there is a need for amendments to future guidance or regulations to ensure marketing incentives for companies are obtainable within a reasonable timeline, which will promote investigation within pediatric populations for rare disease indications. There is also further work to be done regarding more vulnerable pediatric populations such as neonates and infants.

By offering opportunity for expansion of drug indications and a 6-month marketing exclusivity under BPCA, companies who may rely on patent and exclusivity protections as part of their business model may be incentivized to voluntarily complete additional pediatric studies requested by the FDA. Initiation of these voluntary studies will grow the body of literature within the proposed indication(s) and will provide pediatric-specific information on drug labels used in children. To address the current lack of available safety and efficacy data for products used in pediatric populations, industry guidance and legislature will need to continue evolving and devising incentives for companies during product development.

Conclusion

Marketing incentives and administration of WRs promote initiation of pediatric studies by drug development companies and have contributed, along with PREA requirements, to an increase in investigated and approved pediatric indications. Beginning in 2012 through October 3, 2023, there have been 56 products studied under BPCA, 437 products studied under PREA, and 44 products studied under both based on FDA Reviews of Pediatric Studies Conducted under BPCA and PREA.[62] Collectively, the FDA reports there are over 900 drugs with pediatric labeling information resulting from expansion following successful implementation of BPCA and PREA as of June 30, 2020.[61] As of September 13, 2023, there have been 160 approved drugs with a pediatric exclusivity determination, including written request, since September 27, 2007, and some of the most recent include[63]:

- Triumeq (ViiV Healthcare Company – June 7, 2023): fixed-dose combination drug (abacavir/dolutegravir/lamivudine; ABC/DTG/3TC) to treat human immunodeficiency virus-1 (HIV-1)-infected pediatric patients weighing 6 kg to less than 40 kg
- Breo Ellipta (GlaxoSmithKline – April 26, 2023): a fixed-dose combination of fluticasone furoate and vilanterol inhalation dry powder to treat asthma in children 5 to 17 years old when inhaled corticosteroids are not sufficient
- Mekinist (Novartis – February 9, 2023): trametinib tablet to treat pediatric patients with advanced relapsed/refractory malignant solid tumors with activation of the RAS/RAF/MEK signaling pathway and adolescent patients with BRAF V600 mutant-positive malignant melanoma

The regulations and legislation presented here have driven progress of pediatric drug development and provide incentive for the undertaking of clinical studies in these relatively small and previously neglected populations. Although significant progress in pediatric drug development has been observed, there is still a clear need for earlier, intentional planning. Despite the challenges discussed here, regulations under BPCA and PREA are valuable tools that will facilitate the synthesis of a reliable body of literature from which pediatric-specific labeling can be created and accurate evidence-based standards of care can be developed for pediatric populations. Continual progress can be made in this important field through regular evaluation of current processes and future implementation of more efficient and effective drug development strategies.

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