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A Systematic Review of Challenges and Opportunities in Pediatric Drug Development

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Abstract
The availability of safe, effective, and age-appropriate medications for children has been limited by specific scientific, ethical, legal, and operational challenges that pediatric drug development faces. Over the past 20 years, regulatory incentives and methodological improvements—such as pediatric extrapolation, adaptive and platform trial designs, model-informed drug development (MIDD), and the use of real-world data (RWD)—have started to address some of these gaps, but significant obstacles persist. This systematic review not only highlights new opportunities and suggestions to accelerate the development of safe and effective pediatric treatments but also summarizes research on the barriers faced in pediatric drug development. Key findings include ongoing issues related to off-label use and drug availability, difficulties in trial design and recruitment for small and diverse pediatric populations, and ethical restrictions on sampling; however, progress has been made through advances in extrapolation guidance, MIDD, innovative trial platforms, and international regulatory harmonization.

Keywords: Pediatric, Real-world data, model-informed drug development, pediatric drug development

1. Introduction

One of the world's ongoing challenges is the creation of safe and effective medications for children. Due to logistical and ethical issues, pediatric populations were historically excluded from the majority of clinical trials, which led to extensive off-label use and empirical dosing [1, 2]. Extrapolating adult data to children frequently results in suboptimal dose or unexpected side effects because pharmacokinetics (PK) and pharmacodynamics (PD) differ significantly across developmental stages [3].

Regulations such as the European Paediatric Regulation, the Best Pharmaceuticals for Children Act (BPCA), and the U.S. Pediatric Research Equity Act (PREA) have enhanced the requirements and incentives for pediatric studies during the past 20 years [4, 5]. A significant step toward the harmonization of international standards is the recent ICH E11A Guideline on Pediatric extrapolation (2024) [6].

Economic, ethical, and scientific obstacles still exist in spite of these efforts. The information on obstacles and prospects in pediatric drug development is compiled in this systematic review, which focuses on methodological, technological, and regulatory developments that can hasten the process.

2. Methods

2.1 Search strategy and data sources

Between January 2018 and March 2025, a systematic search was carried out in the following regulatory repositories: the International Council for Harmonization (ICH), the European Medicines Agency (EMA), and the United States Food and Drug Administration (FDA).

- Reports from policy and research consortia: WHO, NIH, and MRCT Center

Combinations of "pediatric drug development," "pediatric pharmacology," "model-informed drug development," "pediatric extrapolation," "PREA," "BPCA," "platform trial," and "real-world evidence" were among the search terms used.

2.2 Inclusion and exclusion criteria

Included sources were:

- Peer-reviewed reviews and original research articles
- Regulatory guidance documents (FDA, EMA, ICH)
- Consensus or position statements (2018–2025)

Single-case reports, irrelevant adult research, and grey literature lacking a scientific foundation were also excluded.

2.3 Data synthesis

Due to the variety of study types, themes were classified as opportunities and problems and examined using qualitative synthesis as opposed to meta-analysis.

3. Results

3.1 Key challenges

3.1.1 Regulatory complexity

Multinational studies are hampered by inconsistent regional requirements, despite advancements under PREA, BPCA,

and the EU Paediatric Regulation [4, 6, 7]. Because of this, pediatric labeling frequently takes several years longer than adult authorization.

3.1.2 Small and heterogeneous populations
Small sample sizes or uncommon disorders are common in pediatric indications, which lowers statistical power and lengthens trial duration [8]. Dosing and endpoint selection are made more difficult by recruiting over several developmental stages.

3.1.3 Ethical constraints and consent barriers
Parental consent and child assent must be considered in informed consent procedures. Conventional PK/PD data collection is limited by ethical constraints on blood collection, especially in newborns [9].

3.1.4 Formulation and administration limitations
Many pediatric medications lack formulations that are safe, pleasant, and age-appropriate [10]. Infants may be poisoned by excipients that are safe for adults, and manufacturing is complicated by stability issues.

3.1.5 PK/PD uncertainty across maturation
Drug exposure is changed by the ontogeny of drug-metabolizing enzymes (such as UGTs and CYP3A4). Without adequate modeling, extrapolation from adults runs the danger of toxicity or treatment failure [3, 11].

3.1.6 Endpoint and trial design issues
There are few validated pediatric objectives, and surrogate markers frequently don't accurately reflect developmental outcomes like growth or cognition [12]. For chronic illnesses, recruitment and retention are especially difficult.

3.1.7 Economic disincentives
Investment is discouraged despite substantial demand because pediatric formulations and rare disorders have poor commercial returns [13].

3.2 Opportunities and innovations
3.2.1 Model-informed drug development (MIDD)
MIDD incorporates population PK/PD modeling and PBPK to optimize design, minimize trial size, and guide dosage [14]. Model-based explanations for pediatric dosage and trial waivers are becoming more and more accepted by regulatory bodies [15].

3.2.2 Pediatric extrapolation (ICH E11A)
When disease etiology and exposure-response are similar, the 2024 ICH E11A guideline formalizes extrapolation frameworks and permits partial or complete reliance on adult efficacy data [6]. This strategy reduces needless pediatric trials.

3.2.3 Adaptive and platform trial designs
Efficiency is increased in small pediatric populations by the use of shared controls and the simultaneous evaluation of numerous treatments made possible by innovative trial infrastructures (e.g., Bayesian, adaptive, and master protocols) [16, 17].

3.2.4 Real-world data (RWD) and real-world evidence (RWE)
High-quality RWD from electronic health records and registries can act as external controls and provide information about long-term safety [18]. RWD is increasingly seen by regulators as a supplement to or, in certain situations, a replacement for traditional evidence.

3.2.5 Micro-sampling and minimally invasive assays
Volumetric absorptive microsampling and dried blood spots lessen sample load and enhance the collection of PK data in neonates [19].

3.2.6 International collaboration and harmonization
Study plan requirements are being aligned and redundancy is being reduced because of global harmonization under ICH and enhanced collaboration between FDA and EMA [20].

3.2.7 Incentives and public–private partnerships
Infrastructure and shared data resources are supported by collaborative efforts like the Global Pediatric Clinical Trials Network and NIH-sponsored consortia, which de-risk development for uncommon pediatric diseases [21, 22].

4. Discussion
Evidence-based modeling and harmonized regulation are replacing empiricism in pediatric medication development. There are now reliable substitutes for conventional randomized trials at the nexus of computational pharmacology and regulatory innovation. Extrapolation and the use of MIDD enable logical data borrowing while maintaining patient safety [6, 14].

These possibilities aren't always taken advantage of, though. Implementation is still being delayed by differences in data standards, expertise, and regulatory interpretation. Furthermore, sustained funding and a lack of experience in pediatric formulation continue to be major obstacles [10, 13].

In terms of ethics, developments in decentralized trials and micro-sampling are assisting in balancing scientific requirement with child protection. However, maintaining progress requires ongoing communication between regulators, business, physicians, and patient families.

5. Recommendations
1. To guide dose selection and sampling tactics, incorporate MIDD early in pediatric development programs [14, 15].
2. When the pathophysiology of adults and children is similar, use extrapolation frameworks (ICH E11A) [6].
3. Use platform/adaptive designs for uncommon pediatric illnesses [16, 17].
4. Invest in formulation research to guarantee safe, adaptable, and palatable dose forms [10].
5. To simplify pediatric research planning, improve regulatory harmonization between the FDA, EMA, and PMDA [20].
6. Increase RWD infrastructure to provide safety assessment and long-term monitoring [18].
7. Expand financing and incentives for neglected illnesses and pediatric-focused research [21, 22].

6. Limitations

This review did not conduct a quantitative meta-analysis; instead, it summarized current research and recommendations. Unpublished industry statistics and certain regional policies were not available. Parts of this summary may be superseded by rapidly evolving guidelines (e.g., ICH E11A implementation); therefore, continued regulatory monitoring is advised.

7. Conclusion

Although pediatric medication research is about to enter a transformational age, it is nevertheless complicated from a scientific and ethical standpoint. The generation of pediatric data is changing due to methodological advancements, including MIDD, PBPK modeling, extrapolation, and adaptive trial designs, as well as unified regulatory frameworks and cooperative networks.

It will take consistent funding, cross-sector cooperation, and international regulatory alignment to guarantee that every child has fair access to safe, effective, and suitably tested medications.

Conflict of Interest

Not available

Financial Support

Not available

References

1. Domingues C, *et al*. Pediatric drug development: reviewing challenges and opportunities by tracking innovative therapies. Ther Innov Regul Sci. 2023.
2. Turner MA, *et al*. Unlicensed and off-label drug use in children: implications for safety and ethics. Br J Clin Pharmacol. 2022.
3. Smits A, *et al*. Current knowledge, challenges and innovations in pediatric pharmacotherapy. Br J Clin Pharmacol. 2021.
4. U.S. Food and Drug Administration. Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA) Reports. 2024.
5. European Medicines Agency. EU Paediatric Regulation 1901/2006 Review Report. 2023.
6. International Council for Harmonisation (ICH). Guideline E11A: Pediatric extrapolation. Geneva: ICH; 2024.
7. Rose K, *et al*. Global harmonization challenges in pediatric medicines development. Paediatr Drugs. 2021.
8. Laughon MM, *et al*. Small sample challenges in pediatric clinical pharmacology. Clin Pharmacol Ther. 2020.
9. Caldwell PH, *et al*. Ethics and consent in pediatric clinical trials. Pediatrics. 2022.
10. Kapoor DU, *et al*. Pediatric drug delivery challenges: Enhancing compliance. Int J Pharm Sci Rev Res. 2024.
11. Johnson TN. Ontogeny of drug metabolism and implications for pediatric dosing. Drug Metab Dispos. 2023.
12. O'Hara K, *et al*. Pediatric clinical trial endpoints: current gaps and development strategies. Clin Trials. 2021.
13. Sinha Y, *et al*. Incentives for pediatric drug development: balancing need and feasibility. Orphanet J Rare Dis. 2022.
14. Krishna R, *et al*. State-of-the-art on model-informed drug development. Clin Pharmacol Ther. 2023.
15. FDA. Guidance for Industry: Model-Informed Drug Development Approaches. Silver Spring: FDA; 2023.
16. MRCT Center. Advancing Pediatric Platform Trials — Workshop Report. 2025.
17. Berry SM, *et al*. Adaptive platform trials in small populations: lessons for pediatric research. Stat Biopharm Res. 2024.
18. EMA-FDA Joint Workshop. Real-world data and evidence in pediatric medicines development. 2023.
19. Patel P, *et al*. Microsampling and pediatric pharmacokinetic studies: a paradigm shift. J Clin Pharmacol. 2022.
20. EMA-FDA-ICH. Pediatric strategy alignment report. 2024.
21. NIH Pediatric Trials Network (PTN). Annual Progress Report. 2024.
22. Global Pediatric Clinical Trials Network. Collaborative research roadmap. 2023.

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