

Challenges and opportunities in the development of medical therapies for pediatric populations and the role of extrapolation



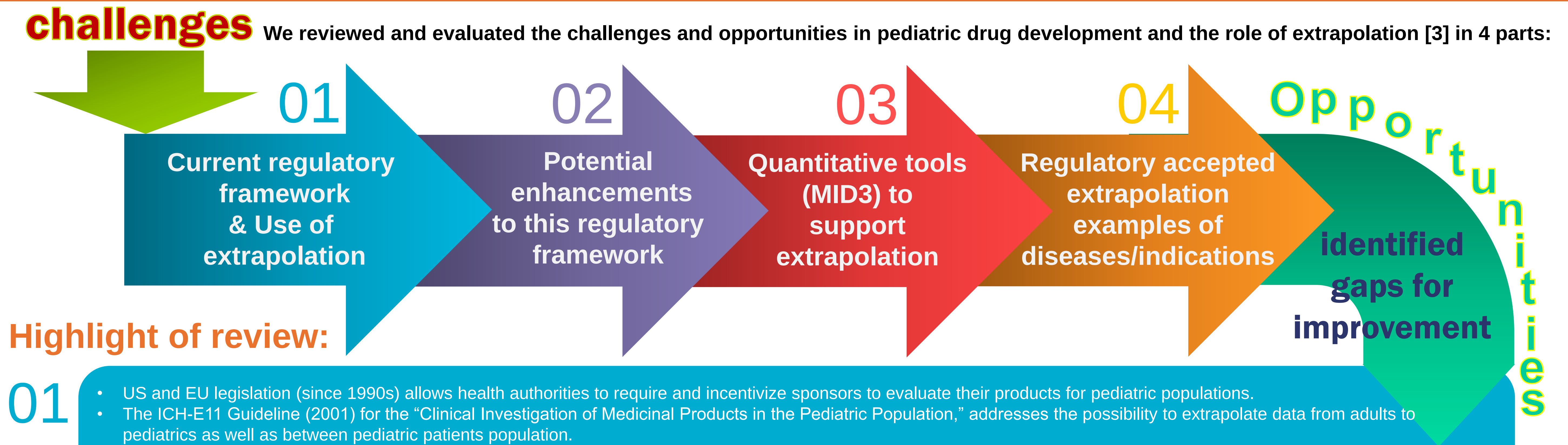
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Objective

Children deserve medical therapies that have been properly evaluated for safety and efficacy and formulated specifically to meet their needs. With the release of pediatric regulations in the European Union (EU) and the United States (US), there are new opportunities for strategies that can provide robust evidence for use of medicinal products in children [1, 2]. Use of innovative approaches such as extrapolation from a reference population is now being applied to pediatric drug development – expediting articulation of dose rationales and/or replacing real clinical trials in children. The IQ consortium - CPLG PWG’s objective is to improve drug development in children by sharing knowledge amongst industry and regulators regarding their experiences related to pediatric product development process.

Method and Result



Highlight of review:

01

- US and EU legislation (since 1990s) allows health authorities to require and incentivize sponsors to evaluate their products for pediatric populations.
- The ICH-E11 Guideline (2001) for the “Clinical Investigation of Medicinal Products in the Pediatric Population,” addresses the possibility to extrapolate data from adults to pediatrics as well as between pediatric patients population.
- The E11 was recently complemented by an addendum to include utility of modeling and simulation (M&S) for extrapolation and clinical trial methodology to optimize pediatric drug development by maximizing the use of prior/pre-existing knowledge.
- FDA draft guidance (2014) include the principles of extrapolation and a decision tree (the Pediatric Study Planning and Extrapolation Algorithm)
- EMA Pediatric Extrapolation Reflection Paper (2017) proposes a quantitative framework for extrapolation of data between source (e.g. adults and/or children) and target population (e.g. other pediatric population).

02

- Development of disease-specific regulatory guidelines allows established knowledge of disease similarity and intervention–response data to could provide more focused guidance, e.g. the recent guidance on Partial Onset Seizures (POS) recently released by the FDA [4]
- Context-specific considerations of the source data available for extrapolation and special provisions regarding therapies targeting the special needs of neonates.
- Any new guidance should consider whether it is appropriate to use extrapolation in order to address safety questions (potentially different for certain age strata) and a definition of the acceptable minimum level of uncertainty/risk in pediatric safety assessment.

03

- Robust quantitative framework (e.g. MID3) [5] is essential to support extrapolation concept/plan/framework (e.g. assessments of disease similarity and exposure-response similarity)
- Various types of modelling including systems pharmacology modelling, empirical modelling and meta-analysis and the value and importance of read-world evidence (RWE) may be considered.

MID3 tools	Example benefit to support extrapolation plan
Key questions	Allows identification of knowledge gaps in terms of differences in efficacy, safety and PK between adult and pediatric population.
Assumptions	Allows transparency in planning and documentation of assumption setting and evaluations. Provides justification/clarity of important assumption that extrapolation rationale for internal decision and regulatory submission.
Modelling approaches	The key questions, the system understanding and the amount of data available drive the choices for the modeling approaches available. Some approaches are fit-for-purpose applications (e.g., empirical approaches) others are meant for more general applications (e.g., mechanistic, system pharmacology).
Documentations	Enables the reviewer from regulatory bodies to assess the appropriateness of activities, evidence and outcome.

04

- Application of extrapolation for 3 situations with a focus on prior knowledge, assumptions, extrapolation rationale and impact in various diseases areas (POS, pain, gastroesophageal reflux disease, type 2 diabetes mellitus and cancer):
 - (1) Similar disease & similar exposure-responses (ER) relationship
 - (2) Similar disease by diagnostic criteria & different ER relationship
 - (3) Different disease & ER relationship to compare the strength & limitation.
- Example below is for POS:

Example	Data Available	Assumption	Extrapolation rationale	Extrapolation impact
Partial onset-seizure (POS) <i>Situation (1) Similar disease & similar ER relationship</i>	Safety and efficacy studies: - Total of 30 trials: as adjunctive therapy in focal seizures were analyzed: 24 trials in adults and 6 in children (2–18 yrs) - Randomized, double-blind, placebo-controlled, partly crossover. After analysis of those 30 trials - Other AEDs (antiepileptic drug) received approval in adults and adolescents (>12 yrs) - Safety and efficacy based on three 3 randomized, double-blind, placebo-controlled, multicenter trials in adult and pediatric patients (n=72)	- Similarities of disease in children (2–18 yrs) and adults in terms of seizure control: Age of onset, Etiology, Pathophysiology - PEACE/DNP: Clinical Expertise, Similarity in Pathophysiology and E-R relationship - Similarities of clinical response to treatment: Clinical endpoint and Response rate. - Different from adults: Infants 1 month to 2 yrs and Neonates	Partial-onset seizure is an exception with similarities in the disease profile and therapeutic responses in epilepsy syndromes comparing adults and pediatric patients	Extrapolating from adult with partial-onset seizure (source population) would avoid unnecessary trials in the target population: Systematic review supports the extrapolation of efficacy results in adults to predict a similar adjunctive treatment response in patients 4 to 18- yrs Efficacy RCT could therefore be performed in infants only (1 month to 2 ys)

Conclusion

There is growing experience of quantitative approaches guiding the appropriate use of extrapolation in the development of new therapies for pediatric populations. However, better alignment of regulatory authorities on the definition of extrapolation and agreement on acceptable uses is still warranted. The successful application of extrapolation for pediatric patients with POS highlights the importance of quantitative approaches and knowledge-sharing/collaboration among stakeholders (sponsors, investigators, and regulators) to reach a mutual understanding about similarities in pathophysiology and responses to therapy. Educating others about what pediatric extrapolation and types of quantitative approaches that can be used may expedite drug development, improve care, and promote collaborations or partnerships to better address improve the way the needs of pediatric patients are addressed in the future.