Ethical and Scientific Considerations for the Use of Pediatric Extrapolation

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Disclosure Statement

- I have no financial interests or relationships to disclose

- The views presented here are personal and do not necessarily represent the views of FDA

Basic Ethical Framework in Pediatrics

1. Children should not be enrolled in a clinical trial unless their participation is necessary to answer an important scientific and/or public health question directly relevant to the health and welfare of children
2. Absent a prospect of direct clinical benefit, the risks to which children are exposed must be “low”
3. Children should not be placed at a disadvantage by being enrolled in a clinical trial
4. Vulnerable populations unable to consent (including children) should have a suitable proxy to consent for them

National Commission. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: U.S. Government Printing Office; 1978

Principle of Scientific Necessity

Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children

- Equitable selection [21 CFR 56.111(a)(1) and (b)]
  - Subjects capable of informed consent (i.e., adults) should be enrolled prior to children
  - Do not enroll children unless essential (i.e., no other option, whether animal or adult human)
- Minimize Risks [21 CFR 56.111(a)(1)]
  - Eliminate any research procedures (as unnecessary) that do not contribute to scientific objective

Scientific Necessity
Practical Application

- Determine the type and timing of clinical trials required for establishing “safe and effective” pediatric use of FDA-regulated products
- “targeted generation of evidence should help to ensure that children only participate in clinical trials with specific objectives that further the scientific understanding of a medicinal product for use in children and, address the requirements for regulatory decision-making”*

*EMA Reflection Paper on Use of Extrapolation (October 7, 2018)

Research Risk

Adult and Pediatric Trials

- Institutional Review Board (IRB) approval of research is generally justified if:
  - risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result [21 CFR 56.111(a)(2)]
- For children
  - a limit exists to the risk that knowledge alone can justify*

*National Commission, Report on Research Involving Children (1978)

Additional Safeguards for Children in Clinical Investigations

21 CFR Subpart D

- Research involving children must either
  - be restricted to “minimal” risk or a “minor increase over minimal risk” absent a potential for direct benefit to the enrolled child [21 CFR 50.51/50.53] OR
  - present risks that are justified by the “prospect of direct benefit” to the child; the balance of which is at least as favorable as any available alternatives [21 CFR 50.52]

FDA Evidentiary Standard

- For product approval, **substantial evidence of effectiveness** for treatment of the proposed indication must be demonstrated (21 CFR 314.50)
  - FDA generally interprets the efficacy standard to consist of two adequate and well-controlled trials to independently substantiate clinical benefit in affected population
  - "FDA is required to exercise scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards." (21 CFR 314.105)
- Pediatric drug development programs and approvals are held to the same standards as adults
  - However, unique considerations may include:
    - Feasibility
    - Vulnerable population

Efficacy Endpoints to Support Drug Approval

- Clinical outcomes
  - Direct measure of how a patient feels, functions, or survives
  - Improvement or delay in progression of clinically meaningful aspects of the disease
- Surrogate endpoints
  - A substitute for how a patient feels, functions, or survives
  - Surrogates reasonably likely to predict clinical benefit
  - Accelerated approval
    - Requires additional trials post-marketing to confirm clinical benefit

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, FDA Guidance for Industry (December 2019)

Extrapolation

General Concepts

- Concept:
  - To extend existing relevant and reliable data from previous studies and/or trials
  - To make inferences to another subgroup of the population, or condition or product
  - To reduce the amount of data needed to be collected to reach conclusions
- Existing information about the disease, the drug pharmacology and the clinical response to treatment should be collated from all data sources and analyzed to identify data gaps

EMA Reflection Paper on Use of Extrapolation (October 7, 2018)

Pediatric Extrapolation

Historical Context

Pediatric Labeling Rule (1994)

- If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults
- Pharmacokinetic (PK) data to allow determination of an appropriate pediatric dose and pediatric safety information may be required, as appropriate

Pediatric Research Equity Act (2003)

"A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another…."

Pediatric Extrapolation

Fundamentals

- Appropriately designed adult trials may help build a foundation for extrapolation of efficacy to pediatrics
- Relies on evidence-based assumptions that reference adult and/or pediatric data
- Dosing and safety generally cannot be fully extrapolated
- Approaches to pediatric extrapolation are evolving

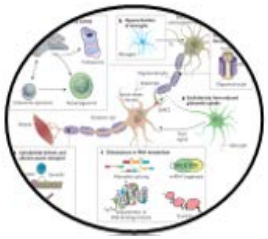
Dunne et al, *Pediatrics* 2011

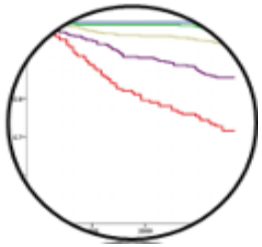
Pediatric Extrapolation

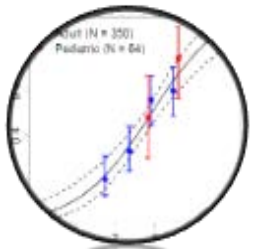
Evaluation of Sufficient Similarity

Consider age/maturational differences in:

Disease	Response to Treatment	Pharmacology
• Pathophysiology • Manifestations • Progression • Diagnostic criteria • Clinical management	• Endpoints • Response to other therapies/products in class	• Absorption, Distribution, Metabolism, Elimination • Mechanism of action • Ontogeny of targets • Pharmacodynamic effects (exposure-response) • Toxicity







EMA Reflection Paper on Use of Extrapolation (October 7, 2018)

Pediatric Extrapolation

Questions to Consider

Existing Data?

- What is the strength of the evidence to support similarity of:
  - disease and response to treatment?
  - exposure-response?
- What are the uncertainties and/or limitations in the existing data?
- What additional adult and/or pediatric data could be leveraged?

New Data?

What additional data are needed? For example, information from:

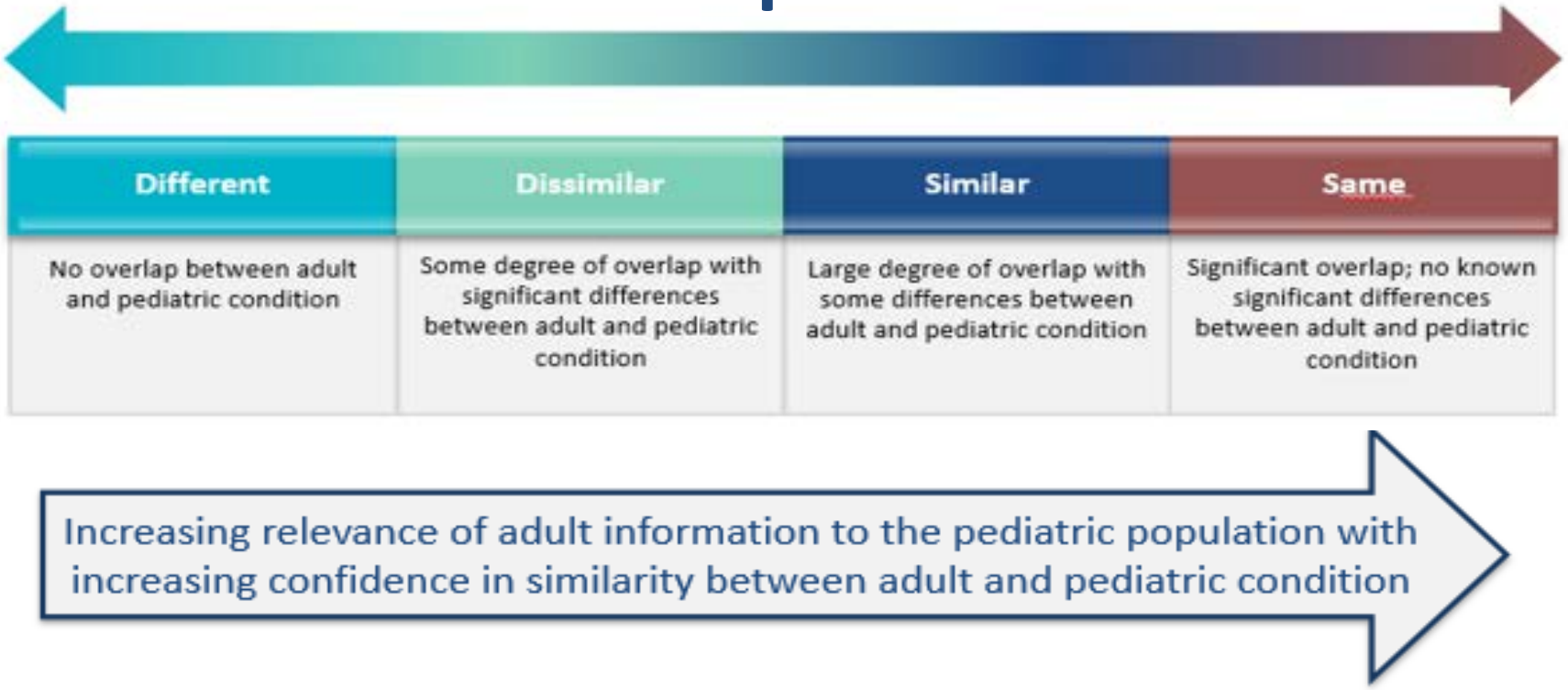
- modelling and simulation
- animal studies
- adult trials

How?

What is the optimal trial design(s) to obtain only the data needed to support approval?

Pediatric Extrapolation

Disease and Response Continuum



Data needed based on similarity of disease and response:

Graphics based on EMA Reflection Paper on Use of Extrapolation (October 7, 2018)

Pediatric Extrapolation

Data Needed to Support Dose & Safety

- Dosing:
  - Pharmacokinetic (PK) studies may be needed to identify dosing that results in exposure range or distribution comparable to those observed in reference population (usually adults)
  - Modelling and simulation can explore pediatric dosing strategies to achieve a target range of exposures. These predictions may need to be confirmed in a pediatric trial
- Safety
  - Developing organ systems may respond differently to drug exposure than mature adult systems
  - Unique safety signals may be identified in children
  - Children may have increased susceptibility to observed safety signal in adults

FDA Scientific Workshop 2009

Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation

- Analgesic trials pose unique scientific, ethical, and practical challenges in pediatrics
- For μ-opioids, local anesthetics, NSAIDs, and acetaminophen:
  - Biological, empirical, and experiential data are adequate to justify extrapolation of efficacy data from adult trials for acute pain to children ≥ 2 years
  - Efficacy data should be collected in patients < 2 years
  - Pharmacokinetics (PK), dose response, and safety should be evaluated in all pediatric patients

Berde et al. *Pediatrics* 2012

Summary

- We have a responsibility to leverage existing data to avoid exposing children to unnecessary research
- Adult clinical trials should be designed to support extrapolation of adult results to children, so children are not exposed to unnecessary or overly burdensome clinical trials
- Pediatric extrapolation
  - relies on a series of evidence-based assumptions on whether a disease course, response to therapy and drug pharmacology are sufficiently similar between adults and children
  - is an approach to improve efficiency and success of pediatric drug development programs and reduce burden to children
- Additional strategies such as adaptive study designs, modeling and simulation and Bayesian approaches may streamline pediatric product development and should be considered

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