Pediatric Drug Development: Challenges and Opportunities in Pediatric Extrapolation

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Disclosure Statement

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

U.S. Evidentiary Standard for Approval

- For approval, pediatric product development is held to same evidentiary standard as adult product development:
- A product approved for children must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease
- Evidence of effectiveness [PHS Act, 505(d)]
  - Evidence consisting of adequate and well –controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling
- Adequate safety information must be included in the application to allow for appropriate risk benefit analysis [FD&C 505(d)(1)]

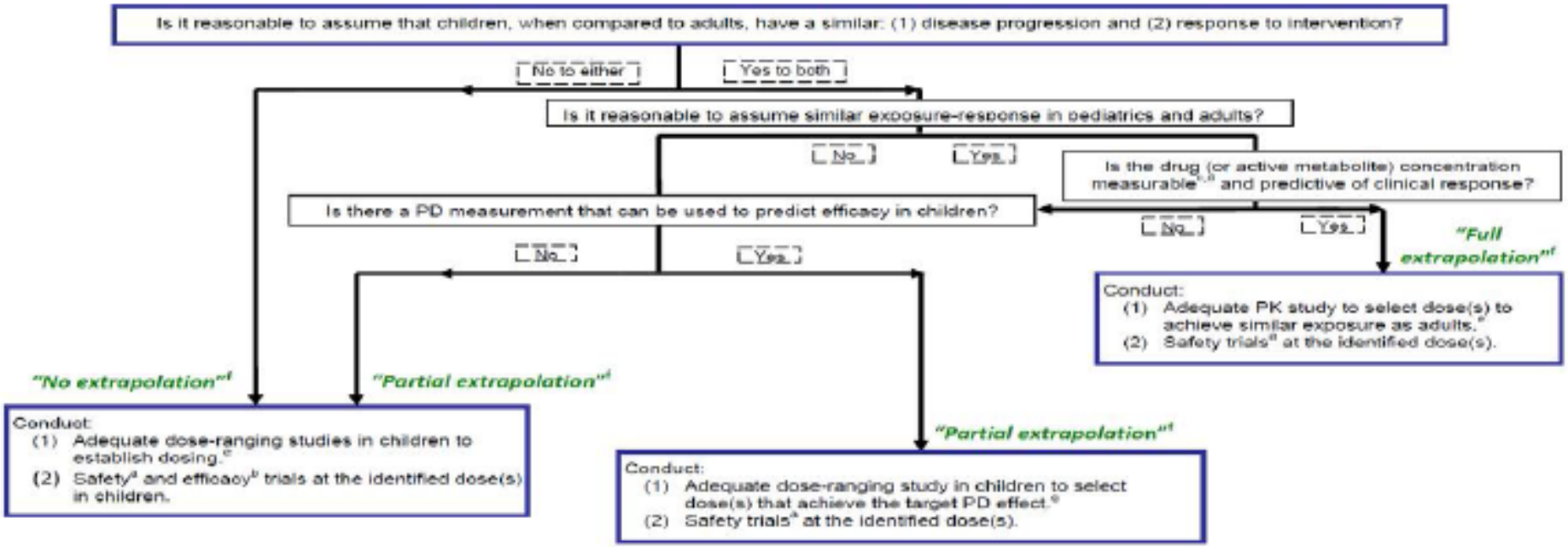
Special Considerations for Pediatric Product Development

- Ethical considerations
  - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
  - Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be "low"
  - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
  - Ethical considerations do play a role in the need to correctly apply pediatric extrapolation
- Feasibility considerations
  - The prevalence and/or incidence of a condition is generally much lower compared to adult populations
  - Feasibility, by itself, is not a scientific justification for use of extrapolation

Pediatric Extrapolation

- 1994: Final Regulation: Pediatric Labeling Rule
- "A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted"
- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  - The course of the disease is sufficiently similar
  - The response to therapy is sufficiently similar
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

FDA Draft Guidance: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, December 2014

Extrapolation framework table

			Pharmacology Drug disposition & effect	Disease manifestation & progression	Clinical response to treatment Efficacy & safety
SOURCE POULATION Adults and/or paediatric	Extrapolation concept	Mechanisms	Age-related differences in - ADME - mode of action - PD effects (E-R) - toxicity	- Age-related differences in - aetiology - pathophysiology - manifestation - progression - indicators	Age-related - differences, - applicability, - validation of efficacy & safety endpoints
		Quantitative evidence	PB-PK/PD models Pop-PK/PD models Covariates: - age, maturation, etc - disease, comorbidity,	Quantitative synthesis of natural disease data Disease progression models Covariates: - age - disease types, severity - comorbidity	Quantitative synthesis or meta-analysis of treatment data Disease response models Covariates: - age - disease types, severity - comorbidity
			➢ existing data ➢ progressive input of emerging data		
TARGET POPULATION Children, different paediatric subgroups		Prediction	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety per paediatric subgroup	Describe/predict differences in natural course of disease progression by paediatric subgroup	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by paediatric subgroup
			➢ refine predictions using emerging data		
	Extrapolation plan		PK studies or PK/PD studies needed for confirmation of doses in target population	Epidemiological data - natural disease course - SOC treatment in target population	- Design of clinical studies - Sample size(s) required in target population to conclude on benefit-risk balance
	Validation & Extrapolation		Validate - modelling approaches - modelling assumptions - confirm predicted differences in PK and PD Establish appropriate doses in the target population	Confirm predicted differences in disease progression Conclude on disease progression in target population	Confirm predicted differences in clinical response Conclude on positive benefit-risk in target population
			➢ alternatively, adapt extrapolation concept and plan		
	Further validation		PK/PD data from - phase III trials - post MA studies	Epidemiological data Other drug developments	Post MA studies Prospective meta-analyses Pharmacoepidemiological data Other drug developments

EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics, October, 2017

Assessment of Disease Similarity and Response to Intervention

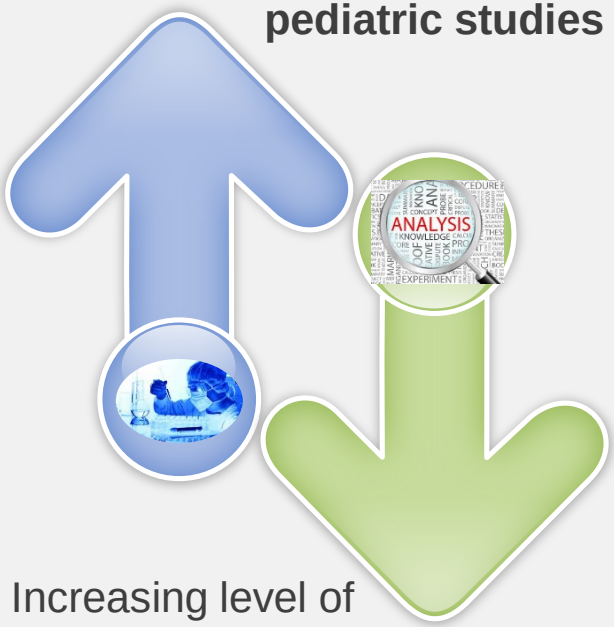
- The assessment is not a simple “yes or no”
- Quantitative assessment of differences between target and source population
  - Evidence of common pathophysiology, natural history
  - Similarity in response as assessed by similar endpoints, mode of action, or biological pathway, experience with drugs in the same therapeutic class
- What assumptions or uncertainties exist in this assessment
  - Quantity of evidence
  - Quality of evidence
- Degree of confidence in similarity will affect the information that will need to be collected to support efficacy

Approaches Pediatric Trial Design

- Trial should be designed to fill gaps in knowledge
  - Amount of information needed will be based on the confidence in assumptions about disease similarity and response to intervention
- Modeling and Simulation
- Innovative Statistical Analyses including Bayesian Statistics
  - Make use of, or borrow, information on adult patients in pediatric trials
- Confidence in both of these approaches depends on multiple factors
  - Quality and quantity of data used
  - Accuracy of assumptions made
- Availability of pediatric-specific biomarkers and endpoints may also affect clinical trial design
- Availability of patients, existing therapies, and operational issues may also affect trial design

Extrapolation approaches in pediatric programs

Increasing level of **evidence required from pediatric studies**



Increasing level of **confidence in similarity of disease/response**

~60% Pediatric Programs
require at least 1 adequate, well-controlled efficacy trial (clinical or surrogate endpoint)

1 or more adequate-well controlled studies powered on a clinically meaningful endpoint
Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, polyarticular JIA (pJIA), bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial seizures (<4 y/o), respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.

1 or more adequate-well controlled studies powered on a surrogate endpoint
Diabetes, anemia, idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.

Controlled study without formal statistical power
Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.

Descriptive efficacy study without concurrent control
Plaque psoriasis, Neurogenic detrusor over-activity, pJIA (NSAIDs), etc.

Small dose-ranging studies (randomization to multiple dose levels)
Sedation, ulcerative colitis, Crohn's, etc.

Small PK/PD studies (single dose level matching adult exposures)
HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension,

PK/safety only (single dose level matching adult exposures)
gastroesophageal reflux disease, bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

List partially adapted from Dunne et al. *Pediatrics* 2011

Summary

- Pediatric extrapolation can be used to maximize the efficiency of pediatric product development while maintaining important regulatory standards for approval
- Pediatric extrapolation has matured over the last 20 years.
- Increases in understanding of disease mechanisms and progression have been an important benefit from pediatric extrapolation
- FDA continues to review assumptions about the acceptability of pediatric extrapolation approaches based on new knowledge gained
- Advances in understanding of basic pathophysiology and natural history are critically important

Regulatory expectations

- No standard, harmonized regulatory “recipe”
- Scientific understanding decreases uncertainty
  - Development of evidence leading to better scientific understanding requires collaboration
- Innovative methodologies can be leveraged and examples include:
  - Modelling and simulation to identify appropriate dosing or patient populations for study
  - Bayesian strategies to provide more structured approach to statistical analyses
  - Big Data to improve on the quantity (and quality?) of data used to make assumptions
  - Pediatric specific biomarkers and endpoints
  - Master protocols, shared control groups, external comparator groups
- Collaboration and common scientific approach
  - Requires commitment of the entire pediatric community to address this issue

Goals for Today

- Increase general understanding of challenges and opportunities in the application of pediatric extrapolation in current pediatric therapeutics development
  - Pediatric Oncology
  - Pediatric Type 2 Diabetes
- Use knowledge gained today to increase the efficiency of pediatric therapeutics development

Thank You