Regulatory interactions: Expectations on extrapolation approaches

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Disclosure Statement

- I am employed by the US Food and Drug Administration and 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.

Pediatric Drug Development: General Principles

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2000

U.S. Pediatric Drug Development Laws

- Best Pharmaceuticals for Children Act (BPCA)
  - Section 505A of the Federal Food, Drug , and Cosmetic Act
  - Provides a financial incentive to companies to **voluntarily** conduct pediatric studies
  - FDA and the National Institutes of Health partner to obtain information to support labeling of products used in pediatric patients (Section 409I of the Public Health Service Act)
- Pediatric Research Equity Act (PREA)
  - Section 505B of the Federal Food, Drug , and Cosmetic Act
  - **Requires** companies to assess safety and effectiveness of certain products in pediatric patients

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

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

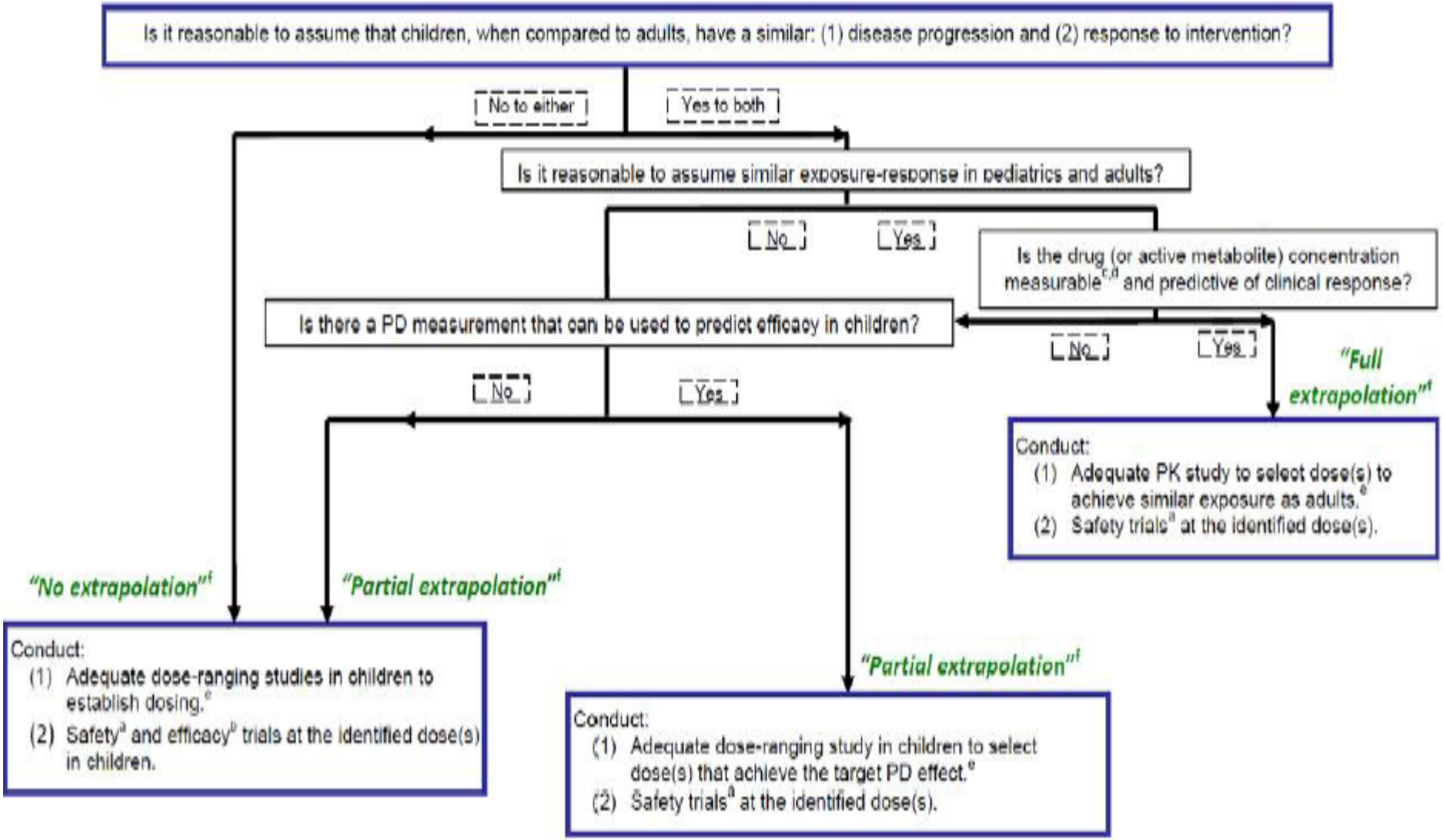
Pediatric Extrapolation

- 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

Summary of Approaches to Extrapolation 1998-2008

Extrapolation	Supportive Evidence Requested From Pediatric Studies	Products n/N (%)	New or Expanded Indication
None	Two adequate, well-controlled, efficacy and safety trials plus PK data.	19/166 (11)	7/19 (37)
	Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial	Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.	67/166 (40)	35/67 (52)
	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.	20/166 (12)	15/20 (75)
	Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.	26/166 (16)	19/26 (73)
Complete	PK and safety data.	10/166 (6)	9/10 (90)
	Safety data only.	14/166 (8)	6/14 (43)

Pediatric Study Planning & Extrapolation Algorithm



Successful Approach: Pediatric Seizures

- At least one adequate and well controlled trial required for adjunctive therapies for pediatric partial onset seizures (POS) 4-12 years of age
  - Full extrapolation in pediatric patients > 12 years of age is acceptable
- Critical Path Institute funded project to evaluate acceptability of extrapolation of efficacy for adjunctive therapies for pediatric partial onset seizures (POS) in patients 4-12 years of age
  - Food and Drug Administration (FDA) led initiative in collaboration with the University of Maryland and the Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE)

Successful Approach: Pediatric Seizures

- Data reviewed for several antiepileptic drugs approved in U.S. for treatment of POS in children
  - Oxcarbazepine, Perampanel, Levetiracetam, Topiramate, Lamotrigine, Gabapentin
- Doses use in clinical trials led to similar reduction in seizure frequency in adults and children
- Concentrations at approved doses similar between adults and children
- Exposure response assessed using agreed upon methodology demonstrated similarity between adults and children
- FDA now supports the use of full extrapolation for evaluation of anti-epileptic drugs indicated as adjunctive treatment for POS for pediatric patients down to 4 years of age

Not so successful approaches

- Adolescent Migraine Studies
  - Review of data submitted for drugs studied for NBD in pediatric patients between 1999-2011
  - Included Rizatriptan, Almotriptan, Sumatriptan, Zolmitriptan, and Eletriptan
  - Only Almotriptan and Rizatriptan were successful in meeting statistically significant reduction in headache at 2 hours
  - High placebo response in pediatric clinical studies (53-57.5%) compared to adult clinical trials (15-42%)
  - One successful study (Rizatriptan) allowed for 2-step randomization (allowing for study only of placebo patients who continued to have headache after 2 hours)
  - PK parameters were statistically comparable between adolescents and adults
- Studies failed to consider differences natural history of resolution of headache between adults and adolescents

Sun, et. al, JAMA Pediatr, 2013

Not so successful approaches

- Pediatric neurogenic bladder dysfunction (NBD) studies
  - Review of data submitted for 4 drugs studied for NBD in pediatric patients
  - Oxybutinin, Tolterodine, Tamsulosin, Alfulzosin
  - Only Oxybutinin demonstrated efficacy
  - Doses targeted for NBP studies based on exposures in adult trials for overactive bladder except for Oxybutinin
  - All studies except Oxybutinin used doses with exposures that were less than adult exposures (based on AUC)
  - Oxybutinin clinical trials allowed for dose titration and only 12.5% of patients received 5-<10 mg/day, the recommended starting dose for OAB in adults
- Failure to consider whether OAB and NBD were similar enough to allow for dose selection based on matching of exposures

Momper, et. al, J Clin Pharmacol., 2014

Follow-up on FDA experience with Pediatric Extrapolation

- Recent analysis of products with new pediatric labeling between 3/1/2009 – 12/31/2014; N=166
- Compared to FDA pediatric extrapolation publication (Dunn, et al.) with new pediatric labeling between 2/1/1998 – 2/2009; N=161
- Preliminary findings include an almost 2-fold number of products were designated “NO extrapolation”
- Final results to be published
- Possible reasons and examples for the pattern shifting:
  - Failures when a single adequate and well-controlled trial was thought to be sufficient
  - Inability to identify an exposure response relationship in the overall pediatric population or in a age subgroup
  - More studies difficult to study in children are now being required or requested

EMA reflection paper

- Extrapolation can only be justified when it is the result of a careful and explicit scientific process that eventually gives rise to knowledge gain, rather than an intuitive ***leap of faith*** that may undermine the possibility of further scientific knowledge generation
  - How far a leap is based on the degree of uncertainty or the degree of skepticism

EMA Reflection Paper

- Quantitative assessment of differences between target and source population
  - Mechanistic vs. Empiric Approach
- These approaches are not mutually exclusive
- Mechanistic approach relies on data that support similarities or differences between target and source population
- Empiric approach relies on establishment of mathematical formula or models that support similarities or differences between the target and source population
  - Modeling and simulation and statistical approaches

Empirical Approaches

- 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
- How much uncertainty is acceptable?

Questions raised from failures

- Easy to accept that assumptions used to support the extrapolation concept were correct when studies are successful
- What about failed studies?
- How does one differentiate between
  - Incorrect empiric assumptions leading to a failed study
  - Incorrect mechanistic assumptions leading to a failed study
  - A failed study because of poor study conduct
  - A failed study because the drug “truly” does not work
- How does the additional knowledge, if the new knowledge includes failed studies, change the empirical approach?
- Until there is a clear path to assess the accuracy of assumptions, confirmatory data will need to be collected

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 and learning has lead to advances in extrapolation (e.g., POS)
- FDA continues to review assumptions about the acceptability of pediatric extrapolation approaches based on new knowledge gained
- Empiric strategies can improve efficiency and decrease the number of patients required but may lead to incorrect conclusions if not confirmed with clinical data
- Advances in understanding of basic pathophysiology and natural history are needed

Regulatory expectations?

- No standard, harmonized regulatory “recipe”
- Common scientific approach
- Both mechanistic and empiric approaches may fall short because there may simply be a lack of information
  - This lack of information leads to increases in uncertainty
- Scientific understanding decreases uncertainty
  - Development of an evidence leading to better scientific understanding requires collaboration
- Collaboration
  - Requires commitment of the entire pediatric community to address this issue

Thank You