What Constitutes a Meaningful Endpoint for Establishing Exposure-Response Similarity Between Adults and Pediatric Patients?

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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

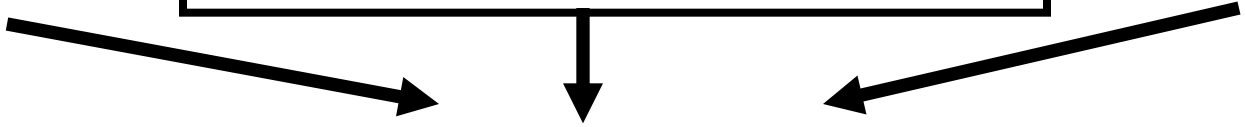
Pediatric Product Development: The Historical Problem

Acknowledged different drug responses, toxicity, and metabolism in adults versus children

Discouraged the study of drugs in children

- Concerns related to ethical issues
- Fears of harming children
- Perceived increased liability of testing drugs in children

Lacked an incentive for drug companies to conduct pediatric trials



Choices for Pediatric Practitioners

- Not treat children with potentially beneficial medications because they are not approved for use in children
- Treat with medications based on adult studies with limited or anecdotal pediatric experience (off-label use)

Pediatric Extrapolation

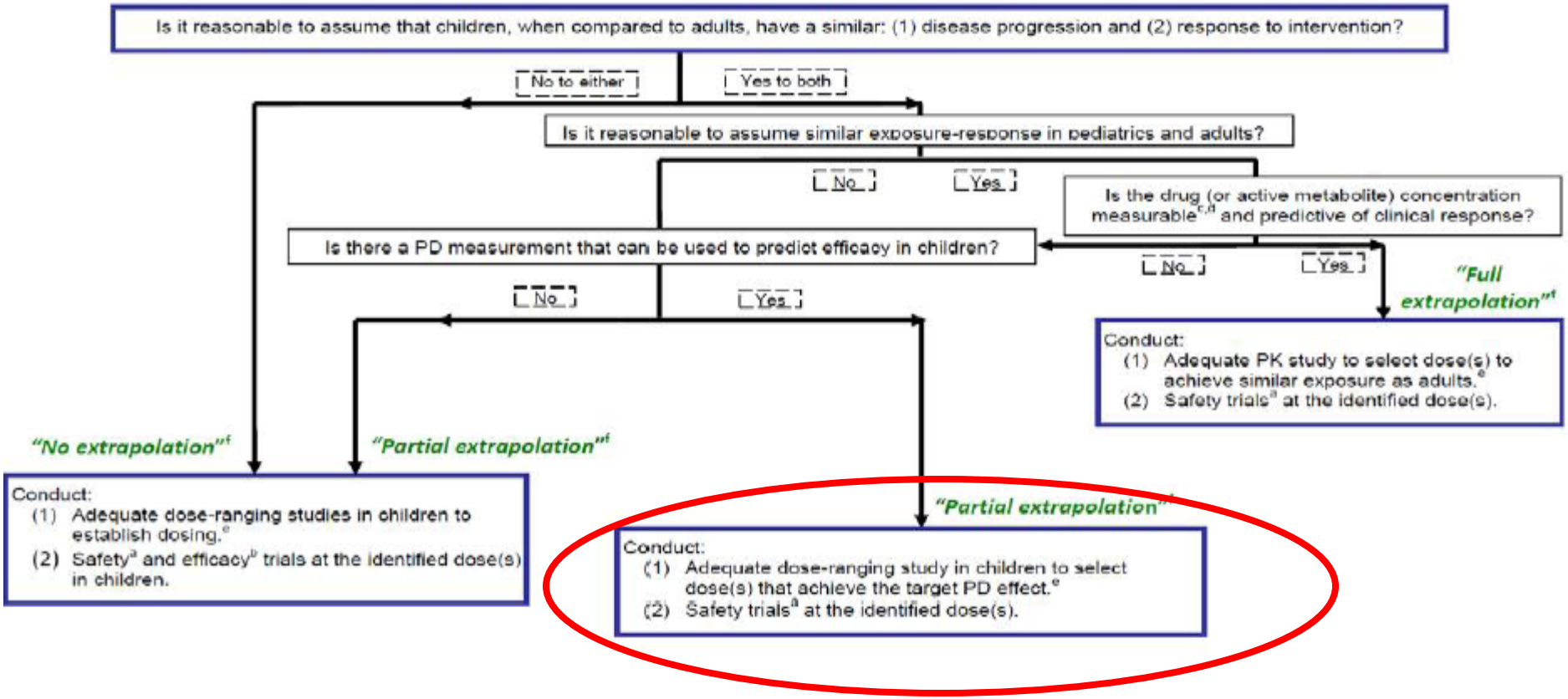
- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  - The course of the disease is sufficiently similar
  - The response to therapy is sufficiently similar
- Dosing cannot be extrapolated
- Safety cannot be extrapolated

Exposure Response and Pediatric Extrapolation

- Full Extrapolation does not require evaluation of similarity of exposure response (similarity of exposure is all that is required)
- Partial Extrapolation requires evaluation of exposure-response similarity

Exposure Response

Pediatric Study Planning & Extrapolation Algorithm



What is "Response"?

- Clinically meaningful endpoint
  - A direct measure of how a patient feels, functions or survives
- Surrogate Endpoint (Biomarker)
  - An endpoint which utilizes a biomarker that is intended to substitute for a clinically meaningful endpoint
  - Change in a surrogate endpoint results in, or is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence
  - Such an endpoint would be useful in establishing exposure-response similarity between adults and children
- Not all biomarkers, even clinically useful biomarkers, are suitable for establishing exposure-response similarity

Definition of a Biomarker

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- Different sources
  - Serum or plasma
  - Radiographic
  - Tissue
- Can be endogenous or exogenous

Biomarkers in Clinical Research

- Identify a target population for study
  - Human Epidermal Receptor-2 (HER-2) positive breast cancer for HER-2 receptor antagonist therapy (e.g., trastuzumab)
  - Anaplastic Lymphoma Kinase (ALK) positive non-small cell lung cancer for tyrosine kinase inhibitors (e.g., crizotinib)
- Population is more likely to respond to treatment based on the disease and the mechanism of action of the drug
- Does not mean that these biomarkers are acceptable for evaluation of exposure-response similarity

Biomarkers in Clinical Research

- Refine dose and/or dosing interval in phase 2 trials
  - Improvement in urinary excretion of glycosaminoglycans (uGAG) in mucopolysaccharidoses (MPS)
- Changes in pharmacodynamic markers are helpful in determining optimal dose for later phase trials
- Does not mean that these biomarkers are acceptable for evaluation of exposure-response similarity

Considerations for use of biomarkers in evaluation of exposure-response similarity

- This evidence should include that the biomarker must be
  - reproducible within patients
  - responsive to clinically meaningful changes in disease activity
  - defined with respect to its temporal relationship with disease activity
  - change in expected direction with known effective treatments
  - that the biomarker of interest lies in the causal pathway of the disease.
- Identification of a potential biomarker that could be used
  - Careful and early planning
  - Discussion and concurrence of plans with the review division

Summary

- Partial extrapolation may speed the development of pediatric products because
  - An adequate and well-controlled trial may not be required
- Partial extrapolation relies on establishment of similarity of exposure-response between adults and pediatric patients
- Confidence in partial extrapolation relies on selection of a response that is
  - clinically meaningful
  - biomarker than can substitute for a clinically meaningful endpoint
- Discussions with FDA as early as feasible about appropriate response measure is strongly encouraged

Thank you