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

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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
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

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?  

- No to either
- Yes to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?  

- No
- Yes

Has a PD measurement that can be used to predict efficacy in children?  

- No
- Yes

Conduct:
- Partial extrapolation

“Full extrapolation”

Conduct:
- Adequate PK study to select dose(s) to achieve similar exposure as adults.
- Safety trials at the identified dose(s).

Conduct:
- Adequate dose-ranging studies in children to establish dosing.
- Safety and efficacy trials at the identified dose(s) in children.
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