The Use of Exposure Matching and Exposure-Response in Pediatric Product Development

Introduction

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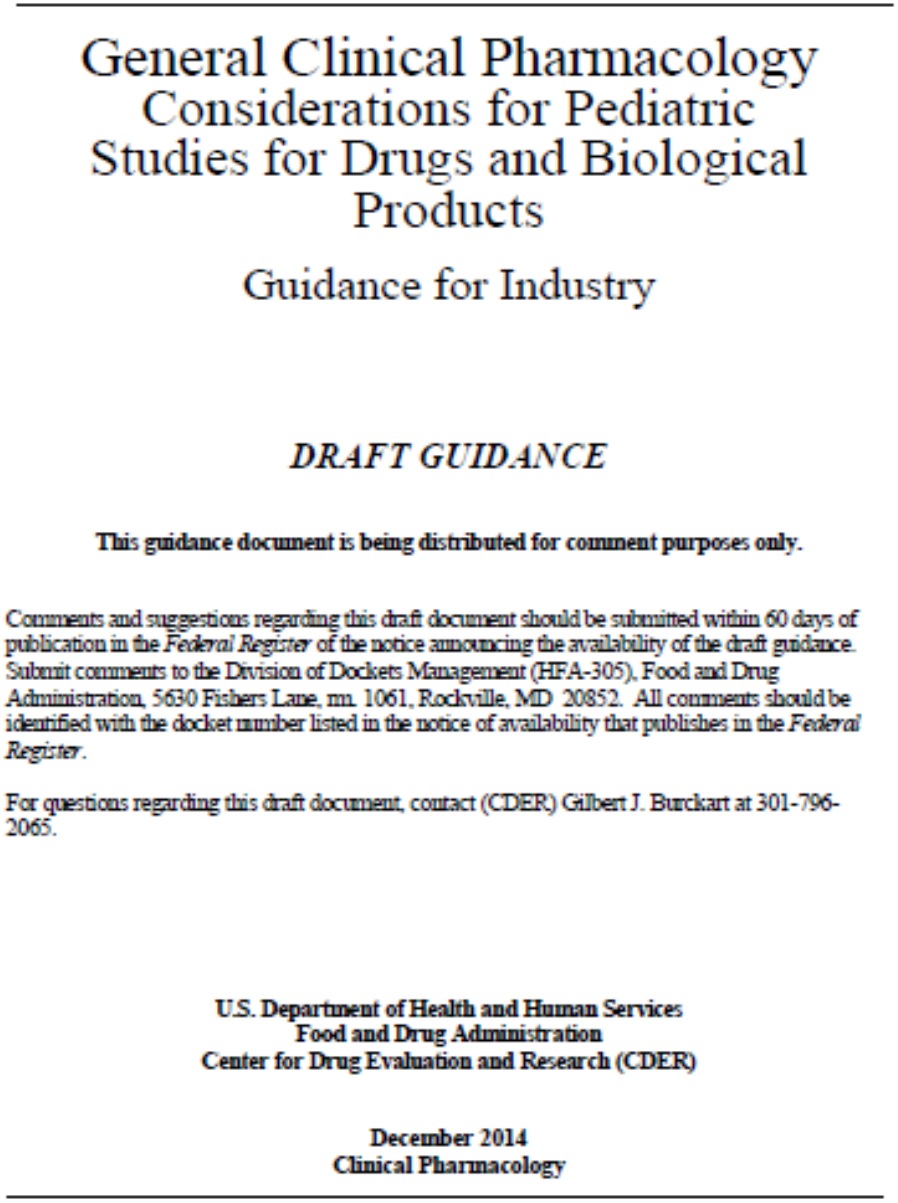

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Gilbert J. Burckart at 301-796-2065.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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- **Comments are due to the docket by February 9, 2015**

Comments can also be sent to gilbert.burckart@fda.hhs.gov

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf

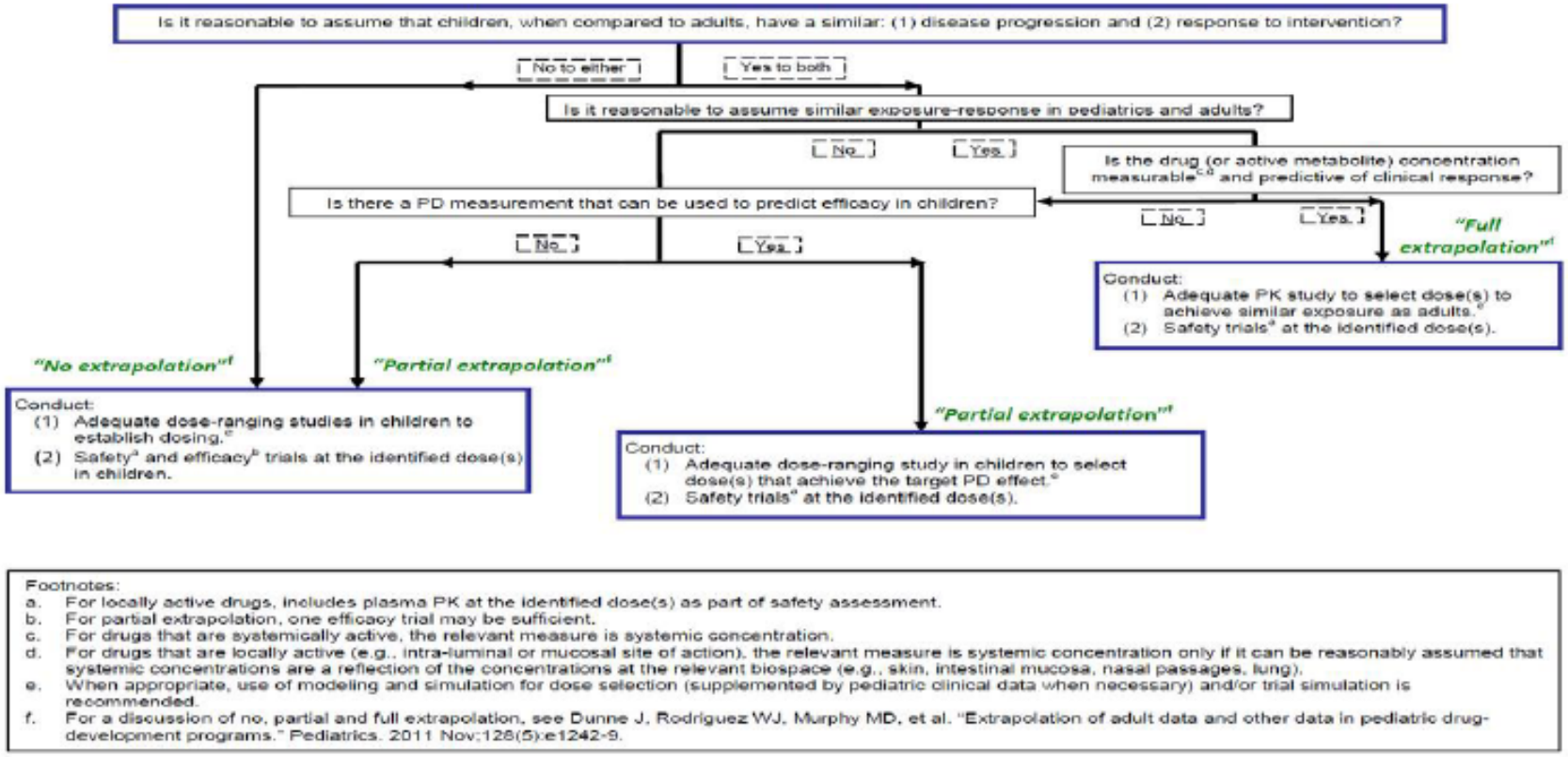
Pediatric Clinical Pharmacology Draft Guidance

I. Introduction
II. Legislative Background
III. Clin Pharm Considerations
- PK / PD / PGx
IV. Ethical Considerations
V. Pediatric Study Plan Design and Points to Consider
  - Approaches to peds studies
  - Alternative approaches
  - Pediatric Dose Selection
  - Pediatric Dosage Formulation
  - Sample size
  - Sample collection
  - Covariates and Phenotype Data
  - Sample analysis
  - Data analysis
  - Report

- Appendix A – Pediatric Study Planning and Extrapolation Algorithm

*Items in Blue are new or heavily revised

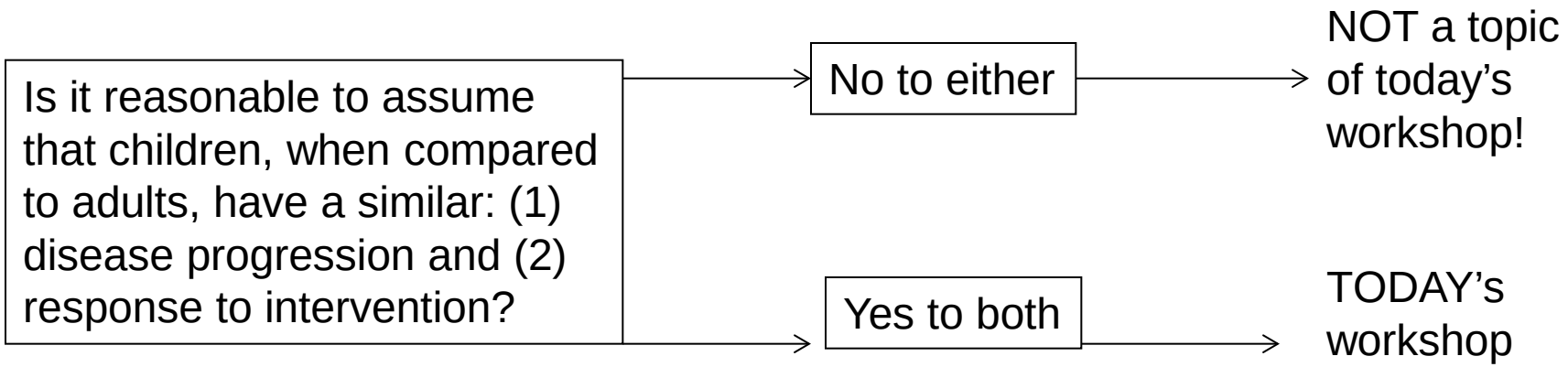
Pediatric Study Planning & Extrapolation Algorithm



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.

Pediatric Study Planning & Extrapolation Algorithm



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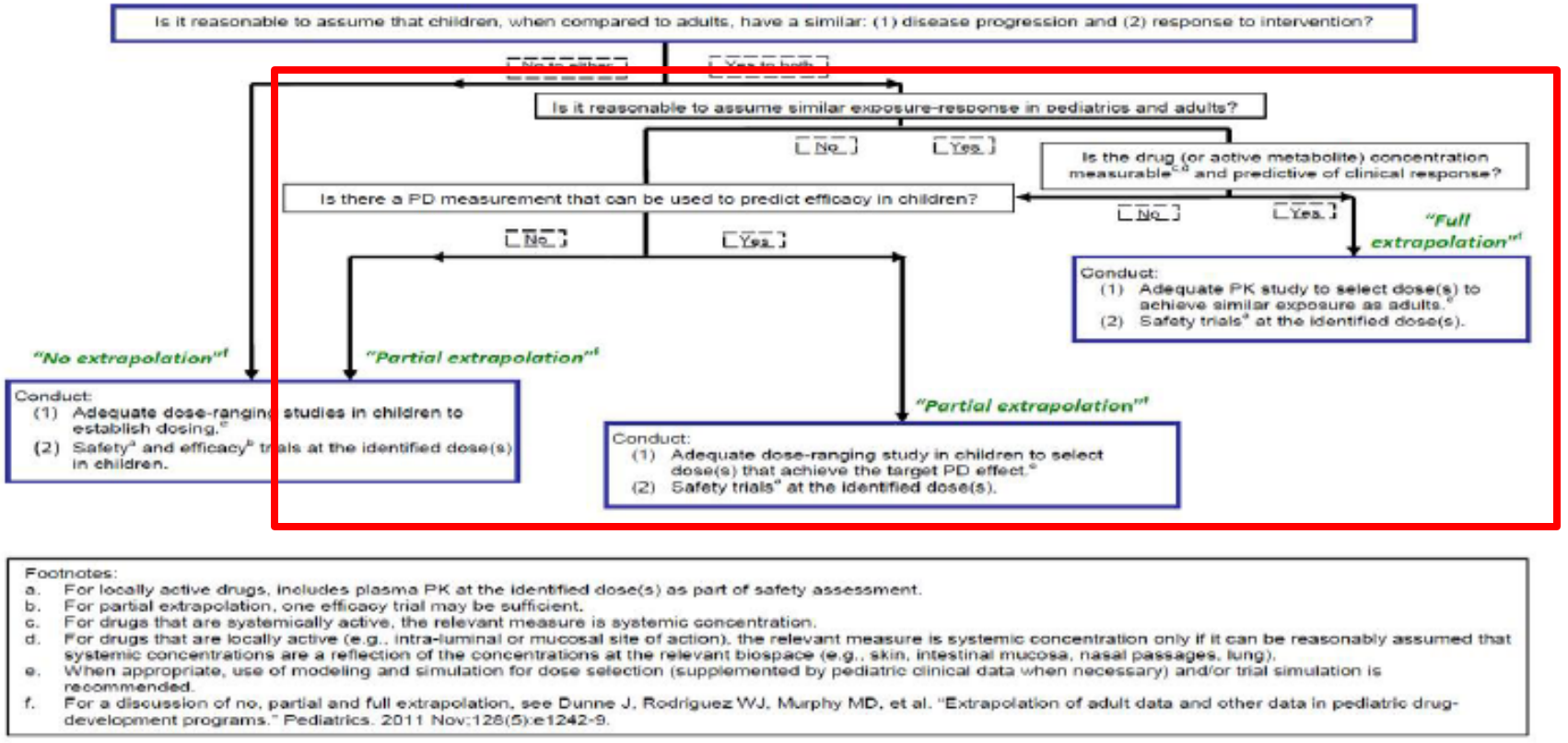

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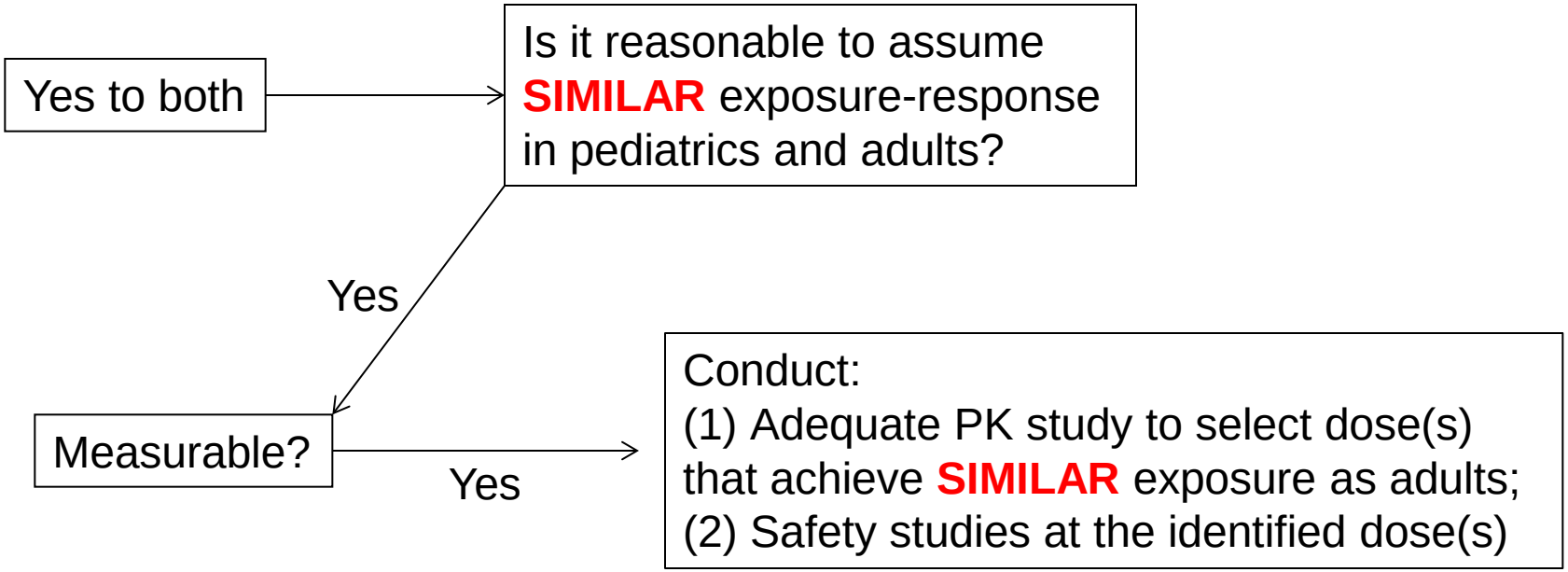
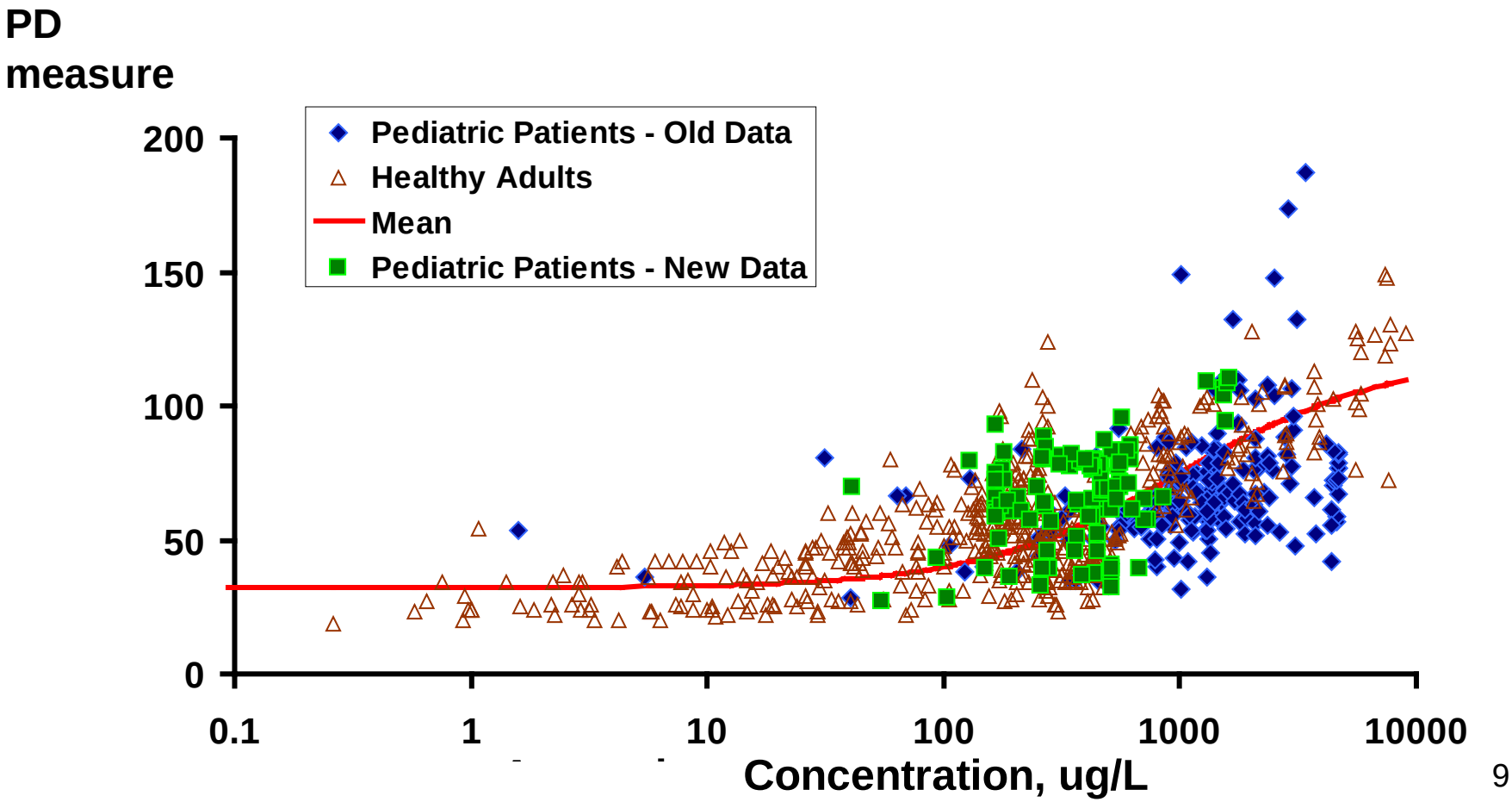


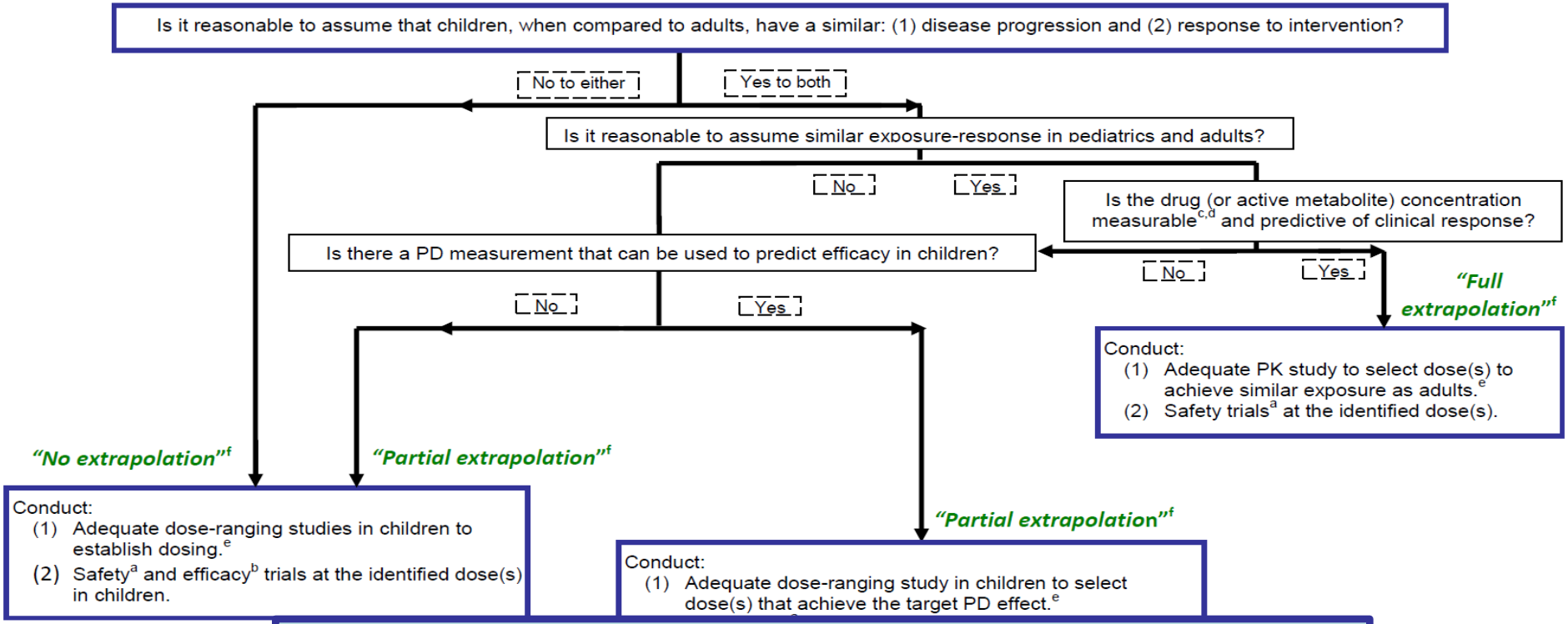
Is similarity of exposure-response or exposure possible to quantify?

- Lily Mulugeta on exposure matching: only 7/86 trials (8.1%) had a pre-defined acceptance boundary to match adult exposures;
- Similarity of exposure-response may be more difficult to assess than exposure;
- Other criteria (risk-benefit or therapeutic index; limiting the concentration range for analysis) may have to be considered.

Concentration – Response Analysis Pediatrics and Adults



Pediatric Study Planning & Extrapolation Algorithm



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Workshop Outline

- Morning session
  - Exposure-response similarity
  - Panel
- Afternoon session
  - Exposure similarity
  - Panel