Pediatric Extrapolation in FDA Submissions – Sources of Data

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Pediatric Extrapolation in the U.S.

- 1992: Proposed Reg-Pediatric Use Subsection introduces concept of Extrapolation
- 1994: Final Reg: Peds Labeling Rule (defines Extrapolation)
- 1997: FDAMA Exclusivity – does not discuss extrapolation
- 1998: Pediatric Rule – Pediatric extrapolation of efficacy included
- 1998: Guidance for Industry: providing Evidence of Clinical Effectiveness for Human Drug and Biologic Products, May, 1998
  - Provides evidence standards for pediatric extrapolation
- 2001: Court enjoins FDA's Pediatric Rule
- 2002: BPCA – does not discuss extrapolation
- 2003: PREA – re-introduces Extrapolation-shortened reference
- 2007: FDAAA - Both BPCA and PREA are renewed for 5 years
- 2012: FDSIA – BPCA and PREA "made permanent"
- 2012: Clinical Pharmacology Advisory Committee on Pediatrics

1994 Final Regulation on Pediatric Labeling

- "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"

Guidance for Industry: Providing Evidence of Clinical Effectiveness for Human Drug and Biologic Products, May, 1998

- Evidence [of effectiveness] that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes:

1. **evidence** of common pathophysiology and natural history of the disease in the adult and pediatric populations,
2. **evidence** of common drug metabolism and similar concentration - response relationships in each population, **and**
3. **experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions**

FDA Prior Extrapolation Experience

- The FDA experience with pediatric extrapolation was reviewed by an Extrapolation Committee during 2009-2010 and the results were published in 2011;
- Each review division from the Office of New Drugs met with the committee and summarized their pediatric extrapolation experience.

Summary of Approaches to Extrapolation
(Assessment of 166 products between 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)

Adapted from Dunne J et al. Pediatrics 2011;128;e1242.

Extrapolation of Efficacy From Sources Other Than Controlled Adult Data for Same Indication

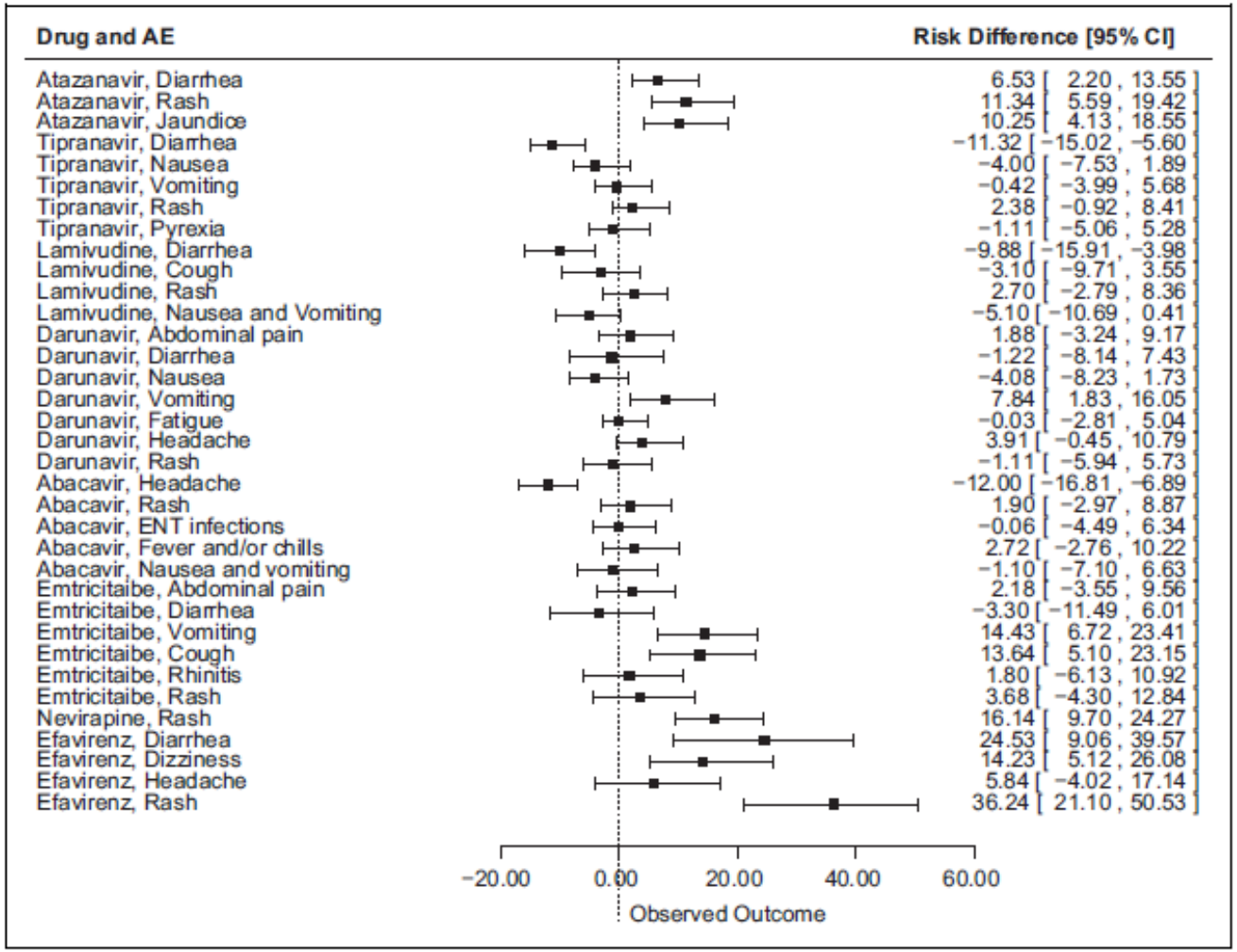
(Extrapolation Committee – 2011)

- Other pediatric age groups
  (different levels of evidence in different age groups)
- Other formulations of same active ingredient
- Related pediatric indications
- Adult indication for (similar) pediatric indication

FDA: Pediatric Safety is Not Extrapolated

- Other sources of safety information do inform the pediatric safety program;
- Safety must be assessed in the pediatric population with the condition of interest;
- May be able to utilize safety from a similar pediatric indication in a similar population (e.g. otitis media, sinusitis).

Incidence of ADEs for Antiretroviral Drugs is Different in Adults and Pediatric Patients



Adverse Event Detection and Labeling in Pediatric Drug Development: Antiretroviral Drugs

Momper JD, Chang Y, Jackson M, Schuette P, Seo S, Younis I, Abernethy DR, Yao L, Capparelli EV, Burckart GJ

Ther Innovation Reg Sci 2015; 49: 302-309

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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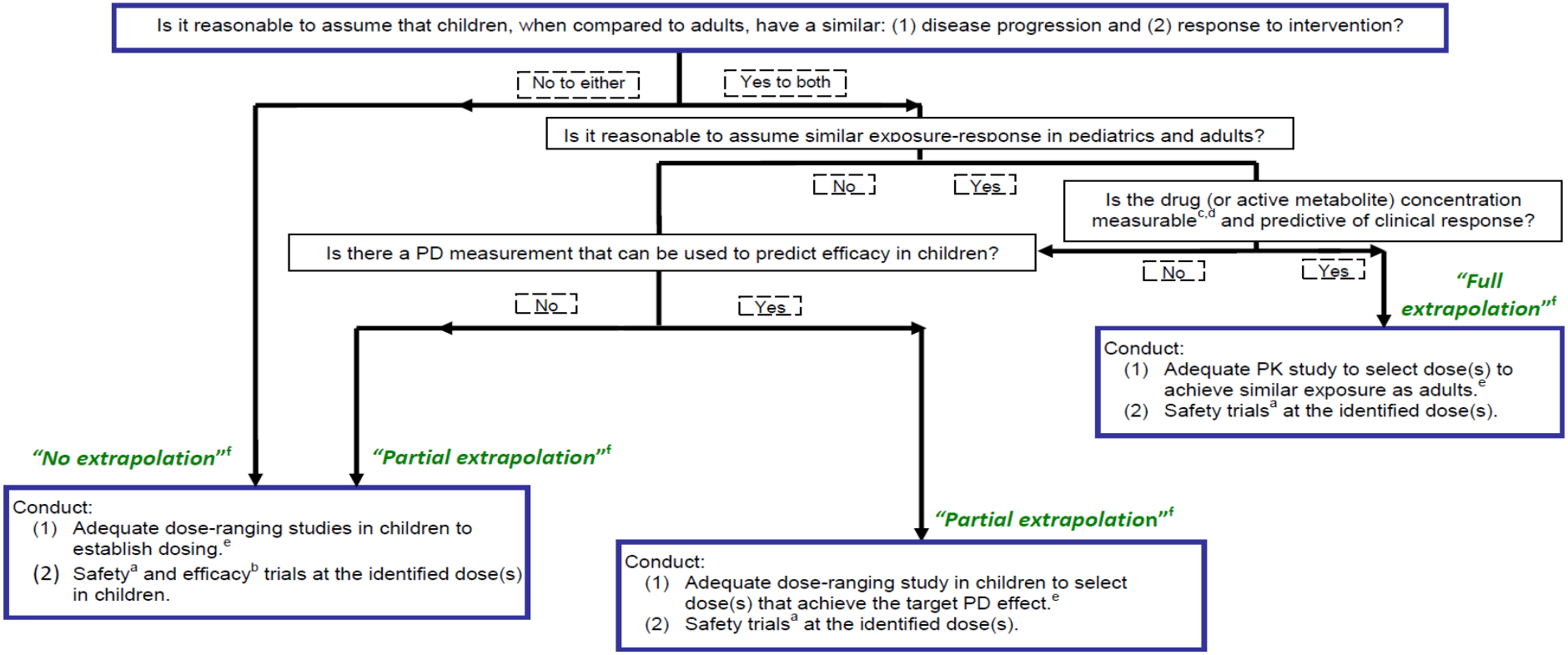
Clinical Pharmacology

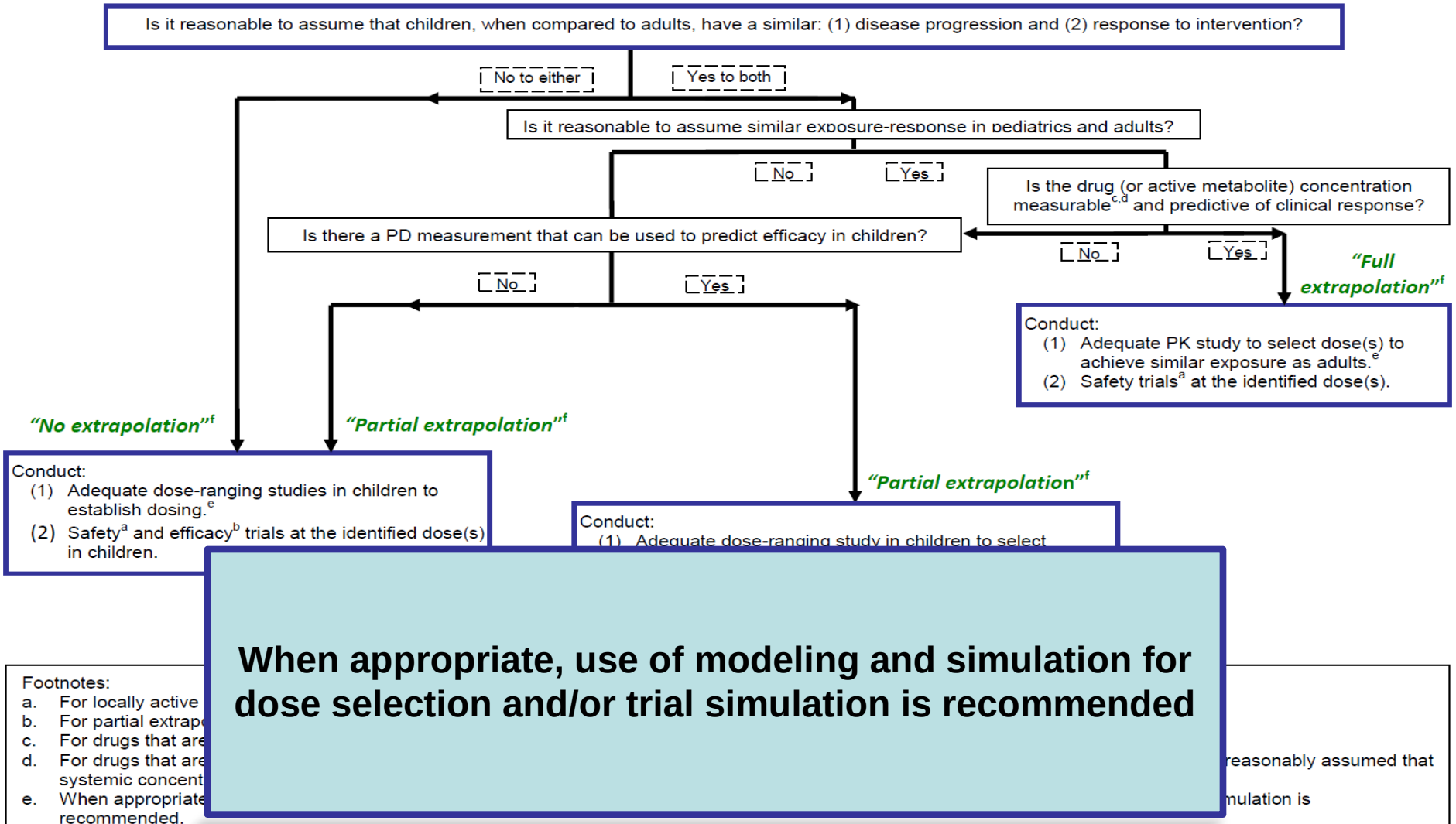
Pediatric Study Planning & Extrapolation Algorithm



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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Clinical Pharmacology Advisory Committee – March, 2012

Focus was on pediatric drug development, and the problems that have been encountered over the past 10 years.

1. Should modeling and simulation methods be considered in **all** pediatric drug development programs?

(**VOTE**) **YES: 13** **NO: 0** **ABSTAIN: 0**

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm

Optimizing the Use of Experience with a Drug or Drug Class or Therapeutic Indication

- **"course of the disease and the drug's effects are sufficiently similar"**
  - Leveraging prior experience (actual adult and pediatric data is always a higher level of evidence, and informs M&S)
    - e.g. Partial onset seizures
  - Clinical trial simulation
  - Disease modeling
- **"evidence of common drug metabolism and similar concentration - response relationships in each population"**
  - Matching pediatric exposure to adult exposure
  - Exposure-response analysis
  - Physiologically-based PK

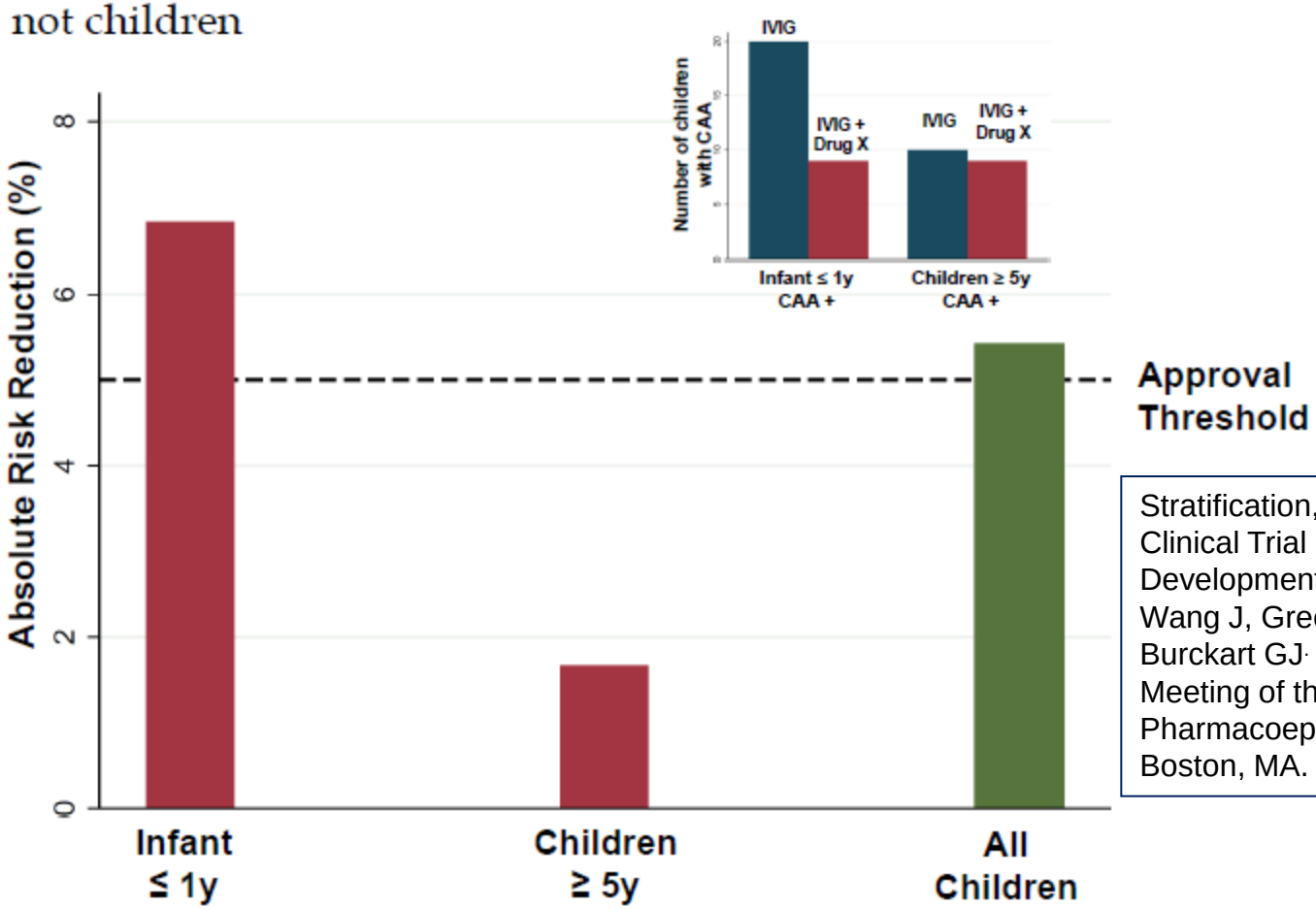
Leveraging Prior Experience in Partial Onset Seizures

Drug	Adult	Pediatrics	Indication	Adjunctive
Gabapentin (Neurontin)	> 12y	3y to 12y	Partial Seizures	3y to 12y
	> 16y	1m to 16y	Partial Onset Seizures	
Levetiracetam (Keppra)	> 12y		Myoclonic Seizure in Patients with Juvenile Myoclonic Epilepsy	Y
	> 16y	6y to 16y	Primary Generalized Tonic-clonic Seizures	
Clonazepam (Klonopin)	Y	> 10y or 30kg	Seizure Disorders Partial Seizures	
Lamotrigine (Lamictal)	Y	>=2y	Primary Generalized Tonic-clonic Seizures Generalized Seizures of Lennox-Gastaut Syndrome	Y
Topiramate (Topamax)	Y	2-16y	Primary Generalized Tonic-Clonic Seizures Seizures of Lennox-Gastaut Syndrome Partial Onset Seizures	Y
Oxcarbazepine (Trileptal)	Y	Y	Partial Seizures	Y
Perampanel (Fycompa)	Y	>12y	Partial-onset seizures with or without secondarily generalized seizures	Y
Tiagabine (Gabitril)	Y	>12y	Partial seizures	Y

Angela Men: http://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/pediatricpbpk/Men - PEACE Initiative.pdf

Clinical Trial Simulation Prediction of Outcome of Pediatric Trials

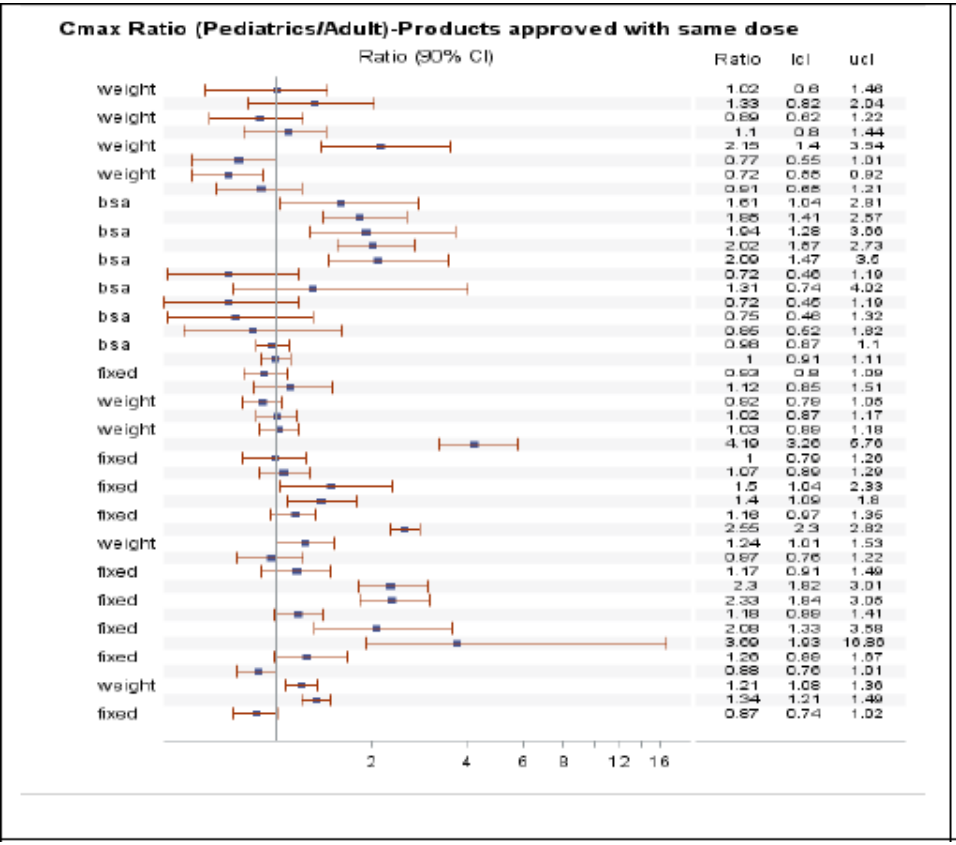
Hypothesis 2: Drug X + IVIG decreases risk of CAA in infants but not children

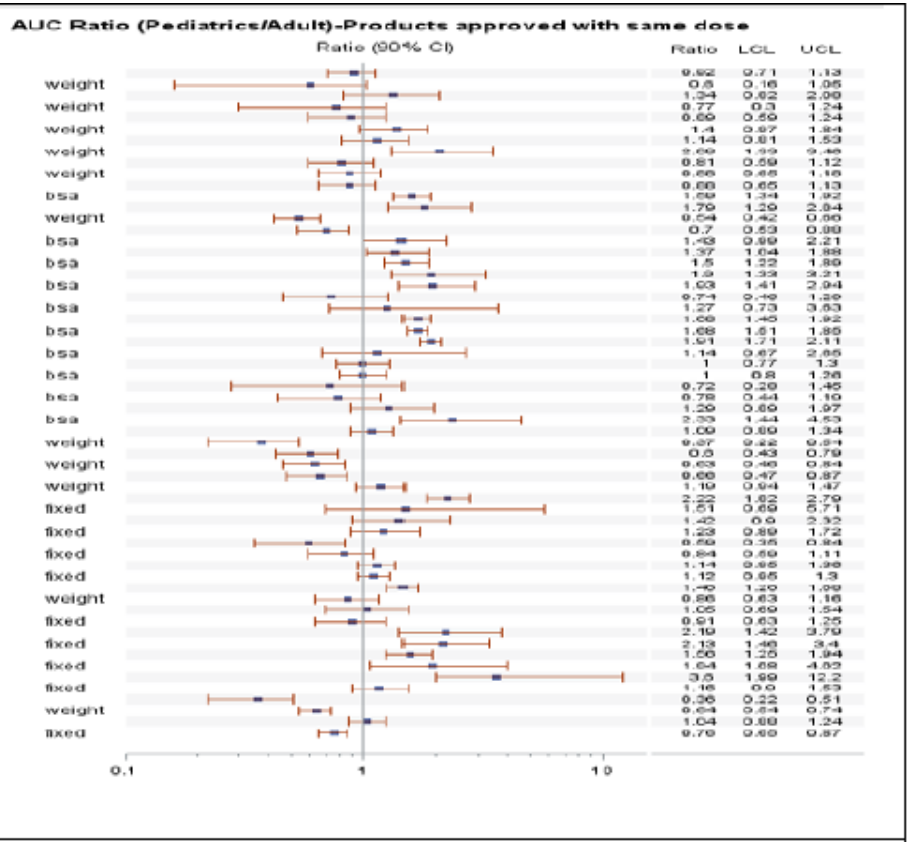


Stratification, Hypothesis Testing, and Clinical Trial Simulation in Pediatric Drug Development. McMahon AW, Watt K, Wang J, Green D, Tiwari R, and Burckart GJ. Presented at the 2015 Annual Meeting of the International Society of Pharmacoepidemiology (ISPE), Boston, MA.

Exposure "matching"

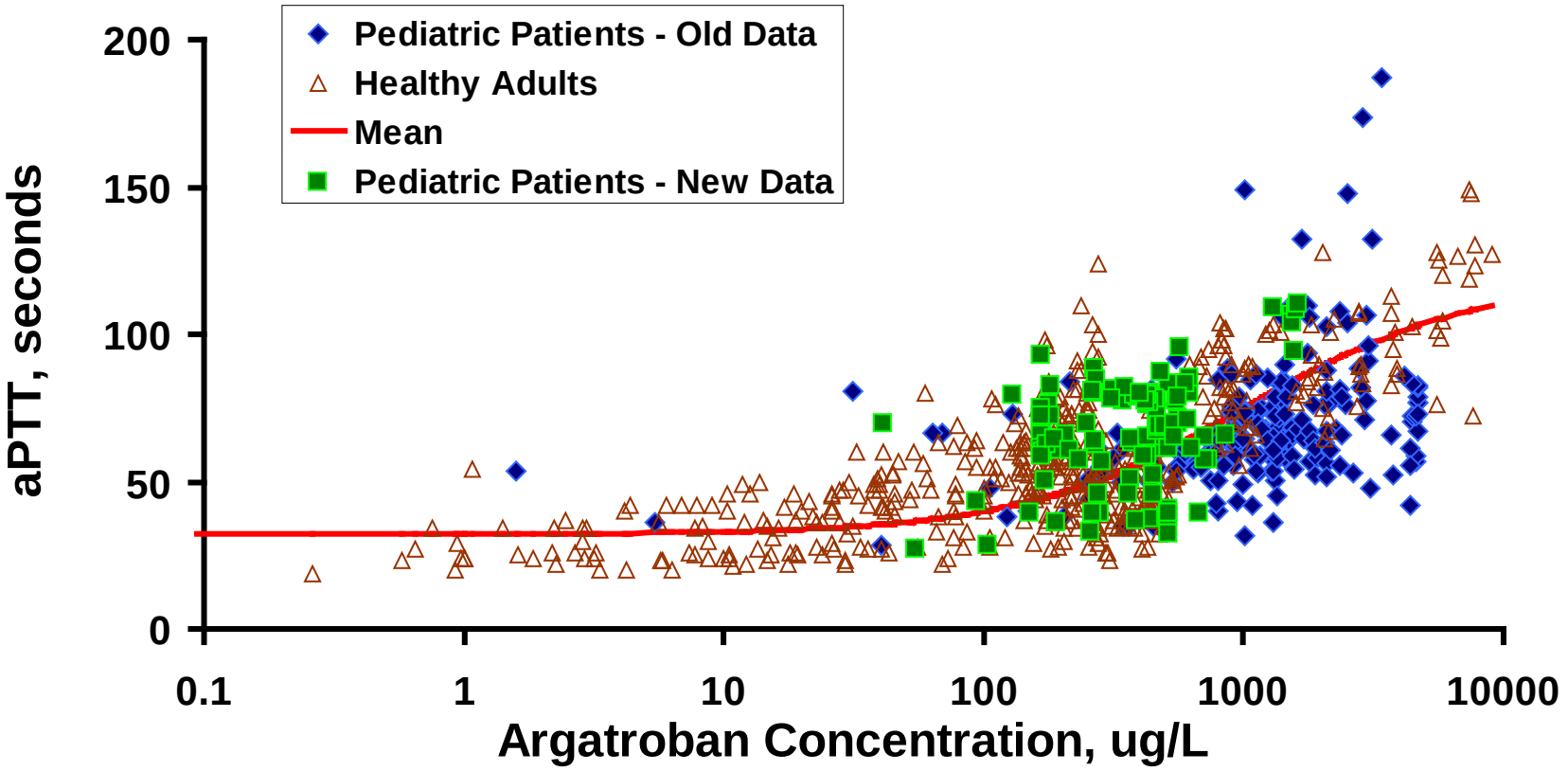
- Only 8% of trials had pre-defined acceptance criteria;
- Some exposure matching studies in infants have failed.





Concentration – Response Analysis

Concentration-aPTT relationship is similar between adults (healthy) and pediatrics (patients)



Summary

- The sources of data available to expedite the pediatric extrapolation process **have not changed** since the 2011 assessment;

- How we can leverage our experience **has changed** based on (a) additional pediatric data available in the disease and in the class of drug, and (b) advancing techniques in modeling & simulation of PK/PD, clinical trials and disease states.
  - M&S can contribute to answering both questions: (1) course of the disease and drug's effects; and (2) similar metabolism and concentration-response relationships