Leveraging adult data in pediatric product development: The role of Bayesian statistics

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This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Outline

- Challenges in Pediatric Studies
- Extrapolation and Bayesian Model
- Prior Information Elicitation
- Bayesian Approaches
- Case Example
- Summaries

Challenges in Pediatric Studies

- Smaller population size
- Less invasive measurement
- Unethical to include a placebo arm
- Shorter trial duration

What Bayesian Can Do for YOU?

- Frustration:
  - Too many failed pediatric trials

- Purpose:
  - Less failed pediatric trials
  - Less inconclusive pediatric trials
  - Less pediatric trials

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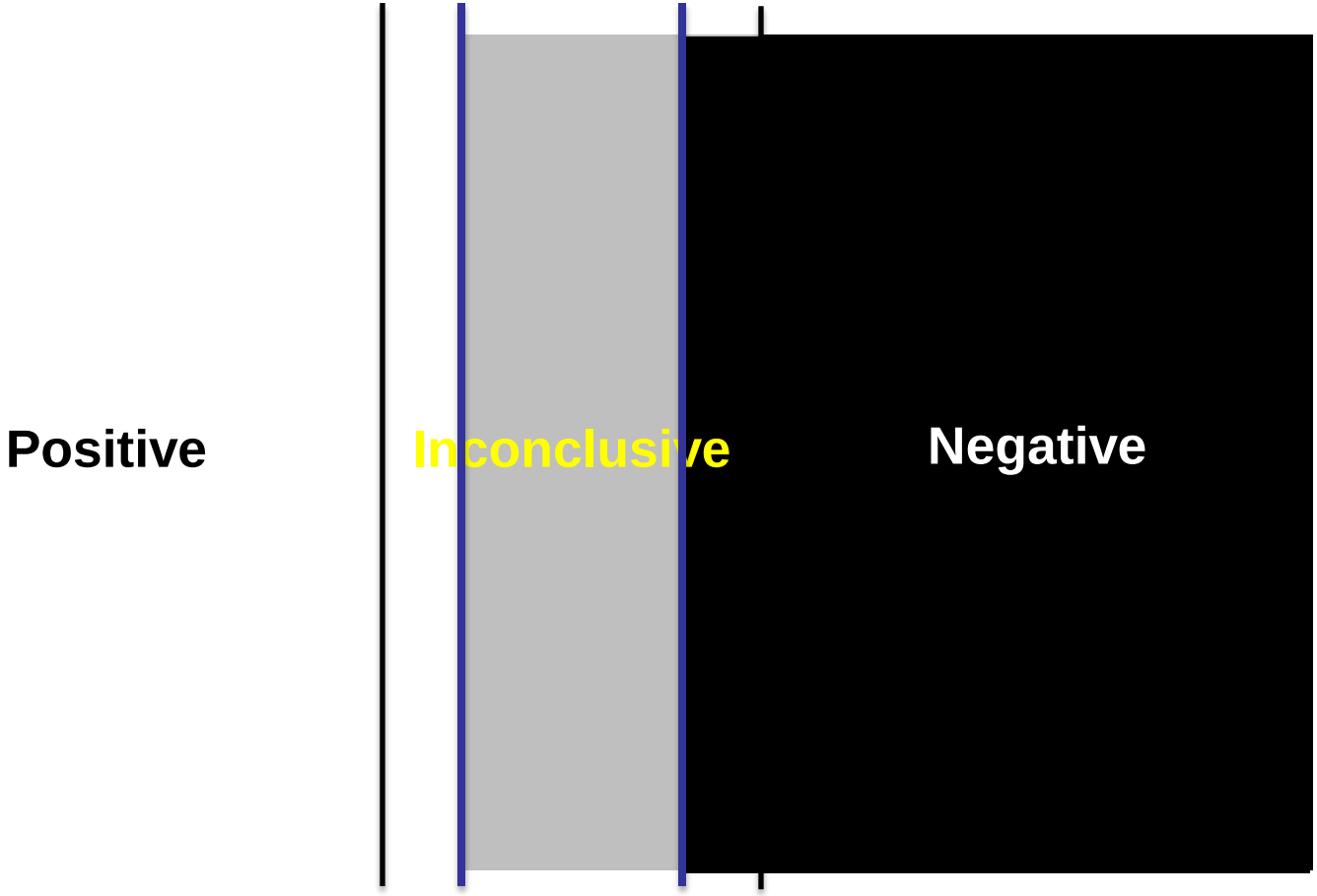
Statistical Significance

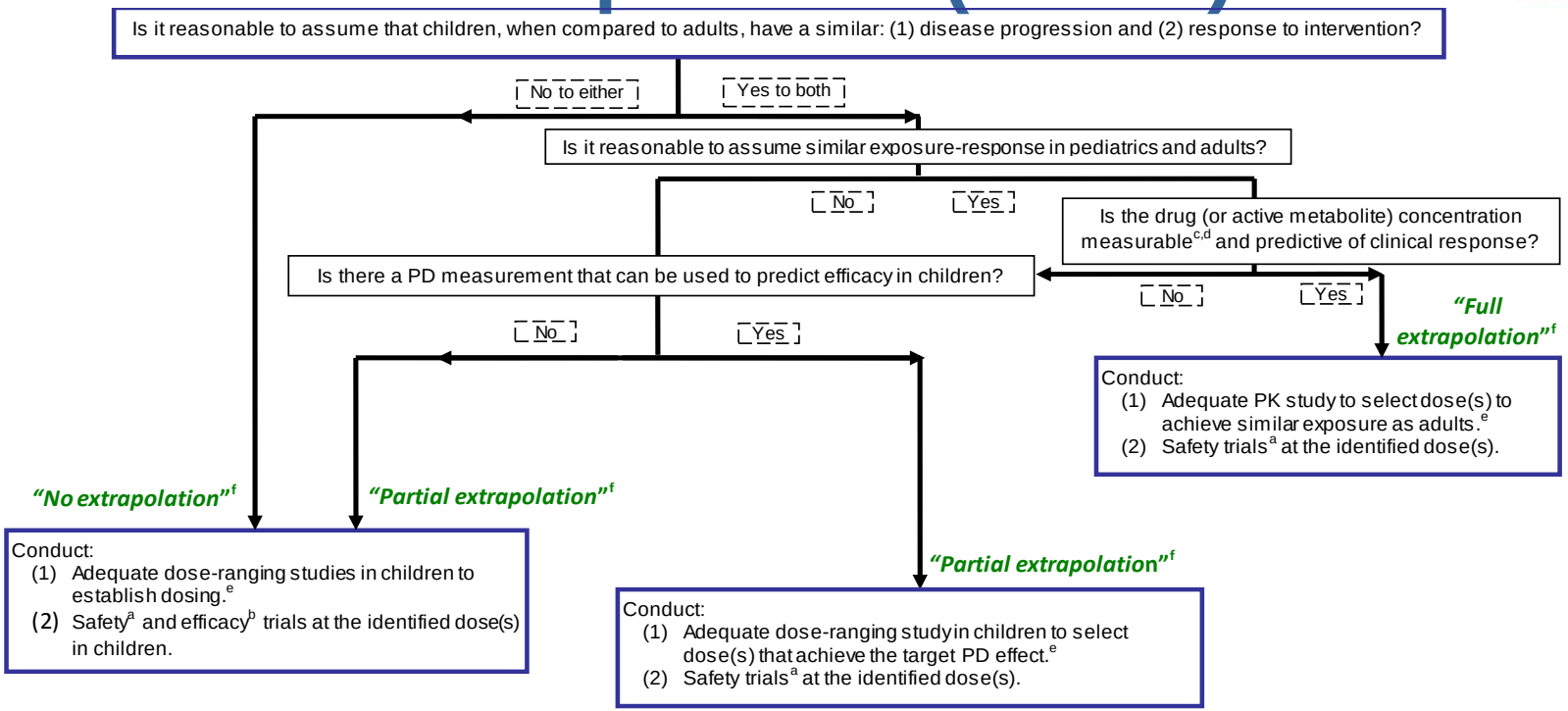
Significant

Insignificant

Conclusion



Extrapolation (CDER)

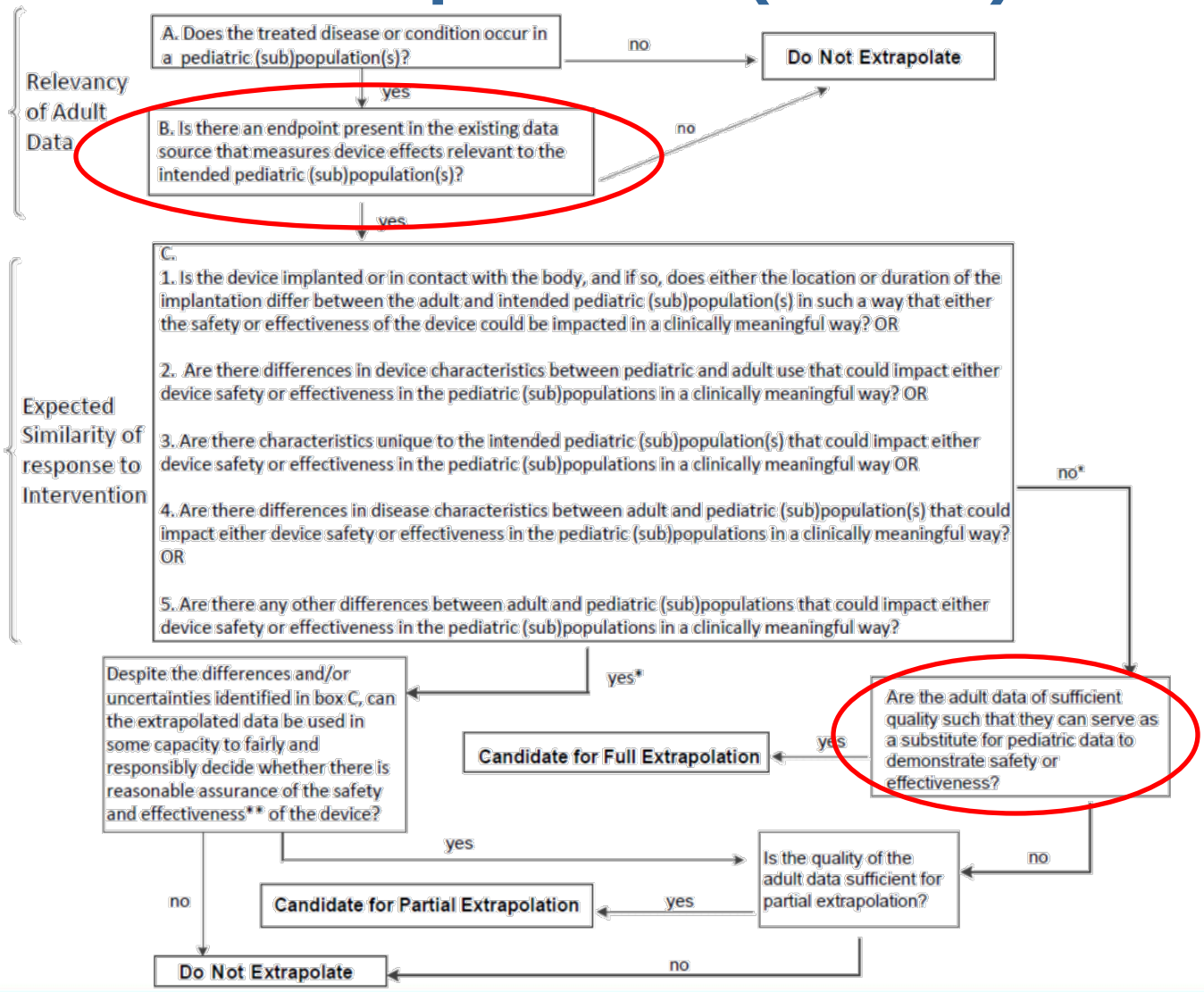


Pediatric Study Planning & Extrapolation Algorithm

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.

Extrapolation (CDRH)



Extrapolation and Bayesian Model

- Extrapolation
  - Full
  - Partial
  - No
- Bayesian Model
  - Borrowing information from adult data (or other reliable data sources)
  - Minimize uncertainty incurred from using adult data

Prior Information Elicitation

- Adult Trial Data
  - Obvious choice?
  - Same disease with same treatment
  - Different population
- Similar Pediatric Trial Data
  - Similar population
  - Same disease with similar treatment
- PK/PD Data
  - Same population with same disease under same treatment
  - Different endpoint

Borrowing Information

- Clinical input for reliable prior information
- Similarity
  - Population
    - Baseline characteristics and demographic information
  - Disease progression
    - Baseline disease characteristics
    - Placebo information
  - Treatment effect
    - Treatment group information
- Pre-specify criteria based on collected data

Bayesian Approaches

1. Derive priors from the adult data
2. Bayesian Hierarchical Modeling

- CDRH 2015 guidance describes (2)
- Drug Information Association (DIA)/FDA Bayesian statistics working group has developed a concept paper describing (1) and (2) both as useful approaches for pediatric trials

Bayesian Approaches (cont.)

- Bayesian Power Priors (Ibrahim & Chen, 2000)
  - Prior is a historical likelihood raised to a "power" to discount the information from the historical data
- Bayesian Commensurate Priors (Hobbs, et al., 2012)
  - Historical study data are on the same level as the current study data (no down-weighting)
  - Current study mean is centered at the historical study mean with precision that determines the commensurability of the studies

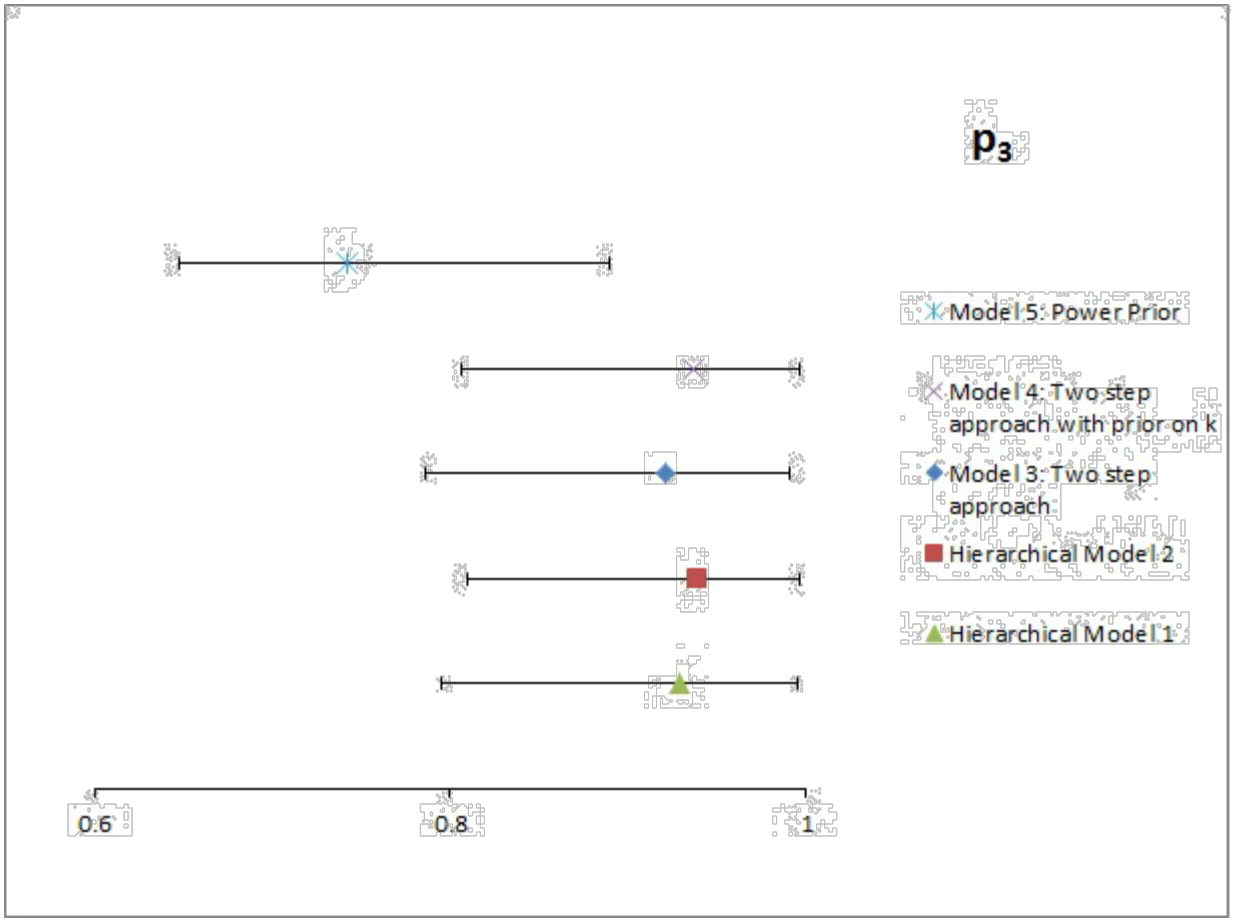
Case Example

- Data: two adult clinical trials on a drug for a chronic disease
- Third trial: pediatric population
- Study treatment:
  - Adult: placebo, low dose & high dose
  - Pediatric: low dose
- Treatment is approved for both adult and pediatric patients based on these three trials

Bayesian Models

- Borrow information on low dose only
- Adults: 121 and Pediatrics: 22
- Endpoint: Clinical response (yes vs. no)
- Model 1: Flat hierarchical model
- Model 2: Tier hierarchical model
- Model 3: Use adult posterior as prior for peds
- Model 4: Same as Model 3 w/ prior on k
- Model 5: Power prior

Results



- Power prior is the most conservative model

Summaries

- Pediatric studies pose unique challenges
- Explore innovative trial designs
- Informative prior data available
- Potential Bayesian models
- More efficient clinical trials

References

- Extrapolation of efficacy and other data to support the development of new medicines for children: A systematic review of methods

  Wadsworth I, et. al., Department of Mathematics and Statistics, Fylde College, Lancaster University, Lancaster, UK

  Statistical Methods in Medical Research; DOI: 10.1177/0962280216631359

- Stratification, Hypothesis Testing, and Clinical Trial Simulation in Pediatric Drug Development

  Ann W. McMahon, MD, MS (FDA), Kevin Watt, MD, MPH (Duke), Jian Wang, PhD (FDA), Dionna Green, MD (FDA), Ram Tiwari, PhD (FDA), and Gilbert J. Burckart, Pharm D (FDA)

Recent CDER Bayesian Work

- Early stage studies (Phase 1, Phase 2)
  - Multi-stage dynamic treatment regime
  - Adaptive design
- Small sample studies
  - Rare diseases / Orphan drugs
  - Pediatric population
- Safety evaluation
  - Low adverse event rate
  - Continuous monitoring

Recent CDER Bayesian Publication

- Meta-Analysis: Meta-Analysis Using Dirichlet Process

  S. Muthukumarana & R.C. Tiwari

  Statistical Methods in Medical Research (July 2012)

- Non-Inferiority Study
  - Non-inferiority and networks: inferring efficacy from a web of data

    J. Lin, M.A. Gamalo & R.C. Tiwari

    Pharmaceutical Statistics, Dec 2015
  - Bayesian Approach to the Design and Analysis of Non-inferiority Trials for Anti-infective Products

    M.A. Gamalo, R.C. Tiwari & L.M. LaVange

    Pharmaceutical Statistics (Aug. 2013)
  - Bayesian Approach to Non-inferiority Trials for Normal Means

    M.A. Gamalo, R. Wu & R.C. Tiwari

    Statistical Methods in Medical Research (May 2012)

Examples from Advisory Committees

- Pediatric ODAC 2015:

  http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm426351.htm
- Remicade UC 7/21/2011:

  http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM266697.pdf
- Reslizumab Asthma 12/9/2015:

  http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM477884.pdf

Thank you!

Questions?