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

Freda W. Cooner, Ph.D.
FDA/CDER
FDA-University of Maryland CERSI Workshop
June 1, 2016
FDA Disclaimer

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
What Bayesian Can Do for YOU?

• Frustration:
  – Too many failed pediatric trials

• Purpose:
  – Less failed pediatric trials
  – Less inconclusive pediatric trials
  – Less pediatric trials
Statistical Significance

- Significant
- Insignificant
Extrapolation (CDER)

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

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

- No
- Yes

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

“Partial extrapolation”

Conduct:
1. Adequate dose-ranging studies in children to select dose(s) that achieve the target PD effect.
2. Safety trials at the identified dose(s).

“Partial extrapolation”

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

“Full extrapolation”

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.
Extrapolation (CDRH)

A. Does the treated disease or condition occur in a pediatric (sub)population(s)?
   - no: Do Not Extrapolate
   - yes: Relevancy of Adult Data

B. Is there an endpoint present in the existing data source that measures device effects relevant to the intended pediatric (sub)population(s)?
   - no: Do Not Extrapolate
   - yes: Expected Similarity of response to Intervention

C. 1. Is the device implanted or in contact with the body, and if so, does either the location or duration of the implantation differ between the adult and intended pediatric (sub)population(s) in such a way that either the safety or effectiveness of the device could be impacted in a clinically meaningful way? OR
   2. Are there differences in device characteristics between pediatric and adult use that could impact either device safety or effectiveness in the pediatric (sub)populations in a clinically meaningful way? OR
   3. Are there characteristics unique to the intended pediatric (sub)population(s) that could impact either device safety or effectiveness in the pediatric (sub)populations in a clinically meaningful way OR
   4. Are there differences in disease characteristics between adult and pediatric (sub)populations that could impact either device safety or effectiveness in the pediatric (sub)populations in a clinically meaningful way? OR
   5. Are there any other differences between adult and pediatric (sub)populations that could impact either device safety or effectiveness in the pediatric (sub)populations in a clinically meaningful way?

Despite the differences and/or uncertainties identified in box C, can the extrapolated data be used in some capacity to fairly and responsibly decide whether there is reasonable assurance of the safety and effectiveness** of the device?

Are the adult data of sufficient quality such that they can serve as a substitute for pediatric data to demonstrate safety or effectiveness?

Candidate for Full Extrapolation

Is the quality of the adult data sufficient for partial extrapolation?

Candidate for Partial Extrapolation

Do Not Extrapolate
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](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm426351.htm)

- Remicade UC 7/21/2011:

- Reslizumab Asthma 12/9/2015:
  [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM477884.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM477884.pdf)
Thank you!

Questions?