Drug development and decision-making in pediatric settings leveraging adult results*

Mark Rothmann
FDA/CDER/OTS/OB
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Disclaimer

* The views expressed in this talk are those of the speaker and not necessarily those of the FDA

Outline

- Background
- Extrapolation of adult results to a pediatric setting
- On operating characteristics
  - Conditional and unconditional type I error (reference point: before the adult studies begin)
- Concluding remark

Background

Pediatric Drug Development

- Pediatric drug development has the same basic standard as for adults:
  - "An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications." – 21CFR314.50
- When we are evaluating evidence to extend an indication into children that has been first evaluated in adults, we can rely on the concept of extrapolation discussed in 21CFR314.55:
  - "Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."
- We have an ethical imperative to minimize the extent of pediatric studies:
  - "A fundamental principle in pediatric drug development requires that children should not be enrolled in a clinical study unless necessary to achieve an important pediatric public health need." – ICH E11 (R1)

Cases considered

- Consider those indications where effects of medical products in children studied after marketing approval in adults (after first shown to be safe and effective in adults) and
- Extrapolation of adult results to pediatrics is reasonable and independent confirmation in pediatric setting is not needed

Cases not considered

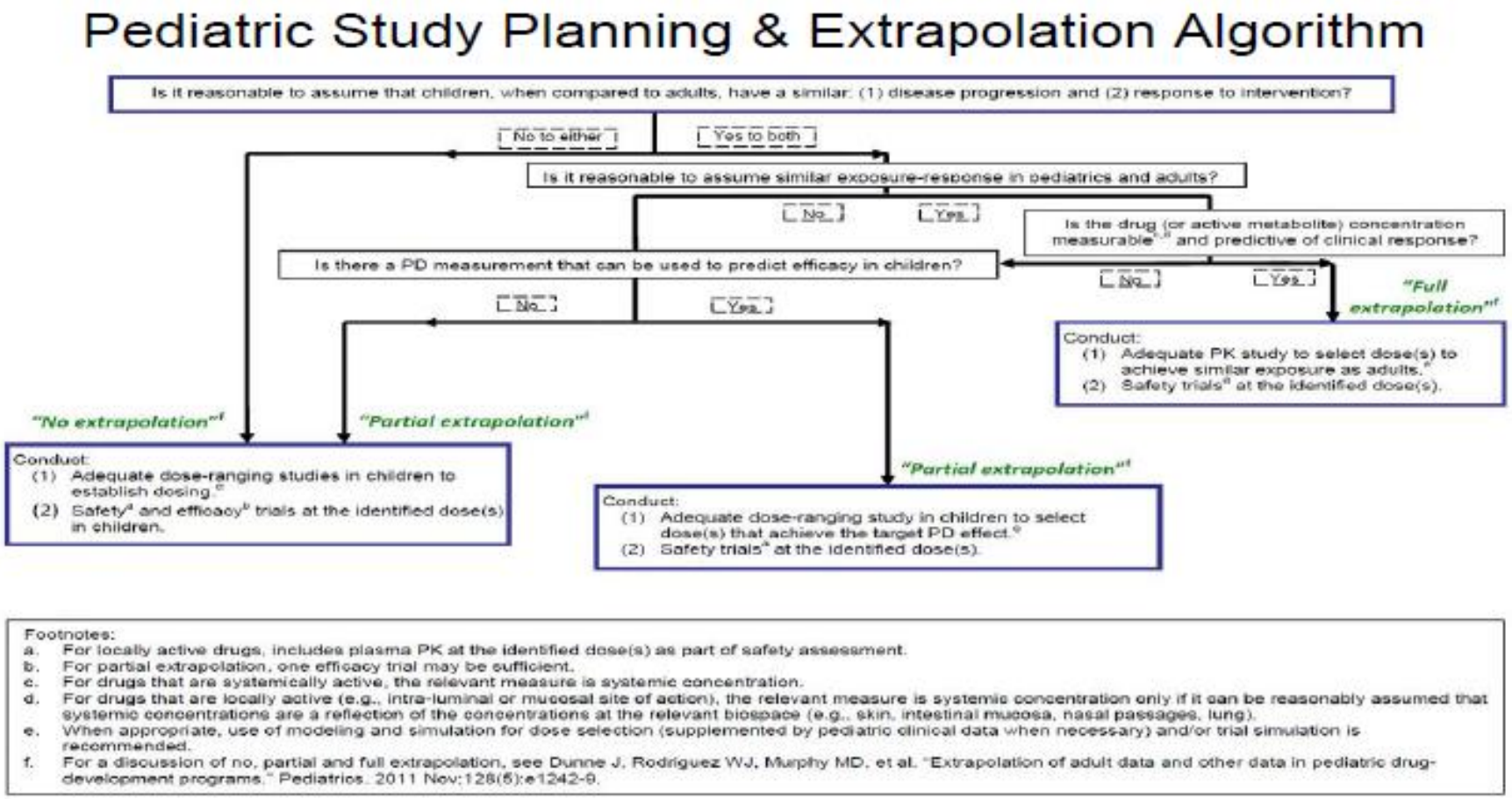
- Cases where independent confirmation in pediatric setting is needed
  - Extrapolation is not reasonable (e.g., human growth hormone deficiency)
  - Important to have very precise information on benefit/risks in pediatric setting (e.g., Type I diabetes)

Beginning of pediatric development

- In cases being considered pediatric development starts when adult studies start
- This should be considered when discussing “operating characteristics” involving decisions in pediatric setting

Extrapolation of adult results to a pediatric setting

Old Extrapolation Framework



FDA Draft Guidance: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, December 2014

Current Pediatric Extrapolation Framework
Disease/response "similarity" is a continuum

Different	Dissimilar	Similar	Same
No overlap between adult and pediatric condition	Some degree of overlap with significant differences between adult and pediatric condition	Large degree of overlap with some differences between adult and pediatric condition	Significant overlap; no known significant differences between adult and pediatric condition

Increasing relevance of adult information to pediatric population with increasing confidence in similarity between adult and pediatric condition

AWC pediatric trial(s) → Bridging biomarker, Bayesian borrowing, etc. → Exposure matching

A reason for doing extrapolation

- Believe treatment effects for adults and for pediatrics are correlated.

A decision-making framework

- Size pediatric study according to what is ethical, feasible, reliable (when also considering adult results) and timely
  - Safety concerns may dictate sample size
- Decision based on considering pediatric results along with adult results

An Art

- There is some “art” to synthesizing results in adult setting with results in pediatric setting to make an inference in the pediatric setting.
- How much information worth of adult results to synthesize with pediatric results?
- How to synthesize?
- An objective: minimize as much as possible chance of getting inconclusive results for pediatric decisions

Studying products in same class

- Two products in same class studied in adults for same indication
- Products studied in same number of adults through similar trial designs with different estimated treatment effects
- Same conclusion on appropriateness of extrapolation of adult results to pediatric setting

Therefore, it would make sense that the same amount of information in respective adult settings are extrapolated (used in the prior distribution) to respective pediatric setting.

Insisting to control conditional type I error rate – borrow less the more effective the product is in adults

Two products in same class

- Products A and B have estimated effects of 1.5 and 1 in adults based on the same amount of information/precision
- Prior for A: Normal (1.5, var = y)
- Prior for B: Normal (1, var = w)
- Inverse relationship between y (w) and amount of information borrowed
- Pediatric likelihood: Normal (θ_j, var = 3), j= A, B
  - Pediatric studies are the same size
- Success criterion: Posterior probability of effect > 0.975

Relative amount of adult information borrowed

One-sided conditional type I error rate	y	w	Amount of information in B borrowed relative to A
0.025	∞	∞	No information borrowed
0.05	1.46	0.47	3.09
0.10	0.97	0.38	2.55
0.15	0.81	0.34	2.38

Bayesian analysis using a mixture prior

Multiple approaches

- Will discuss one approach – use of a mixture prior distribution

Mixture priors

- Consist of two components
  - one allows for a specific amount of borrowing from external data when such borrowing is considered reasonable and
  - another component that does not allow any borrowing of external data/results (e.g., a skeptical prior/fairly noninfluential).
  - Weights can be based on “applicability” or on how much to “hedge”

Skeptical Prior

"Data need to convince a skeptic"

- A prior distribution that would require stronger evidence from the data to conclude the drug is effective than if no prior distribution were used (or a non-influential prior distribution were used).

Example

Ye, J., and Travis, J., *A Bayesian Approach to Incorporating Adult Clinical Data into Pediatric Trials* presented September 8, 2017 at the FDA Workshop on Pediatric Trial Design and Modeling: Moving into the Next Decade [PDF of Power Point Slides] https://www.fda.gov/downloads/Drugs/NewsEvents/UCM576645.pdf

Adult Study Results

- Continuous endpoint, a change from baseline to a timepoint
- Combined analysis of the adult studies
  - estimated treatment difference of -0.33
  - 95% confidence interval of (-0.58, -0.08)
    - Reflect with adult prior normal distribution mean -0.33 with 95% probability between -0.58 and -0.08

Choice of Skeptical Prior

- Normal mean 0 and variance 0.48
  - In example, like starting with group difference of 0 based on 18 subjects per group

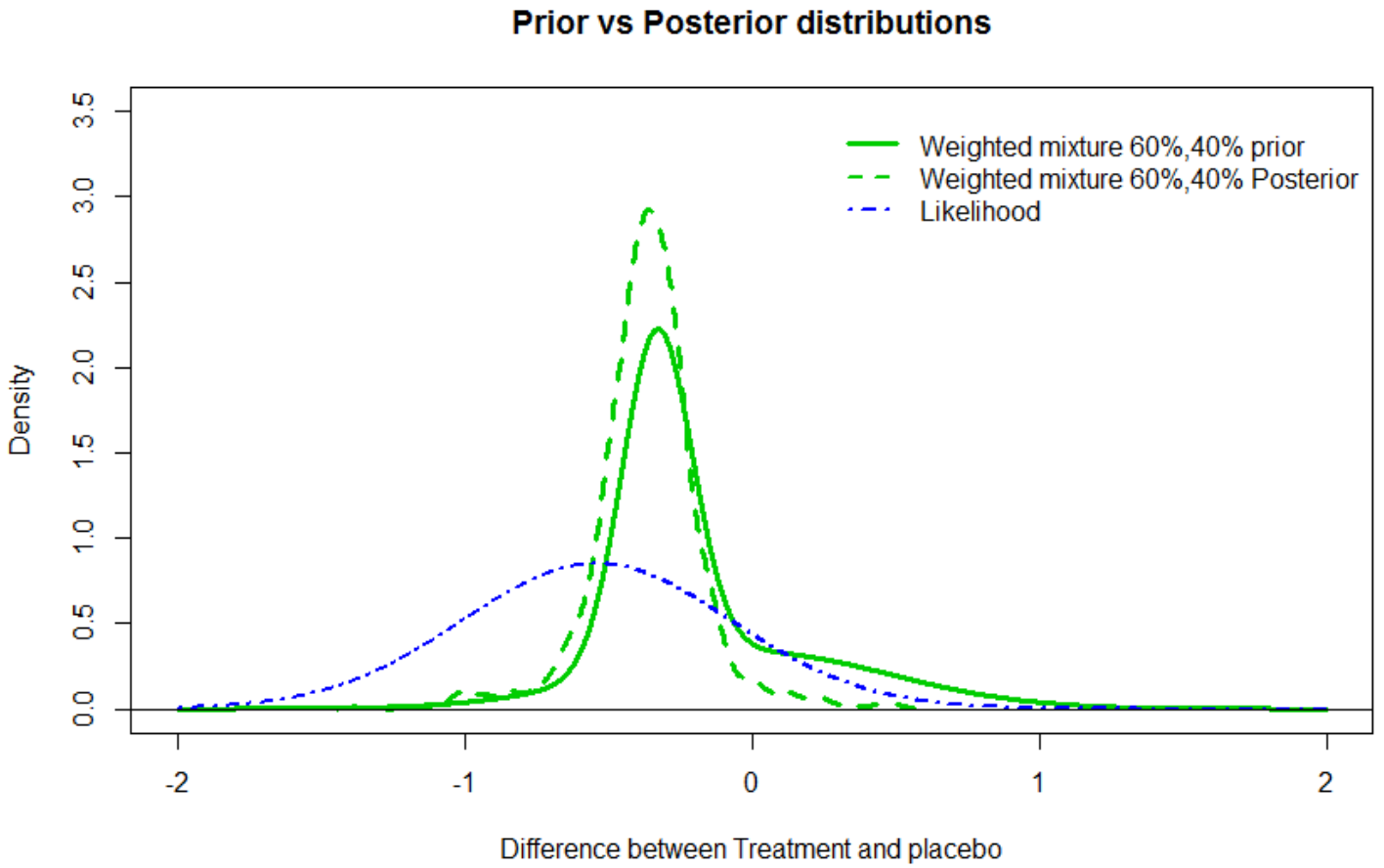
Solicit Expert Opinions

- Ten experts (within FDA) asked to rate applicability of adult data to the pediatric setting on a scale from 0 to 10
  - Rating of 0 meaning the adult data are completely irrelevant to the pediatric setting
  - Rating of 10 meaning that adult data are as meaningful as pediatric data in the pediatric setting.
  - Mean and Median rating were both 6 out of 10 (60% applicability)
    - Weights of 60% and 40% were used in the mixture prior of adult data and a skeptical prior, respectively.

Pediatric Study Results

- Estimated treatment difference of -0.54
- 95% confidence interval of (-1.40, 0.32)
  - "Likelihood" corresponds to normal distribution mean -0.54 with 95% probability between -1.40 and 0.32

Prior, Likelihood, Posterior



Posterior Probability

- Posterior probability treatment difference is negative is 0.973

Other FDA References to Mixture Priors

Abstract 2865

FDA U.S. FOOD & DRUG ADMINISTRATION

Application of Bayesian Statistics to Support Approval of Intravenous Belimumab in Children with Systemic Lupus Erythematosus in the United States

2019 ACR Annual Scientific Meeting
November 13, 2019

Pottackal G, Travis J, Neuner N, Rothwell R, Levin G, Niu J, Marathe A, Nikolov NP
Office of New Drugs
Office of Biostatistics
U.S. Food and Drug Administration

Concluding Remark

Concluding Remark

- Drug development and decision making in pediatric settings starts with adult studies
  - design of adult studies
  - evaluating decision making operating characteristics
- Risk-Benefit assessment should, when possible, include pediatric efficacy results
- Objective : minimize the chance of inconclusive results
- Extrapolation: being done because we believe treatment effects in adults and children are positively correlated

Thank you

Questions?

Extra

Operating Characteristics

State of Nature and Actions

Actions	State of Nature: Null True	State of Nature: Null False
Reject Null	a%	b%
Do not reject Null	c%	d%

100%

Probability of a type I error = [a/(a+b)] x 100%
Probability of a type II error = [d/(c+d)] x 100%

Primary analyses of clinical trials represented in the table. Table provides information on how well the drug development process works.

We are interested in the whole table. Therefore, we need to know three percents to get the whole table.

State of Nature and Actions

- Two probabilities/percents known
  - Probability of a type I error and Probability of a type II error
  - False discovery rate and False omission rate
- Three probabilities/percents known
  - Probability of a type I error, Probability of a type II error and probability drug is effective
    - Related to needing to know the probability drug is effective to properly interpret a p-value
  - False discovery rate, False omission rate and rate of concluding benefit

State of Nature and Actions in Pediatrics relative to all products studied in adults

State of Nature in Pediatrics

Action in Pediatrics	Drug Not Effective	Drug Effective
Conclude Drug Effective	a_1%	b_1%
Don't conclude Drug Effective	c_1%	d_1%

100%

Table represents the collection of drugs/trials *studied in adults*.

State of Nature and Actions in Pediatrics relative to all products found to be safe and effective in adults

Action in Pediatrics	State of Nature in Pediatrics: Drug Not Effective	State of Nature in Pediatrics: Drug Effective
Conclude Drug Effective	a_2%	b_2%
Don't conclude Drug Effective	c_2%	d_2%

100%

Table represents the collection of drugs/trials *found to be safe and effective in adults*.

An Illustration

Illustration -in Adults relative to all products studied in adults

Action in Adults	State of Nature in Adults: Drug Not Effective	State of Nature in Adults: Drug Effective	
Conclude Drug Effective	20 (2%)	320 (32%)	340
Don't conclude Drug Effective	580 (58%)	80 (8%)	660
	600	400	1000

1000 drugs *studied in adults*.

Illustration - in Pediatrics relative to all products found to be safe and effective in adults

Action in Pediatrics	State of Nature in Pediatrics: Drug Not Effective	State of Nature in Pediatrics: Drug Effective	
Conclude Drug Effective	4 (1%)	270 (80%)	274
Don't conclude Drug Effective	36 (11%)	30 (9%)	66
	40	300	340

340 drugs *found to be safe and effective in adults*.

Illustration in Pediatrics relative to all products studied in adults

Action in Pediatrics	State of Nature in Pediatrics: Drug Not Effective	State of Nature in Pediatrics: Drug Effective	
Conclude Drug Effective	4 (0.4%)	270 (27%)	274
Don't conclude Drug Effective	626 (63%)	100 (10%)	726
	630	370	1000

1000 drugs *studied in adults*.

Illustration in Pediatrics relative to all products studied in adults

- Type I error rate = 4/630 = 0.6%
- Type II error rate = 100/370 =27%

- False Discovery Rate 4/274 = 1.5%
- False Omission Rate = 100/726 = 14%

1000 drugs *studied in adults*.